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Industrial Pharmacy-I

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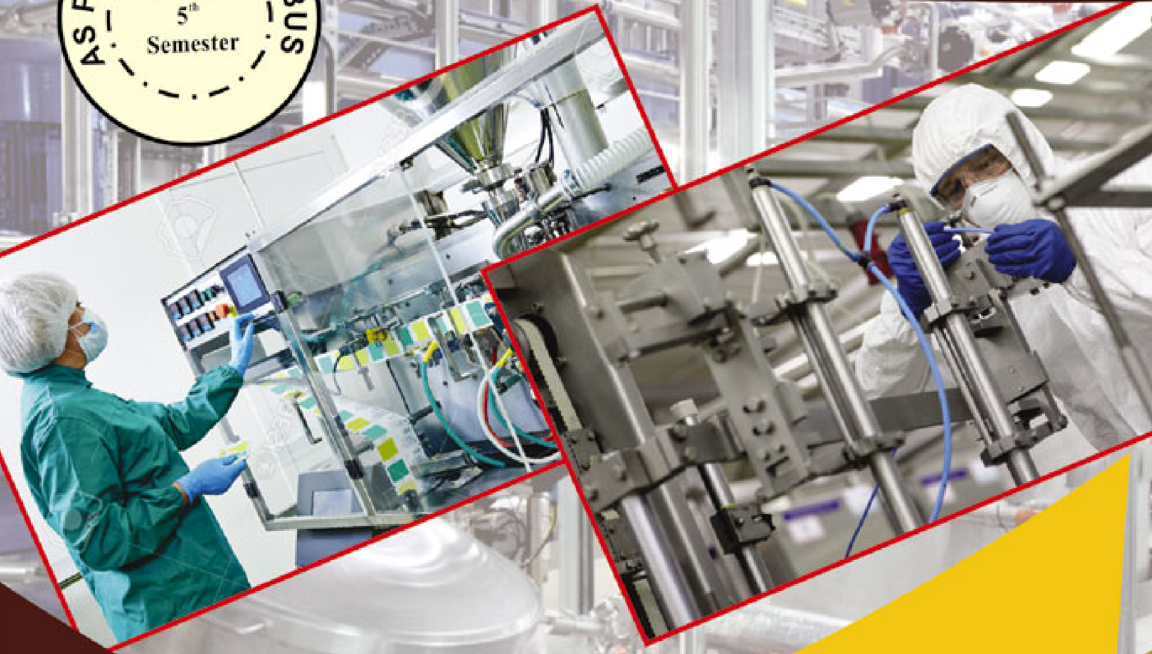
B.Pharm
5th
Semester



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INDUSTRIAL PHARMACY-I

B.Pharm, Semester-V

According to the syllabus based on **'Pharmacy Council of India'**

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Industrial Pharmacy-I

Edition 2019

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“Dedicated
to
*my **Parents & my Dear Children**”*

- Dr K. L. Senthilkumar

“Dedicated
to
*my **Parents** & well wishers”*

-Dr. Atishkumar S. Mundada

“Dedicated
to
*my Beloved **Students**”*

-Dr. Rani S. Kankate

Preface

It gives us immense pleasure to place before the **B.Pharm Fifth Semester** pharmacy students the book on **"Industrial Pharmacy-I"**.

This book has been written strictly in accordance with the current syllabus prescribed by Pharmacy Council of India, for B.Pharm students. Keeping in view the requirements of students and teachers, this book has been written to cover all the topics in an easy-to-comprehend manner within desired limits of the prescribed syllabus, and it provides the students fundamentals of preformulation for tablets, capsules, pellets, liquid orals, parenteral and ophthalmic products, cosmetics, and aerosols which are required by them during their pharmaceutical career.

All efforts have been made to keep the text error-free and to present the subject in a student friendly and easy to understand. However, any suggestions and constructive comments would be highly appreciated and incorporated in the future edition.

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Acknowledgement

I feel great pleasure to introduce this book Industrial Pharmacy -I for B.Pharm V semester as per PCI (new) syllabus which is designed in such a way to fulfill the needs of students and provide potential knowledge.

My gratitude to my mentors **Dr B. Jayakar**, Registrar, VM University, Salem and **Dr S. Gopalakrishnan**, Retired Professor, MMC, Chennai for their ideas, suggestions and moral support in every step. I am grateful to **Mr. & Mrs. D.N.C. Manivannan**, Chairman and **Mr Deepak Manivannan**, Director, Sri Vijay Vidyalaya College of Pharmacy, Dharmapuri, Tamil Nadu for their consistent and cheerful support. I thank my Parents, wife, my children and friends from bottom of heart for sustained support and encouragement.

I also extend my gratitude and thanks to **Thakur Publication Pvt. Ltd.** for their cooperation and follow up while publishing this book.

- Dr K. L. Senthilkumar

This book would not have been possible without constant back-up and persuasion from the originator, **Thakur Publication Pvt. Ltd**.

I owe my special thanks to ***Sharadbhau,*** my elder brother, who is my guide, friend and Philosopher. I am very much thankful to my life partner "*MONA*" for her unflagging love and support throughout my life.

I am grateful to my **Parents**, **Brothers, Sisters**, **Nieces** and **Nephews** who always supported me in pursuing my goals.

I extend my gratitude to the love of my life, mychildren, **Advika** and **Advait**. Last but not least, I express my sincere gratitude to the Principal and Management of SNJB's SSDJ College of Pharmacy for their support and encouragement.

-Dr. Atishkumar S. Mundada

I would like to thank all people who have helped and inspired me during my book writing. It is a pleasure to convey my gratitude to them all in my humble acknowledgment.

I am grateful to **God** for giving me the strength to successfully complete book writing process andto sustain my efforts which many a times did oscillate.

I am grateful to **Thakur Publication Pvt. Ltd** especially, **Ms. Tuhina Banerjee** (Copy Editor) and **Mr. Sharad Kushwaha** (Marketing Coordinator), for giving me book writing excellent opportunity.I am very much thankful to **Shri Samir Bhujbal** and **Dr. Shefali Bhujbal**, Trustee, Chief Administrator, MET's Institute of Pharmacy, Bhujbal Knowledge City for their kind support and inspiration.

I gratefully acknowledge **Dr.Sanjay J. Kshirsagar**, Principal, Bhujbal Knowledge City, MET's Institute of Pharmacy. My sincere thanks to all my family members for their constant encouragement.

-Dr. Rani S. Kankate

Syllabus

Module 01 **07 Hours**

Pre-formulation Studies

- Introduction to pre-formulation, Goals and Objectives, Study of Physicochemical Characteristics of Drug Substances.
- **Physical Properties:** Physical form (Crystal and Amorphous), Particle Size, Shape, Flow Properties, Solubility Profile (pKa, pH, Partition Coefficient), Polymorphism
- **Chemical Properties:** Hydrolysis, oxidation, reduction, racemisation, polymerization
- BCS classification of drugs and its significant
- Application of pre-formulation considerations in the development of solid, liquid oral and parenteral dosage forms and its impact on stability of dosage forms.

Module 02 **10 Hours**

Tablets

- Introduction, Ideal Characteristics of Tablets, Classification of Tablets. Excipients, Formulation of Tablets, Granulation Methods, Compression and Processing Problems. Equipments and Tablet Tooling
- **Tablet Coating:** Types of Coating, Coating Materials, Formulation of Coating Composition, Methods of Coating, Equipment Employed and defects in Coating.
- **Quality Control Tests:** In Process and Finished Product Tests.

Liquid Orals

- Formulation and Manufacturing Consideration of Syrups and Elixirs Suspensions and Emulsions; Filling and Packaging; Evaluation of Liquid Orals Official in Pharmacopoeia.

Module 03 **08 Hours**

Capsules

Hard Gelatin Capsules

- Introduction, Production of hard Gelatin Capsule shells. Size of Capsules, Filling, Finishing and Special Techniques of Formulation of hard Gelatin Capsules, Manufacturing Defects.
- In Process and Final Product Quality Control Tests for Capsules.

Soft Gelatin Capsules

- Nature of shell and Capsule Content, Size of Capsules, Importance of Base Adsorption and Minim/Gram Factors, Production, In Process and Final Product Quality Control Tests.
- Packing, Storage and Stability Testing of Soft Gelatin Capsules and their Applications.

Pellets

- Introduction, Formulation Requirements, Pelletization Process, Equipments for Manufacture of Pellets.

Module 04 **10 Hours**

Parenteral Products

- Definition, types, advantages and limitations. Pre-formulation factors and essential requirements, vehicles, additives, importance of isotonicity.
- Production procedure, production facilities and controls, aseptic processing,
- Formulation of injections, sterile powders, large volume parenterals and lyophilized products.
- Containers and closures selection, filling and sealing of ampoules, vials and infusion fluids. Quality control tests of parenteral products.

Ophthalmic Preparations

- Introduction, formulation considerations; formulation of eye drops, eye ointments and eye lotions; methods of preparation; labeling, containers; evaluation of ophthalmic preparations.

Module 05 **10 Hours**

Cosmetics

- **Formulation and Preparation of the following Cosmetic Preparations :** Lipsticks, Shampoos, Cold Cream and Vanishing Cream, Toothpastes, Hair Dyes and Sunscreens.

Pharmaceutical Aerosols

- Definition, Propellants, Containers, Valves, Types of Aerosol Systems ; Formulation and Manufacture of Aerosols; Evaluation of Aerosols; Quality Control and Stability Studies.

Packaging Materials Science

- Materials used for Packaging of Pharmaceutical Products , Factors Influencing Choice of Containers, Legal and Official Requirements for Containers, Stability Aspects of Packaging Materials, Quality Control Tests.

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Module 3

Chapter 4: Capsules - I

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Chapter 6: Pellets

Module 4

Chapter 7: Parenteral Products

Chapter 8: Ophthalmic Preparations

Module 5

Chapter 9: Cosmetics

Chapter 10: Pharmaceutical Aerosols

Chapter 11: Packaging Materials Science

CHAPTER 1

Pre-formulation Studies

1.1. PRE-FORMULATION CONSIDERATIONS IN THE DEVELOPMENT OF DOSAGE FORMS

1.1.1. Introduction

When a drug (recently synthesised) produces such pharmacological effects in animal models that allow evaluation in man, it indicates the beginning of pre-formulation. During the pre-formulation study, the physicochemical properties of the new drug which can alter the drug's performance and development of an efficient dosage form should be considered carefully. A rationale for formulation design and support for the need of molecular modification will be provided if the physicochemical properties of the new drug are thoroughly studied. In simple words, it can be said that pre-formulation studies are performed to make sure that there are no obstacles in the development of drug. **Table 1.1** describes some evaluation parameters used in the pre-formulation of drug development:

Table 1.1: Evaluation Parameters used in the Pre-formulation of Drug Development

	Parameters	Evaluation Parameters
1)	i) Stability ii) Solid State iii) Solution	Temperature, light, and humidity Solvent and pH Solvent and pH
2)	Solid state compatibility	TLC and DRS analysis
3)	Physicochemical properties – colour, odour, particle size, shape crystallinity	Molecular structure, weight, and melting point
4)	i) Thermal analysis profile solubility ii) Water and other solvent	DTA, DSC, and TGA Salt forms, co-solvent, complexation, pro-drug, and pH
5)	Absorbance spectra	UV and IR
6)	Other properties hygroscopicity	Potential bulk characterisation volatility, optical activity, solvate formation, crystallinity, and polymorphism
7)	Physico-mechanical properties	Tapped density and compressibility photomicrograph
8)	*In vitro* availability properties rat everted gut technique	Dissolution and analysis of drug crystal
9)	Other studies plasma protein-binding, ionisation constant	Effect of compatible excipients on dissolution, kinetic studies of solution degradation, and use of radiolabelled drug

1.1.2. Goals and Objectives

The goals of pre-formulation are:

1) To establish the physicochemical parameters of a new drug substance,
2) To establish the physical characteristics of a new drug substance,

3) To establish the kinetic rate profile of a new drug substance,
4) To establish the compatibility of the new drug substance with the common excipients, and
5) To choose the correct form of a drug substance.

The objectives of pre-formulation are:

1) To develop elegant, stable, effective, and safe dosage forms.
2) It is required to have an understanding of the physical description of a drug substance before the development of any dosage form.
3) Pre-formulation is the first step in rational development of a dosage form of a drug substance before the development of dosage form.

1.1.3. Study of Physicochemical Characteristics of Drug Substances

Following are the major physicochemical characteristics of drug substances evaluated in the pre-formulation research:

1) **Physical properties**
    i) Bulk characterisation:
        a) Physical form,
        b) Polymorphism,
        c) Particle size,
        d) Particle shape, and
        e) Flow properties.
    ii) Solubility analysis:
        a) Ionisation constant – pKa,
        b) pH solubility profile, and
        c) Partition coefficient.
    iii) Stability analysis:
        a) Stability in toxicology formulations,
        b) Solution stability – pH rate profile, and
        c) Solid state stability:
            - Bulk stability, and
                - Compatibility.
2) **Chemical properties**
    i) Hydrolysis
    ii) Oxidation,
    iii) Reduction,
    iv) Racemisation, and
    v) Polymerisation.

1.2. PHYSICAL PROPERTIES

1.2.1. Introduction

The development process results in the alteration of the bulk properties of a solid, **e.g.,** particle size, bulk density, surface morphology, etc. It is known that solubility or stability of a compound depends on its crystallinity, therefore, pre-formulation bulk lots should be completely characterised. This also avoids the predictions of stability or solubility which are false.

1.2.2. Physical Form

Solid is one of the three classical states of matter (the others being gas and liquid). It is characterised by structural rigidity and resistance to changes in shape or volume. A solid molecule is made up of atoms tightly bound to each other either in a regular geometric lattice (crystalline solids that include metals and ordinary water ice) or irregularly (amorphous solid, such as a common window glass).

Figure 1.1 represents the classification of the compound's internal structure:

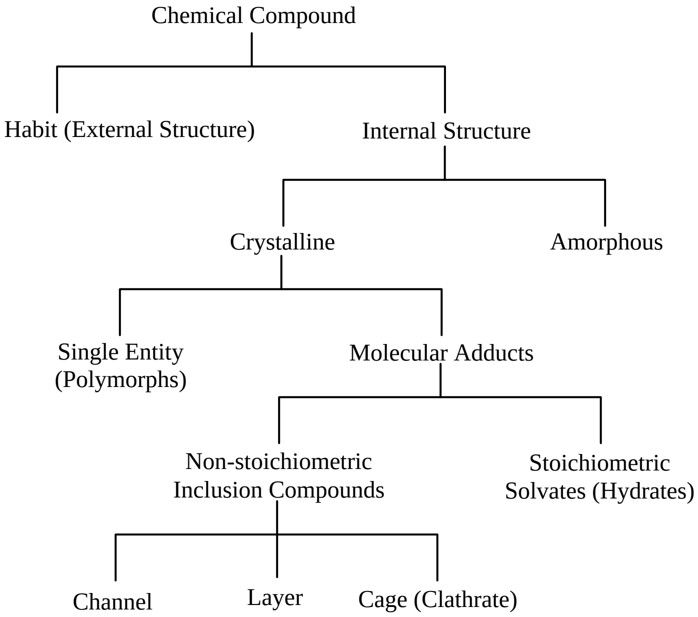


Figure 1.1: Classification of the Internal Structure of a Compound

1.2.2.1. Crystal

The bulk and physicochemical properties of a drug (ranging from flowability to chemical stability) are affected by its crystal habit and internal structure. The outer appearance of a crystal is known as **habit** and the arrangement of molecules within the solid is termed as **internal structure**. The internal structure of a compound can be either crystalline or amorphous. The compound is said to be **crystalline** if its atoms or molecules are arranged repetitively in a 3-D array.

The amount of crystallisation solvent in a crystalline compound can be either **stoichiometric** or **non-stoichiometric**, which are parts of molecular adducts. **Solvate**, a stoichiometric adduct is a molecular complex in which the crystallising solvent molecules are incorporated within the crystal lattice into specific sites.

A stoichiometric adduct in which the entrapped solvent is water is said to be a **hydrate** and its hydrated forms with molar equivalents of water corresponding to half, one, and two are termed as hemihydrate, monohydrate, and dihydrate, respectively.

Clathrate, a non-stoichiometric adduct entraps solvent molecules within the crystal lattice. A compound is said to be **anhydrous** if the crystal structure does not contain water within it.

1.2.2.2. Amorphous

Amorphous solids are the ones in which the atoms or molecules are arranged in a random manner (as in a liquid). In these solids, different bonds have different strength, there is no regularity in their external structure, and also they do not have sharp melting points (due to the variable strength of bonds present between the molecules, ions, or atoms).

Bonds having low strength break at once when exposed to heat; however, the strong bonds take some time to break. Amorphous solids are isotropic in nature, i.e., their physical properties will remain the same in all the directions.

The stability of amorphous compounds increases on storage. The major **disadvantage** that occurs during the development of an amorphous form is the thermodynamic instability occurring during bulk-processing or within the dosage forms.

Table 1.2 enlists the major differences between the crystalline and amorphous solids:

Table 1.2: Differences between Crystalline and Amorphous Form

Have fixed internal structure.	Do not have any fixed internal structure.
Have lower thermodynamic energy.	Have higher thermodynamic energy.
Are more stable.	Are less stable.
Have lesser solubility.	Have greater solubility.
Have lesser tendency to change their form during storage.	Tend to revert to more stable forms during storage.

1.2.3. Polymorphism

The ability of a substance to exist in more than one crystalline form is **polymorphism** and the various crystalline forms are termed as **polymorphs**. There are **two types** of polymorphs:

1) **Enantiotropic Polymorphs:** By altering the temperature or pressure, the enantiotropic polymorphs can be changed into another in a reversible manner, **e.g.,** sulphur.
2) **Monotropic Polymorphs:** Under all the conditions of temperature and pressure, the monotropic polymorphs remain unstable, **e.g.,** glyceryl stearate.

The polymorph with lower free energy which corresponds to lower solubility or vapour pressure is thermodynamically stable below the melting point of the solid.

It is essential that during the pre-formulation studies, the polymorphs which are stable at room temperature should be identified. Determination of whether or not polymorphic transitions may occur within the temperature range used for stability studies and during processing (drying, milling, etc.) is also important.

1.2.4. Particle Size

The term **particle size** is used to compare the dimensions of solid particles (flakes), liquid particles (droplets), or gaseous particles (bubbles).

Size, shape, and surface morphology of the drug particles put a direct effect on the bulk flow, formulation homogeneity, and surface-area controlled processes, such as dissolution and chemical reactivity. Preparation of homogeneous samples is facilitated and surface area of drug for interactions is enhanced during pre-formulation when each new drug candidate is tested with the smallest particle size.

Characterisation of drug particles with respect to their size and shape can be done using a light microscope with a calibrated grid. The steps of sampling and slide preparation should be done carefully to obtain a representative dispersion. Size of several hundred particles should be determined, and the obtained mean and size range should be represented on a histogram. This task can be done easily by using photomicrographs and a haemocytometer slide, along with other sizing techniques. Being a time-consuming process, light microscopy has few restrictions on particle shape.

The characterisation of a compound's size distribution can be done conveniently by using stream counting devices, such as the Coulter counter and HIAC counter, along with light microscopy. Preparation of samples to be analysed by Coulter counter method is done by dispersing the material in a conducting medium (isotonic saline) with the help of ultrasound and a few drops of surfactant. 0.5-2ml of the resultant suspension is drawn into a tube through a small aperture with 0.4-800µ diameter and voltage is applied across it.

When each particle passes through the hole, they are counted and sized depending on the resistance developed when conducting medium of that particle's volume is displaced. A histogram of frequency *versus* size is generated within the limits of the particular aperture tube; since, the instrument has been calibrated using standard spheres. Single particles are counted accurately by using aperture tubes of different sizes. Light blockage or laser light scattering for sizing each particle are the principles on which other stream counters rely.

The **Coulter counter method** is quick and statistically meaningful, still it assumes that resistance develops from spherical particles, therefore, non-spherical particles are sized inaccurately. Sometimes, the aperture hole is blocked by the needle-shaped crystals, or the compounds undergo dissolution in the aqueous conducting medium, or particles undergo stratification within the suspension.

These are other limitations of this method. Image analysis and sieve analysis are other methods of particle size analysis. When large quantity of samples having large particle size up to 100µ is used, sieve analysis technique is used for particle size determination.

Brunauer, Emmett, and Teller (BET) **nitrogen adsorption technique** is used for measuring the surface area more precisely. In this method, the sample adsorbs a layer of nitrogen molecules on its surface at –196°C temperature. When the sample's surface adsorption attains equilibrium, it is heated up to room temperature, nitrogen gas is desorbed, and its volume is measured which is converted into the number of adsorbed molecules with the help of ideal gas law.

The surface area per gram for each pre-weighed sample should be computed immediately as an area of 16cm^2 is occupied by each nitrogen molecule (N_2). The surface area of the true monolayer can be obtained by the determination of the surface area at several partial pressures of nitrogen (5-35% N_2 in He) and extrapolation to zero nitrogen partial pressure. Although, measurement by BET technique using commercial equipment is precise and quick, use of impure gases and volatile surface impurities (**e.g.,** hydrates) results in errors.

Scanning Electron Microscopy (SEM) is used for monitoring the surface morphology as it observes the surface area in a qualitative manner. The sample to be prepared for SEM is made conductive by exposing it to high vacuum during the process of gold coating. Removal of water or other solvents gives a false morphology of the surface.

The effect of sample preparation on surface morphology can be confirmed by treating the sample with vacuum before coating it with gold. Surface metal ions can be analysed by energy dispersive X-ray spectroscopy, the technique provided by modern SEM instruments. A problem related to instability or incompatibility can be determined by the energy dispersive X-ray spectroscopy technique.

Significance of Particle Size

1) Particle size of drug affects the formulation and its efficacy.
2) Its distribution affects some of the physical and chemical properties of drug substances, such as drug dissolution rate, content uniformity, texture, stability, flow characteristics, and sedimentation rates.
3) It affects the oral absorption profiles of some drugs.
4) Particle size and equal distribution of the active ingredients throughout the formulation affects the content uniformity in solid dosage forms.

1.2.5. Particle Shape

The term **particle shape** is used to express the geometrical shape and surface regularity (rugosity) of the material (**figure 1.2**). Moreover, particle shape affects the surface area, flow, packing, and compaction properties of the particles.

The particle shape, either spherical or asymmetrical can be determined. In order to differentiate the shape of spherical or asymmetrical objects, it is necessary to know that the sphere has minimum surface area per unit volume.

By means of surface area measurement, the following expressions for an asymmetric particle can be obtained:

Properties	**Sphere**	**Particle**
Surface area	πd_s^2	$\alpha_s \times d_p^2$
Volume	$(1/6)\ \pi d_s^3$	$\alpha_v \times d_p^3$

Where, α_s = Surface area factor.
α_v = Volume factor.

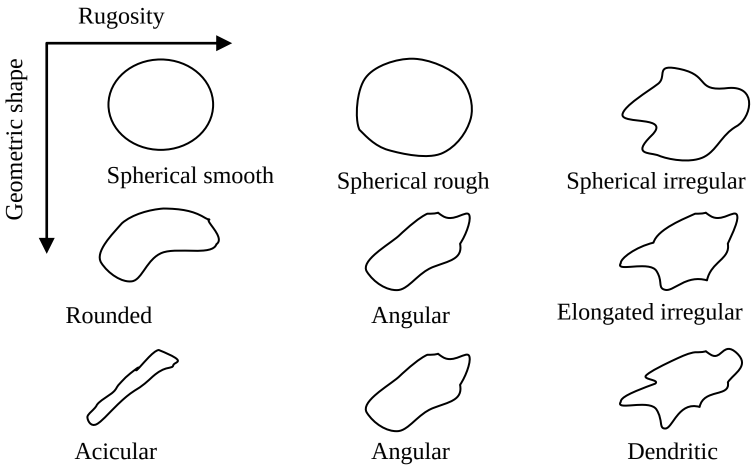


Figure 1.2: Characteristic Particle Shapes related to Geometric Shape and Surface Irregularity

The surface area and volume factor (α_s and α_v) can be represented as:

$$\alpha_s = \frac{\pi d_s^2}{d_p^2} \quad \text{and} \quad \alpha_v = \frac{\pi d_s^3}{6 d_p^3}$$

If $d_s = d_p$, the relationship can be written as:
$\alpha_s = \pi = 3.124$ and $\alpha_v = \pi/6 = 0.524$

The **shape factor** of a particle is the ratio of surface area factor to volume factor, and is expressed as:

$$\text{Shape factor} = \frac{\alpha_s}{\alpha_v} = \frac{3.124}{0.524} = 6$$

For a **sphere**, the minimum possible value for **shape factor is 6**, and for any **asymmetric particle**, the **ratio exceeds** this factor 6.

The commonly used descriptions of particle shape (**figure 1.3**) are given below:

1) **Equant:** Cubical and spherical particle of similar length, width, and thickness.
2) **Acicular:** Slender and needle-like particle of similar width and thickness.
3) **Columnar:** Long and thin particle with a width and thickness greater than that of an acicular particle.
4) **Flake:** Thin and flat particle of similar length and width.
5) **Plate:** Flat particle of similar length and width but with greater thickness than a flake.
6) **Lath:** Long, thin, and blade-like particle.

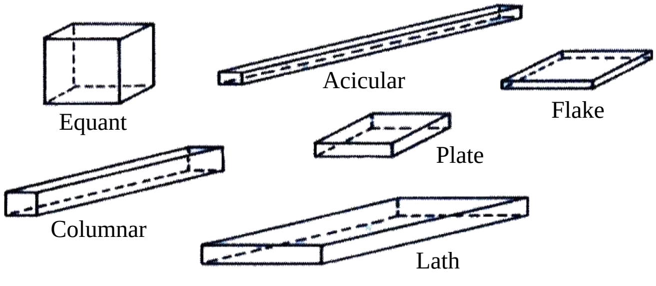


Figure 1.3: Commonly Used Descriptions of Particle Shape

1.2.6. Bulk Density

Method of crystallisation, milling, or formulation makes a significant change in the compound's bulk density. When a high-dose capsule's size or a low-dose formulation's homogeneity (in which large differences exist between densities of drug and excipient) is considered, bulk density plays a significant role.

The bulk drug which has been sieved previously through a 40-mesh sieve is poured into a graduated cylinder with the help of a large funnel and the volume and weight is measured, thus, determining the **apparent bulk density** (gm/ml). A graduated measuring cylinder with a known mass of drug or formulation is placed on a mechanical tapper apparatus operating at a fixed number of taps (~1000). When the bed volume of powder reaches minimum level, the weight and volume of the drug in the cylinder is measured from which **tapped density** can be calculated.

In order to calculate void volume or porosity of packed powder beds, determination of **true density** along with the bulk density of a powder is required. True density of a powder can be determined by suspending drug particles in solvents (of varying densities) in which the compound is insoluble. When a small quantity of surfactant is added to the solvent mixtures, wetting and pore penetration can be enhanced. The samples are centrifuged after vigorous agitation and then allowed to stand aside until floatation or settling has reached equilibrium. The sample which does not settle down and remains suspended gives the true density of the drug.

1.2.7. Flow Properties

Free-flowing or **non-free-flowing/cohesive** are the two types of pharmaceutical powders. Changes in particle size, density, shape, electrostatic charge, and adsorbed moisture (arising from processing or formulation) significantly affects the flow properties of a powder.

The pharmaceutical consequences of each process improvement should be assessed by the pre-formulation study of powder flow. This also guides the project team of formulation development by providing them information regarding the formulation recommendations such as granulation or densification via slugging, the need for special auger feed equipment, or a test system for evaluating the improvements in flow brought about by formulation.

Using a **simple flow rate apparatus** that consists of a grounded metal tube from which drug flows through an orifice onto an electronic balance connected to a strip chart recorder, helps in the characterisation of free-flowing powders. At each variety of orifice size ranging between ⅛-½ inches, flow rate should be determined in gm/sec. Greater the standard deviation between multiple flow rate measurements, greater is the weight variation in powder products.

Jones and **Pilpel** proposed an equation (1) to present the dependence of flow rate (W) on true particle density (ρ), gravity (g), and orifice diameter (D_o), when several samples of drug are tested under different conditions. Both (A) and (n) are constants depending upon the material and its particle size.

$$D_o = A\left(\frac{4W}{60\pi\rho\sqrt{g}}\right)^{1/n} \qquad \text{.....(1)}$$

The equation below shows compressibility of a free-flowing powder that has been calculated from the density of powder:

$$\%\text{Compressibility} = \left(\frac{\rho_t - \rho_o}{\rho_t}\right)\times 100 \qquad \text{.....(2)}$$

Where, ρ_t = Tapped bulk density

ρ_o = Initial bulk density

1.2.8. Solubility Profile

The drug-solvent systems through which the drug is delivered helps in the pre-formulation solubility studies. **For example**, solubility of an orally administered drug in media with isotonic chloride ion concentration and acidic pH can be determined. The administration routes are not clearly defined at this point; still the formulation work can be carried out by understanding the solubility profile of the drug and mechanism of solubility. Pre-formulation solubility studies involve pKa determination, temperature dependence, pH solubility profile, solubility products, mechanisms of solubility, and dissolution rate.

HPLC, UV spectroscopy, fluorescence spectroscopy, and gas chromatography are the analytical methods used for measuring solubility. Solubility data for most of the drugs can be obtained accurately and efficiently by reverse phase HPLC technique which possesses the following **advantages**:

1) Analysis of aqueous samples,
2) High sensitivity, and
3) Chromatographic separation of drug from impurities or degradation products results in specific determination of drug concentration.

1.2.8.1. BCS Classification of Drugs and its Significance

Biopharmaceutics Classification System (BCS) is a fundamental guideline for determining the conditions under which *In-Vitro In-Vivo* Correlations (IVIVC) are expected. BCS is also used as a tool for developing the *in-vitro* dissolution specifications. This classification is based on the drug dissolution and absorption model, which identifies the following **key parameters** controlling drug absorption as a set of dimensionless numbers:

1) **Absorption Number (An):** Ratio of mean residence time to absorption time.

$$A_n = T_{res}/T_{abs} + \{\pi R^2 L/Q)/(R/P_{eff})$$

2) **Dissolution Number (Dn):** Ratio of mean residence time to mean dissolution time.

$$D_n = T_{res}/T_{diss} + (\pi R^2 L/Q)/(pr_0^2/3DC_s^{min})$$

3) **Dose Number:** Mass divided by an uptake volume of 250ml and the drug's solubility.

$$D_o = Dose/(V_o/C_s^{min})$$

The BCS for correlating *in vitro* drug product dissolution and *in vivo* bioavailability is proposed based on recognising that drug dissolution and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. The drugs as per the BCS are divided into the following high/low-solubility and permeability classes:

Class I: High solubility-High permeability,

Class II: Low solubility-High permeability,

Class III: High solubility-Low permeability, and

Class IV: Low solubility-Low permeability.

The classes of BCS are discussed below:

1) **Class I (High Solubility-High Permeability Drugs):** The drugs of this class behave like oral solutions having **fast dissolution** and **rapid bioavailability**. The dissolution and absorption of these drugs is very fast, thus bioavailability and bioequivalence are unnecessary for such drug products. These drugs are good candidates for controlled drug delivery. Gastric emptying is the rate limiting step in absorption of these drugs.

2) **Class II (Low Solubility-High Permeability Drugs):** The drugs of this class have low solubility and high permeability, hence, the dissolution rate becomes the rate limiting step for bioavailability. These drugs have **variable bioavailability**, which can be improved by enhancing their dissolution rate by different methods. These drugs are also suitable candidates for controlled release development.

3) **Class III (High Solubility -Low Permeability Drugs):** Permeation through the intestinal membrane is the rate limiting step for the drugs of this class. Since absorption is permeation rate limited, bioavailability is independent of drug release from the dosage form.

   For example, ranitidine products having different dissolution profiles produce superimposable plasma concentration *versus* time profile *in-vivo*. The drugs of class III have **low bioavailability** and their permeability needs to be enhanced. These drugs are not considered as suitable candidates for controlled release development.

4) **Class IV (Low Solubility -Low Permeability Drugs):** The drugs of this class have **poor and variable bioavailability**. The overall bioavailability is governed by the factors like dissolution rate, intestinal permeability, gastric emptying, etc. These drugs are not considered as suitable candidates for oral drug delivery; and if used, some special drug delivery technologies (such as nanosuspensions) are needed.

Some of the common drugs belonging to the classes of BCS are given in **table 1.3**:

Table 1.3: Biopharmaceutical Classification System

Solubility	**Permeability**	
	High	**Low**
High	**Class I**	**Class III**
	Propranolol, Metoprolol, Diltiazem, Verapamil, etc.	Acyclovir, Neomycin B, Peptides, Captopril, Enalaprilat, Alendronate, Ranitidine, etc.
Low	**Class II**	**Class IV**
	Ketoconazole, Mefenamic acid, Nisoldipine, Nifedipine, Nicardipine, etc.	Chlorothiazide, Furosemide, Tobramycin, Cefuroxime, etc.

Significance of BCS

This concept underlying the BCS led to the possibility of waiving *in vivo* bioequivalence (BE) studies in favour of specific comparative *in vitro* testing to conclude bioequivalence of oral Immediate Release (IR) products with systemic actions.

In terms of BE, it is assumed that highly permeable and soluble drugs incorporated in rapidly dissolving drug products will be bioequivalent. It is also believed that unless major changes are made to the formulation, dissolution data can be used as a replacement for pharmacokinetic data to demonstrate BE of two drug products.

Thus, the BCS allows the manufacturers to reduce the cost of approving scale-up and also the post approval changes to some of the oral drug products without conceding the public safety interests.

BCS is a drug-development tool that determines the influence of dissolution, solubility and intestinal permeability on oral drug absorption from IR solid oral dosage forms.

It was first introduced into regulatory decision making process in the guidance document on immediate release solid oral dosage forms.It is an indicator of developing an extrapolative IVIVC and also enables to examine the importance of drug dissolution and permeability on IVIVC validity (**table 1.3**).

Table 1.4: *IVIV* Correlation Expectation for Immediate Release Product Based on Biopharmaceutic Class

Class	Solubility	Permeability	*IVIV* Correlation for IR Products
I	High	High	*IVIV* correlation if dissolution rate is slower than gastric emptying rate, otherwise limited or no correlation.
II	Low	High	*IVIV* correlation if *in vitro* and *in vivo* dissolution rate is similar, unless dose is very high.
III	High	Low	Absorption (permeability) is rate determining and limited or no *IVIV* correlation with dissolution rate.
IV	Low	Low	Limited or no *IVIV* correlation expected.

1.2.8.2. pKa

Solubility and absorption undergo change by the orders of magnitude with change in pH, therefore, dissociation constant of a drug that can ionise within a pH range of 1 -10 should be determined. At a particular pH, an estimate of the ionised and unionised drug concentration can be obtained by the Henderson-Hasselbalch equation.

For acidic compounds:

$$\mathrm{pH} = \mathrm{pKa} + \log\frac{[\text{Ionised drug}]}{[\text{Unionised drug}]}$$

For basic compounds:

$$\mathrm{pH} = \mathrm{pKa} + \log\frac{[\text{Unionised drug}]}{[\text{Ionised drug}]}$$

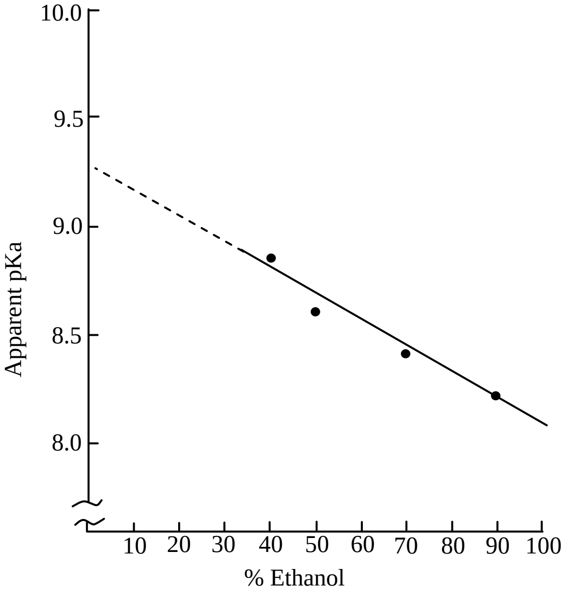


Figure 1.4: pKa determination for an organic amine candidate whose unionised form is exceedingly insoluble in water

The unionised form of a weakly acidic drug (whose pKa value is >3) resides in the stomach's acidic medium but the drug ionises in the intestine's neutral medium. The ionised form of basic drugs (erythromycin and papaverine with pKa value ~ 8 -9) is present in stomach, as well as in intestine. There are various analytical techniques which are used for determining the pKa value which is affected by buffer, temperature, ionic strength, and cosolvent; therefore, these parameters should be controlled during pKa determination. Analysis of dilute aqueous solutions can be done directly, therefore, **detecting the spectral shifts by UV or visible spectroscopy** is the preferred method.

Another method that can be employed is **potentiometric titration** which is highly sensitive for compounds with pKa value ranging between 3-10. Since, the drug is required in high concentration in order to produce a titration curve; the unionised form of the drug undergoes precipitation, thus, hindering the titration process. This precipitation however can be prevented by using methanol or dimethylsulfoxide (cosolvent) in which the unionised drug is soluble. At various concentrations of cosolvent, titration data is collected from which the pKa value is extrapolated (**figure 1.4**). Dissociation constant's dependency on cosolvent is highly significant and extrapolations provide only an estimate of pKa value. Cosolvent yields higher pKa values for acids and lower values for bases than the pure water.

1.2.8.3. pH

The pKa of the ionising functional group and the intrinsic solubilities for both the ionised and unionised forms of acidic or basic drug influence their solubility. The total molar solubility (S_t) for a basic drug is expressed as:

$$S_t = [BH^+] + [B] \qquad .....(1)$$

Where, BH^+ = Protonated species

B = Free base

pH_{max} is the pH at which both base and salt species are simultaneously saturated. It can also be represented as:

$$S_t,\ pH = pH_{max} = [BH^+]_s + [B]_s \qquad .....(2)$$

Where, subscript (s) = Saturation

The molar solubility for weak bases in the pH region where the solubility of the protonated form is limiting is represented as:

$$S_t,\ pH < pH_{max} = [BH^+]_s + [B] \qquad .....(3)$$

$$= [BH^+]_s\left(1 + \frac{K_a}{H^+}\right)$$

In a similar manner, in the pH region where the free base is limiting, the solubility is represented as:

$$S_t,\ pH > pH_{max} = [BH^+] + [B]_s \qquad .....(4)$$

$$= [B]_s\left(1 + \frac{H^+}{K_a}\right)$$

The pH_{max} can be defined as:

$$pH_{max} = pKa + \log\frac{[B]_s}{[BH^+]_s} \qquad .....(5)$$

The free base and salt form can exist simultaneously in equilibrium with a saturated solution at a solution pH equivalent to pH_{max}. By taking samples of the precipitated drug from the equilibrated solution and confirming the presence of both drug forms, the pH_{max} can be verified.

The solubility determining factor is the paired counter, ion's concentration, when the solubility-limiting species in the solution is the ionised or salt form of a drug. The equilibrium between the solid and ionised species in a solution for a hydrochloride salt of a basic amine is represented as:

$$[BH^+Cl^-]_{solid} \overset{K_{sp}}{\rightleftharpoons} [BH^+] + [Cl^-] \quad .....(6)$$

Where, K_{sp} = Solubility product for the protonated species and chloride counter ion, or it can also be expressed as:

$$K_{sp} = [BH^+][Cl^-] \quad .....(7)$$

The total drug solubility decreases with the increase in chloride ion concentration if the contribution of the unionised species is negligible when compared to the protonated form. In such cases, the apparent solubility product is represented as:

$$K_{sp} = S_t\,[Cl^-] \quad .....(8)$$

When a solubility product is determined experimentally , the pH should be measured, and the drug and counter ion concentration should be assayed. The thermodynamic solubility product can be calculated by converting the concentrations into activities with appropriate corrections for activity coefficient dependence on ionic strength.

Aqueous solubility profiles for ionisable compounds over large pH ranges with varying counter-ion concentrations are functions of many variables, which for an organic amine drug can be represented as:

$$S_t = f(pH, pKa, [B]_s, K_{sp}, anions) \quad .....(9)$$

Ionic strength, temperature, and aqueous media composition are other factors which influences the above mentioned parameters. As a result, for compounds with similar functional group, the pH solubility profiles appear dramatically different.

1.2.8.4. Partition Coefficient

The ratio of unionised drug distributed between the organic and aqueous phases at equilibrium is the partition coefficient. The oil/water partition coefficient in systems such as octanol/water and chloroform/water is the measurement of a drug's lipophilicity and an indication of its ability to cross the cell membranes.

$$P_{o/w} = \left(\frac{C_{oil}}{C_{water}}\right)_{equilibrium}$$

Partition coefficient also provides an empiric handle in screening of some biological properties of a series of compounds. The data of partition coefficient provides a better understanding of *in vivo* absorption and also a means of characterising the lipophilic/hydrophilic nature of drug.

1.2.9. Stability Profile

For analysing the chemical stability of a new drug quantitatively, pre-formulation stability studies play an important role. Conditions typical for handling, formulation, storage, and administration of a drug candidate are maintained for carrying out the pre-formulation stability studies for both solid and solution state. Several bulk lots are produced during the development of drug reflecting scale-up and process improvements in yield, purity, and possibly crystallinity. The first lot used for the pre-formulation stability studies does not represent the commercial bulk product but provides baseline data. Parallel testing of the initial bulk lot of drug with the new bulk or formulation helps to form concluding results about the project's progress, in further evaluations.

When the initial stability tests are completed, one or more challenge models which indicate the stability are developed. These models are used for limited testing on future bulk lots or formulations.

1.2.9.1. In Toxicology Formulations

In the beginning of drug development, toxicology studies are performed, therefore, evaluation of the samples of toxicology preparations for stability and potential homogeneity problems should be done. Animals are administered with drugs either in their feed or drug suspension in an aqueous vehicle or by oral gavage of a solution.

The shelf-life of a drug gets reduced severely due to the presence of water, vitamins, minerals (metal ions), enzymes, and a multitude of functional groups in the feed. The composition of feed varies with the consumer which decreases the enzyme activity and moisture levels with time. Therefore, a relevant stability data can be obtained by using a fresh sample of feed for the toxicology test. The storage temperature for this stability study should be of the toxicology laboratory because the enzyme activity and mobility of adsorbed water vary with temperature.

Toxicologic preparations in solution and suspension form should be checked for ease of manufacture and then stored at various temperatures in flame-sealed ampoules. The dispersibility of the suspensions should also be checked (apart from chemical stability) by occasionally shaking the ampoules. The drug solubility (at the same temperature) and pH obtained from the analysis of the suspension data indicates that only drug in solution decomposes.

1.2.9.2. Solution Stability

Identifying the desired conditions to form a stable solution is the major objective of this pre-formulation study which includes the study of the effects of oxygen, pH, light, temperature, ionic strength, and cosolvent.

Studies of solution stability are started with probing experiments for confirming the decay at the extremes of pH and temperature (**e.g.,** 0.1N HCl, water, and 0.1N NaOH at 90°C). The samples which are degraded intentionally are used to confirm the specificity of assay and to provide estimates for maximum degradation rates. For identifying the pH of maximum stability, a complete pH-rate profile should be developed after the initial experiment. Solutions over a wide pH range with constant levels of drug, cosolvent, and ionic strength are produced using aqueous buffers.

The desired drug concentration for analytical sensitivity or for producing a defined initial condition is achieved by cosolvents. Most of the pharmaceutical solvents contain hydroxy groups, thus, the cosolvent belonging to alcohol family prove out to be beneficial. The apparent rates of decay vary linearly with the reciprocal of the resulting solution dielectric constant, if several cosolvent levels are used for preparing the initial samples. Due to the presence of cosolvent, the apparent pH of a buffer solution also varies.

After the preparation of stability solutions the aliquots are placed in flint glass ampoules, sealed with flame for preventing evaporation, and stored at constant temperatures (not exceeding the boiling point of the most volatile cosolvent or its azeotrope). To provide data for calculating activation energies, some ampoules are stored at different temperatures. **Light stability test** which includes protective packaging in amber and yellow-green glass containers should also be carried out for some of these solution ampoules. The control samples for this light stability test should be either wrapped in aluminium foil or stored in cardboard packages.

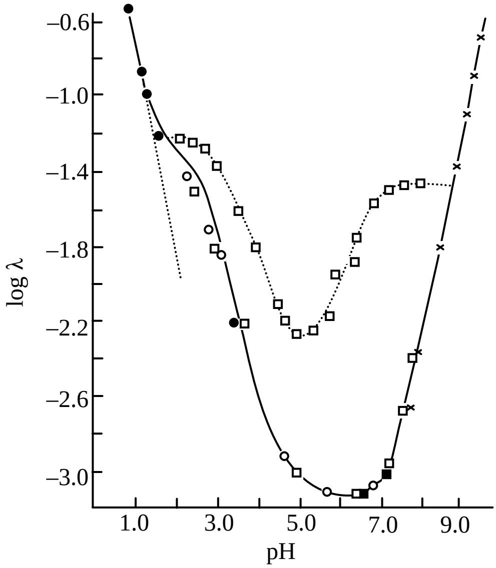


Figure 1.5: The pH-rate profiles for ampicillin degradation in solution at 35°C and constant ionic strength (μ = 0.5). Dotted line is the apparent rate profile in the presence of buffer, while the solid line is the theoretic rate profile at zero buffer concentration.

The stability data obtained at each condition of pH and temperature should be analysed kinetically to obtain the apparent decay rate constants essential for generating a pH-rate profile. Then all the rate constants at a single temperature should be plotted as a function of pH (**figure 1.5**).

The minimum in this curve is the pH of maximum stability. This plot on approaching its limits often provides an insight into the decay mechanism involving hydrogen or hydroxide ions.

By plotting the apparent decay rate constant logarithm against the reciprocal of the absolute temperature (at which each buffer solution was stored during the stability test), an Arrhenius plot is constructed. In order to justify extrapolation to “use” conditions, stability storage temperatures should be selected that incrementally (Δt ~10°C) approach the anticipated “use” temperature.

In this case, the relationship is linear, a constant decay mechanism at this temperature range can be assumed and activation energy (Ea) can also be calculated from the slope (–Ea/R) of the line.

$$\ln k = \frac{-\mathrm{Ea}}{\mathrm{R}}\left(\frac{1}{\mathrm{T}}\right) + \mathrm{C}$$

Where, C = Constant of integration
R = Gas constant

A change in the rate-limiting step of the reaction or a change in decay mechanism is indicated by a broken or non-linear Arrhenius plot. This results in unreliable extrapolation. The apparent decay rate constant in a solution-state oxidation reaction decreases with an increase of temperature due to the decrease in solubility of oxygen in water.

Excipients or buffers undergo degradation at high temperatures to give products incompatible with the drug under study. The changes in decay mechanism can be confirmed by inspecting the HPLC chromatograms of decay products. An appropriate kinetic equation and the decay rate constant obtained from the Arrhenius plot are used for calculating the shelf-life ($t_{10\%}$) of a drug at "use" conditions. The shelf-life for a first-order decay process can be calculated as:

$$t_{10\%} = \frac{-\ln 0.90}{k_1} = \frac{0.105}{k_1}$$

Where,

$t_{10\%}$ = Time for 10% decay to occur with apparent first-order decay constant k_1.

The pH-rate profile against $t_{10\%}$ shelf-life data can be plotted by using the value of obtained $t_{10\%}$. The course of action is indicated by the results obtained from these initial solution stability studies. Liquid formulation development can be started if the compound's stability is sufficient enough. On the other hand, further investigations are carried out if the compound is unstable.

1.2.9.3. Solid State Stability

Identifying stable storage conditions for solid state drug and compatible excipients for a formulation is the major objective of this pre-formulation study. Changes in purity and crystallinity (resulting from process improvements) affect these stability studies.

The reactions of solid state are slow and their interpretation is difficult than the reactions of solution state. This is because of the reduced number of molecular contacts between the drug and excipient molecules and occurrence of multiple-phase reactions.

The kinetic analysis of slow solid state degradation (based on retention) fails to quantitate the compound's shelf-life because assay variation may equal or exceed the limited apparent degradation at low temperatures at which a room temperature shelf-life can be established.

The above situation can be corrected on analysis of the appearance of decay product(s) which makes only 1-5% of the sample. Determination of the kinetics of decay product(s) appearance and establishment of a room temperature shelf-life for the drug candidate can be done from the analytical data obtained from studies such as TLC, fluorescence, or UV/VIS spectroscopy.

More than a specific assay is required for the intact compound in order to study the many possible solid state reactions. Differential Scanning Calorimetry (DSC) or quantitative Infrared Analysis (IR) is used for detecting the polymorphic changes.

Surface reflectance measurements on tri-stimulus or diffuse reflectance equipment are more sensitive than HPLC assay in case of surface discolouration due to oxidation or reaction with excipients. These additional tests are accommodated in the solid state stability study by additional samples.

The solid state stability profile of a new compound can be determined by placing the weighed samples in open screw cap vials and exposing them directly to different temperatures, humidities, and light intensities for 12 weeks.

Three 5-10mg weighed samples at each data point for HPLC analysis and 10-50mg of sample for polymorph evaluation by DSC and IR (~2mg in KBr and ~20mg in Nujol) constitute the samples. For testing surface oxidation, samples are stored in 25ml vials for injection capped with a Teflon-lined rubber stopper and the headspace flooded with dry oxygen. A second set of vials should be tested by flooding the atmosphere with dry nitrogen.

This is done to confirm that the decay occurs only due to the presence of oxygen and not reduced humidity. These samples are removed after a fixed exposure time and the chemical stability, polymorphic changes, and discolouration are checked by several methods.

The decay process is analysed by either zero-order or first-order kinetics (if the amount of decay is less than 15-20%) after the results of the initial screening have been tabulated. The data at each temperature should be analysed by the same kinetic order. A follow-up stability test at three or more levels of a given parameter for full quantitation of its involvement may be required by the samples exposed to oxygen, light, and humidity.

An Arrhenius plot is constructed when the humidity does not affect drug stability. If the resultant plot is linear, it is extrapolated to "use" conditions for predicting a shelf-life. In case drug stability is affected by humidity, psychrometric charts are used for determining the concentration of water in the atmosphere from the relative humidity and temperature. Stability data (at various humidities) is linearised with respect to moisture using the following apparent decay rate constant:

$$k_H = [gpl] \cdot k_o$$

Where,

[gpl] = Concentration of water in the atmosphere in units of grams of water per litre of dry air.

k_o = Decay rate constant at zero relative humidity.

For example, at 37°C, a 75% relative humidity atmosphere is equivalent to 0.0405 grams of water per litre (gpl) of dry air. On examining the effect of moisture on chemical stability, a comparison between solution state stability and hygroscopicity data suggests an aqueous reaction occurring in the drug-saturated water layer on the crystal surface.

Another assumption for analysing solid state stability data is that compound should partially liquefy before decomposition. If the mole fraction of the solid that has liquefied (F_m) is directly proportional to its decay rate, the following equation results:

$$\ln k_{app} \ \alpha \ \ln F_m = \frac{-\Delta H_{fus}}{R}\left[\frac{1}{T} - \frac{1}{T_m}\right]$$

Where,

ΔH_{fus} = Molar heat of fusion

T_m = Absolute melting point (°Kelvin)

T = Absolute temperature of the stability study

R = Gas constant

After the determination of the stability of bulk drug, its compatibility with the excipients used to manufacture solid dosage forms should be established. On considering the results obtained from solid and solution state stability profiles, the number of excipients can be reduced. **For example,** anhydrous excipients should be used for the formulation of a compound with bulk instability at high humidity. In the similar manner, the pH of maximum drug stability should be equal to the pH of an aqueous suspension or solution of the drug and excipient.

A list containing the commonly used excipients and the hypothetic formulations using these excipients is prepared. Each excipient can be blended with the drug at levels that are realistic with respect to a final dosage form (**e.g.,** 10:1 drug to disintegrant and 1:1 drug to filler such as lactose) because the approximate dose of the drug is known usually.

Each of the blends (divided into weighed aliquots) is tested for stability at 50°C temperature that is lower than the melting point of the ingredients. If these stability samples are inspected at an early stage (ΔT~2 days), they may be rejected with a phase change and retested at a lower temperature.

The drug-excipient contact can be increased and testing can be accelerated by forming pellets from the blends of drug and excipient. Apart from excipient compatibility testing, hypothetic capsule or tablet formulations should be prepared in small batches (2 or more) and tested to check for possible incompatibilities arising from a multi-component formulation in the same stability protocol.

In solid formulations, the flow, density, or homogeneity can be improved by granulating the drug-excipient blend. The stability during the granulation process of the unformulated bulk, excipient-drug blends and the hypothetic formulations can be checked by excessive wet down and drying of their samples for 48 hours in a 50°C forced air oven.

Only pharmaceutically acceptable solvents, with and without such approved binders as methylcellulose and polyvinyl pyrrolidone, should be used by the wet downs. After considering the drug's solubility profile, the list of granulating solvents can be reduced. Apart from checking the chemical stability of the unformulated bulk samples (exposed to each granulation solvent), their crystallinity, polymorph conversion, and solvate formation should also be checked as these parameters could affect the dissolution or bioavailability.

1.3. CHEMICAL PROPERTIES

1.3.1. Introduction

Chemical stability study includes the ways that cause instability of drug through chemical reactions resulting in a reduction of potency.

The following chemical properties should be evaluated during a pre-formulation research:

1) Hydrolysis,
2) Oxidation,
3) Reduction,
4) Racemisation, and
5) Polymerisation.

1.3.2. Hydrolysis

Hydrolysis is the most common degradation pathway since water plays an important role in many processes, especially in solution and also in solids (in which water may be present in low concentrations). Hydrolysis occurs via nucleophilic attack of the water molecule on labile bonds with susceptibility dependent on the bond type and decreasing from lactam > ester > amide > imine.

This can be influenced by pH if the molecule is ionisable and has maximum instability in ionised form, since it has the greatest solubility and therefore exposure. This brings a change in the reaction rate of hydrolysis with pH with the shape of the pH/hydrolysis curve related to the underlying chemical processes. In case water is not used as the solvent, solvolysis occurs as a result of reaction between the solvent and the compound.

Preventive Measures against Hydrolysis

Hydrolysis reactions occurring due to the presence of moisture and catalytic species, H^+ and OH^- ions can be prevented as follows:

1) **Buffer:** It is used for product stabilisation.
2) **Complexing Agent:** It forms a complex with drug, prevents its hydrolysis, and thus prolongs the shelf-life.
3) **Suppression of Solubility:** Less solubility reduces the drug concentration in solution phase and also reduces the hydrolysis rate.
4) **Removal of Water:** Presence of water should be avoided by storing the drug in dry form and by using water immiscible vehicle.

1.3.3. Oxidation

The environmental phenomenon of oxidation requires oxygen (or an oxidising agent), light, and trace metals that can catalyse the reaction. If molecular oxygen is involved, the reaction is rapid and termed **auto-oxidation**. Chemically, oxidation involves loss of electrons, which requires an electron acceptor or an oxidising agent [**for example**, iron converting from ferric (Fe^{3+}) to ferrous (Fe^{2+})].

Oxidation reactions involve **free radical chain reactions**. Initial free radical is formed as a result of thermal or photolytic bond cleavage or a redox process involving a trace metal ion. Once the radical is formed it can be propagated and catalysed by the metal ions present, until a suitable chemical inhibitor (antioxidant) or termination reaction get involved. Oxidation reactions produce highly coloured degradation products that can be detected by eye before their chemical detection.

Many drugs undergo oxidation; **for example**, adrenaline produces an intensely pink adrenochrome, and degradation is initiated by free radicals induced by light and further catalysed by multivalent metal ions.

Preventive Measures against oxidation

Oxidation reaction occurs due to the presence of moisture, oxygen, trace metals, H^+ and OH^- ions. Oxidation can be prevented by:

1) Using antioxidants (**e.g.,** tocopherol), chelating agents, and buffers,
2) Preventing light exposure,
3) Maintaining oxygen free environment, and
4) Storing the product at a low temperature.

1.3.4. Reduction

Reduction is a relatively common pathway of drug metabolic process. Hepatic microsomes catalyse diverse reductive chemical reactions with the use of NADPH. Cytochrome P450 catalyses the azo and nitro reduction reaction. The enzyme alcohol dehydrogenase catalyses the reduction of chloral hydrate into trichloroethanol (its active metabolite). Prednisolone and cortisone reduces to hydrocortisone (their active metabolites). The intestinal flora reduces the azo dyes (used as colouring agents in pharmaceutical or food products) into amines in the liver.

1.3.5. Racemisation

Racemisation involves the conversion of one enantiomer of a compound, such as an L-amino acid, into the other enantiomer. The compound then alternates between each form while the ratio between the (+) and (–) groups approaches the ratio 1:1, at which it becomes optically inactive.

If racemisation occurs in a mixture containing enantiomers in equal quantities, the resulting sample is termed as **racemic** or a **racemate**.

The inter-conversion from one isomer into another also alters the pharmacokinetic (ADME), pharmacological and toxicological properties. **For example**, L-epinephrine is 15 to 20 times more active than D-form, while the activity of racemic mixture is half of the L-form.

Biological Significance

The different isomers of many psychotropic drugs show dissimilar activities; **for example,** amphetamine is dispensed as racemic salts; the more active dextro-amphetamine is used for severe indications; and one isomer of methadone acts as an opioid agonist and the other as an NMDA antagonist.

1.3.6. Polymerization

Polymerisation is a continuous reaction occurring between molecules. A polymer is formed by the reaction between more than one monomer. **For example**, glucose solution darkens due to polymerisation of the breakdown product [5-(hydroxyl methyl) furfural]; HCHO polymerises into *para*-HCHO that crystallises out from the solution.

1.4. SUMMARY

The details given in the chapter can be summarised as follows:

1) During the pre-formulation study, the physicochemical properties of the new drug which can alter the drug's performance and development of an efficient dosage form should be considered carefully.
2) The development process results in the alteration of the bulk properties of a solid, **e.g.,** particle size, bulk density, surface morphology, etc.
3) A solid molecule is made up of atoms tightly bound to each other either in a regular geometric lattice (crystalline solids that include metals and ordinary water ice) or irregularly (amorphous solid, such as a common window glass).
4) The outer appearance of a crystal is known as **habit** and the arrangement of molecules within the solid is termed as **internal structure**.
5) The compound is said to be **crystalline** if its atoms or molecules are arranged repetitively in a 3-D array.

6) The amount of crystallisation solvent in a crystalline compound can be either **stoichiometric** or **non-stoichiometric**, which are parts of molecular adducts.
7) A molecular complex in which the crystallising solvent molecules are incorporated within the crystal lattice into specific sites is called **solvate**.
8) A stoichiometric adduct in which the entrapped solvent is water is said to be a **hydrate.**
9) **Clathrate**, a non-stoichiometric adduct entraps solvent molecules within the crystal lattice.
10) A compound is said to be **anhydrous** if the crystal structure does not contain water within it.
11) **Amorphous solids** are the ones in which the atoms or molecules are arranged in a random manner (as in a liquid).
12) The ability of a substance to exist in more than one crystalline form is **polymorphism** and the various crystalline forms are termed as **polymorphs**.
13) The term **particle size** is used to compare the dimensions of solid particles (flakes), liquid particles (droplets), or gaseous particles (bubbles).
14) **Brunauer, Emmett, and Teller** (BET) **nitrogen adsorption technique** is used for measuring the surface area more precisely.
15) **Scanning Electron Microscopy** (SEM) is used for monitoring the surface morphology as it observes the surface area in a qualitative manner.
16) The term **particle shape** is used to express the geometrical shape and surface regularity (rugosity) of the material.
17) **Free-flowing** or **non-free-flowing/cohesive** are the two types of pharmaceutical powders.
18) Biopharmaceutics Classification System (BCS) is a fundamental guideline for determining the conditions under which *In-Vitro In-Vivo* Correlations (IVIVC) are expected.
19) The ratio of unionised drug distributed between the organic and aqueous phases at equilibrium is the partition coefficient.
20) If molecular oxygen is involved, the oxidation reaction is rapid and termed **auto-oxidation**.
21) Racemisation involves the conversion of one enantiomer of a compound, such as an L-amino acid, into the other enantiomer.
22) If racemisation occurs in a mixture containing enantiomers in equal quantities, the resulting sample is termed as **racemic** or a **racemate**.
23) Polymerisation is a continuous reaction occurring between molecules. A polymer is formed by the reaction between more than one monomer.

1.5. EXERCISE

1.5.1. True or False

1) If molecular oxygen is involved, the oxidation reaction is rapid and termed auto-oxidation.
2) Amorphous solids are the ones in which the atoms or molecules are arranged in a random manner.
3) Scanning Electron Microscopy (SEM) is used for monitoring the surface area.
4) A compound is said to be anhydrous if the crystal structure contain water within it.
5) The compound is said to be amorphous if its atoms or molecules are arranged repetitively in a 3-D array.

1.5.2. Fill in the Blanks

6) A polymer is formed by the reaction between more than one _________.
7) If molecular oxygen is involved, the oxidation reaction is termed ___________.
8) __________ is used for monitoring the surface morphology.
9) The ability of a substance to exist in more than one crystalline form is __________.
10) A compound is said to be _________ if the crystal structure does not contain water within it.
11) A stoichiometric adduct in which the entrapped solvent is water is said to be a _________.

Answers

1) True
2) True
3) False
4) False
5) False
6) Monomer
7) Auto-oxidation
8) Scanning Electron Microscopy
9) Polymorphism
10) Anhydrous
11) Hydrate

1.5.3. Very Short Answer Type Questions

1) Discuss the goals and objectives of pre-formulation.
2) Give the physicochemical characteristics of drug substances.
3) Discuss crystalline form.
4) What is polymorphism? Discuss its types.
5) What is the significance of particle size?

1.5.4. Short Answer Type Questions

1) Discuss particle shape in detail.
2) Give the evaluation parameters used in the pre-formulation of drug development.
3) Discuss flow properties.
4) Write a short note on racemisation and polymerisation.

1.5.5. Long Answer Type Questions

1) Briefly discuss the pre-formulation considerations for physical properties.
2) Write a detailed note on stability profile.
3) Give a detailed account on solubility profile.

CHAPTER 2

Tablets

2.1. TABLETS

2.1.1. Introduction

Tablets are solid unit dosage form of medicaments with or without suitable diluents and prepared either by moulding or compression. They are solid, flat, or biconvex discs in shape. They vary greatly in shape, size, and weight which depend upon the amount of medicament used and mode of administration. They also vary in hardness, thickness, disintegration and dissolution characteristics, and in other aspects depending on their intended use and manufacture method.

According to the **Indian Pharmacopoeia**, pharmaceutical tablets are solid, flat or biconvex discs, unit dosage form, prepared by compressing drugs or a mixture of drugs, with or without diluents. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of a tablet. All medicaments are available in the tablet form except where it is difficult to formulate or administer.

2.1.2. Ideal Characteristics of Tablets

The objective of formulation and fabrication of tablet is to deliver the correct amount of drug in proper form at or over proper time. An ideal tablet should possess the following characteristics:

1) It should be attractive having its own identity.
2) It should befree from defects such as cracks, chips, contamination, discolouration, etc.
3) It should be chemically and physically stable to maintain its physical integrity over time.
4) It should be capable of preventing any alteration in the chemical and physical properties of medicinal agent(s).
5) It should be capable of withstanding the rigors of mechanical shocks encountered during its production, packaging, shipping, and dispensing.
6) It should release the medicament(s) in body in predictable and reproducible manner.

2.1.3. Advantages

Various advantages of tablets are:

1) They are unit dosage forms that provide an accurate, stable dose with greatest precision and least content variability.
2) They are easy to use, handle and carry by the patient.
3) They are attractive and pleasing in appearance.
4) They are the most stable dosage form with respect to their physical, chemical and microbiological attributes.
5) Their manufacturing cost is low as compared to other dosage forms and their manufacturing speed is also quite high.
6) Their packaging and shipping is comparatively easy and cheap.
7) Their unpleasant taste and odour of medicament(s) can be easily masked by sugar coating.

8) The incompatibilities of medicament(s) and their deterioration due to environmental factors are less in case of a tablet.
9) Whenever a fractional dose is required, tablets are divided into halves and quarters by drawing lines during manufacturing to facilitate breakage.
10) They are more suitable for large scale production than the other oral dosage forms.
11) They provide administration of even minute dose of drug in an accurate amount.
12) Their identification is probably the easiest because of variety of shapes and colours.
13) They are formulated with certain special release profile products such as enteric or delayed release products.
14) They are economical as their cost is lowest as compared to other oral dosage forms.

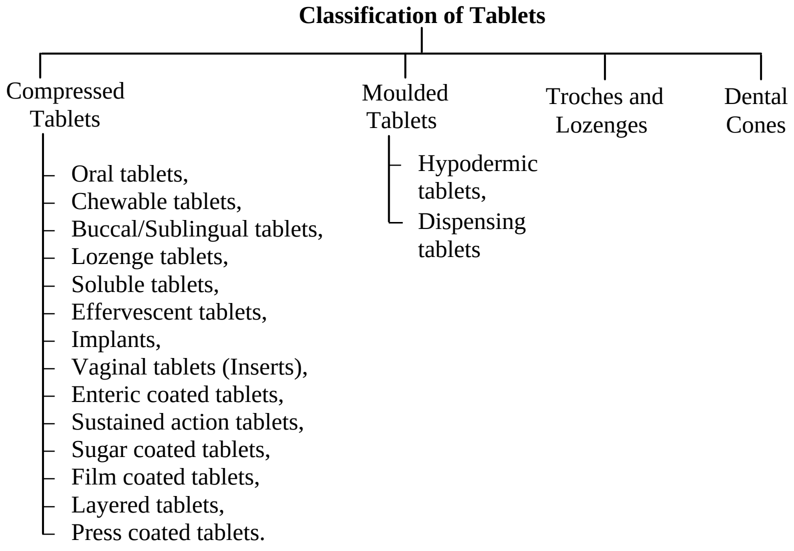
2.1.4. Disadvantages

Various disadvantages of tablets are:

1) The amorphous drugs or those having low density are difficult to compress into a tablet.
2) Hygroscopic drugs are not suitable candidates for compressed tablets.
3) Drugs having poor wetting properties, slow dissolution profile, and high optimal gastrointestinal absorption are difficult to formulate as a tablet.
4) Drugs having a bitter taste and objectionable odour require special treatment like coating or encapsulation which may increase their production cost.
5) Drugs sensitive to oxygen may require certain treatment like special coating as well as packaging which may increase the overall manufacturing cost.
6) High dose drugs are difficult to formulate as tablets.
7) Some drugs which get absorbed from the upper part of GIT may cause bioavailability problem in tablet dosage form.
8) Liquid drugs are difficult to formulate as a tablet.
9) Swallowing of tablets, especially by children and critically ill patients is very difficult.

2.1.5. Classification of Tablets

Mainly the tablets are classified into the following classes:



The types of tablets listed above are discussed below:

1) **Compressed Tablets:** These tablets are of the following types:

    i) **Oral Tablets:** These tablets are placed over the tongue and swallowed with water or any other suitable liquid. Most of them are formulated in such a way that they disintegrate in the stomach and dissolve in the gastric fluid. Some of these tablets (like enteric coated tablets) pass the stomach and disintegrate in the intestines from where they get absorbed. Among the compressed tablets, the oral tablets constitute the major group because majority of the compressed tablets are meant for oral administration.

    ii) **Chewable Tablets:** These tablets are chewed before ingestion. They are given to the children who have difficulty in swallowing and to adults who dislike swallowing. A number of antacid tablets and multivitamin tablets are prepared as chewable tablets. They should have acceptable taste and flavour. They should disintegrate within a short time and produce cool sweet taste. They can be administered even if water is not available.

    iii) **Buccal/Sublingual Tablets:** These tablets are placed below the tongue (sublingual) or in the side of the cheek (buccal) for slow release of the medicament (except in case of nitroglycerine and mannitol hexanitrate tablets which should dissolve in 1-2 minutes to produce immediate effect). Generally, these tablets contain drugs which are destroyed, inactivated or not absorbed in the GIT but are directly absorbed through the mucosal tissues of the oral cavity.

    iv) **Lozenge Tablets:**These tablets should not disintegrate in the oral cavity but should dissolve slowly in the mouth to produce a continuous effect on the mucous membrane of throat. They can be prepared by moulding, as well as by compression method. In the formulation of lozenges, no disintegrating agent is included; rather the quantity of binding agent is increased so as to produce slow dissolution.

    v) **Soluble Tablets:** These tablets dissolve completely in the liquid to produce solution of definite concentration. The solutions prepared by dissolving these tablets include mouth washes, gargles, skin lotions, douches, antibiotics, and certain vitamins. For the preparation of soluble tablets, all the ingredients used should be completely soluble in the solvent.

    vi) **Effervescent Tablets:** These tablets contain the active medicament along with other ingredients like sodium bicarbonate, citric acid, and tartaric acid which react in the presence of water liberating carbon dioxide and producing effervescence leading to disintegration of the tablet. This hastens solution formation and increases the palatability.

    vii) **Implants:** These are small tablets meant for insertion under the skin by making a small surgical cut, which is later stitched. Since, these tablets are to be implanted intramuscularly or subcutaneously, they should be prepared under aseptic conditions and packed in unit dose sterile containers. Implants provide a slow and continuous release of the drug over prolonged periods of time ranging from 3-6 months or even more.

    viii) **Vaginal Tablets (Inserts):** Antibiotics and steroids are formulated as vaginal tablets. Soluble additives are used for their preparation. They are generally ovoid or almond shaped to ease insertion. Plastic tube inserters can also be used for placing these tablets in the vaginal tract.

    ix) **Enteric Coated Tablets:** These tablets disintegrate in the intestines (and not in the stomach). They are coated which aids them to pass through the stomach unchanged but break in the alkaline medium of the intestines.

x) **Sustained Action Tablets:** These tablets, after oral administration, release the drug at a desired time and prolong the effect of the medicament. Repeat action tablets are used to periodically release a complete dose of the drug in the GIT fluids, thus maintaining a constant blood concentration.

xi) **Sugar Coated Tablets:** These tablets are given a sugar coating to mask the objectionable taste and odour of the drug as well as to protect the substances from atmospheric conditions. To make them attractive they can be given a suitable colour coating.

xii) **Film Coated Tablets:** These tablets are given a thin coating of water soluble materials which protect the drug substances from atmospheric conditions. Various polymers are used for film coating.

xiii) **Layered Tablets:** In these tablets, the granules of incompatible substances are compressed into two or more layers successively in the same tablet. Special tablet making machines are required for making layered tablets.

xiv) **Press Coated Tablets:** In these tablets, the granules of incompatible ingredients are compressed around the previously compressed tablet. They are made on special tablet making machines in two successive compressions. They can also be used for giving enteric coating and sustained release to the medicaments.

2) **Moulded Tablets or Tablet Triturates (TT):** These small, disk-shaped tablets are prepared by forcing the soft mass into the cavities of mould. Generally potent medicaments and highly toxic drugs in small doses are used for preparing these tablets.

These tablets can be **prepared** as follows:

i) The potent medicament is diluted with a diluent (like lactose, dextrose, sucrose, or a mixture of lactose and sucrose).
ii) The mixed powders are moistened with a suitable dilution of alcohol (generally 50% alcohol) and mixed thoroughly to get a soft mass.
iii) This soft mass is pressed into the perforations of the mould with a spatula. The excess of mass is removed by applying pressure over the spatula.
iv) This perforated plate of the mould filled with the mass is placed over another plate having exactly the same number of projecting pegs as that of perforations and these projecting pegs completely fit into the holes.
v) A little pressure is applied over the top plate to force the plate to move downward, leaving the moulded tablets on the projecting pegs.
vi) The ejected tablets are spread in single layers on a clean surface and dried either by keeping in a warm place or hot air oven.

The following are the types of moulded tablets:

i) **Hypodermic Tablets:** These tablets are soft, readily soluble, and made in a tablet triturate mould. They are used for preparing solutions to be injected, therefore, the ingredients used should be completely and readily soluble and no insoluble particles should be present. These tablets should be free from bacterial contamination and proper precautions regarding contamination and cleanliness should be taken during their moulding.

ii) **Dispensing Tablets:** These tablets are prepared for providing an accurate and convenient quantity of a drug that can be incorporated readily in compounding other dosage forms (**e.g.,** liquids, powders, or capsules), thus, eliminating the necessity of weighing small quantities of potent substances.

3) **Troches and Lozenges:** These tablets are intended to exert a local effect in the mouth or throat. They are commonly used to treat sore throat or to control coughing in the common cold. They may contain local anaesthetics, various antiseptic and antibacterial agents, demulcents, astringents, and anti-tussives. Lozenges were originally termed **pastilles**, but are more commonly called **cough drops**. They are made with the drug incorporated in a flavoured hard-candy sugar base. They may be prepared by compression but are usually formed by fusion or by a candy-moulding process. Troches, on the other hand, are manufactured by compression. These two classes of tablets are designed not to disintegrate in the mouth but to dissolve or slowly erode over a period of perhaps 30 minutes or less.

4) **Dental Cones:** These are a relatively minor tablet form designed to be placed in the empty socket remaining after a tooth extraction. Their usual purpose is to prevent bacterial multiplication in such sockets by employing a slow-releasing antibacterial compound, or to reduce bleeding by containing an astringent or coagulant. The usual vehicle of these tablets is sodium bicarbonate, sodium chloride, or an amino acid. They should not be formulated with a component that might provide media for bacterial proliferation. They should be formulated to dissolve or erode slowly in the presence of a small volume of serum or fluid, over a period of 20-40 minutes, when loosely packed in the extraction site.

2.1.6. Excipients or Formulation of Tablets

Substances other than the active ingredients are commonly referred to as **excipients** or **additives**. Tablet excipients should meet the following **criteria in the formulation**:

1) They should be non-toxic and acceptable to the regulatory agencies in all the countries where the product is to be marketed.
2) They should be commercially available in an acceptable grade in all the countries where the product is to be manufactured.
3) Their cost should be acceptably low.
4) They should be physiologically inert.
5) They should be physically and chemically stable by themselves and in combination with the drug(s) and other tablet components.
6) They should be free of any unacceptable microbiologic load.
7) They should be compatible to colour (not producing any off-colour appearance).
8) If the drug product is also classified as food (**e.g.,** certain vitamins products), the diluents and other excipients used should be approved as food additives.
9) They should not affect the bioavailability of the added drug(s).

The different excipients used in formulation of tablets are enlisted in **table 2.1**:

Table 2.1: Excipients Used in Solid Dose Formulations

Excipients	Examples
Fillers/diluents	Lactose, sucrose, glucose, and microcrystalline cellulose.
Binders	Polyvinyl pyrrolidone, starch, gelatin, and cellulose derivatives.
Lubricants	Magnesium stearate, stearic acid, polyethylene glycol, and sodium chloride.
Glidants	Fine silica, talc, and magnesium stearate.
Anti-adherents	Talc, cornstarch, and sodium dodecylsulphate.
Disintegrants and superdisintegrants	Starch, sodium starch glycollate, and cross-linked polyvinyl pyrrolidone.
Colouring agents	Iron oxide and natural pigments.
Flavouring and sweetening agents	Flavour oil, sugar, mannitol, saccharin, and aspartame.

2.1.6.1. Fillers/Diluents

Fillers (or diluents) are inert substances added to increase the bulk to make the tablet of a practical size for compression.

Properties of an Ideal Diluent

Ideally, diluents should be chemically inert, non-hygroscopic, and hydrophilic. An acceptable taste is important for oral formulations, and cost is always a significant factor in excipient selection.

Examples: Diluents like **mannitol**, **lactose**, **sorbitol**, **sucrose**, and **inositol** when present in sufficient quantity can impart properties to some compressed tablet that permit disintegration in the mouth by chewing (chewable tablet). **Microcrystalline cellulose** is usually used as an excipient in direct compression formula. Hydroxy Propyl Methyl Cellulose (**HPMC**) is used to prolong the release of active ingredient from the tablet and also as a film former in tablet coating . An inert substance is frequently added to increase the bulk of a tablet for processing and handling.

2.1.6.2. Binders

Binders impart cohesive qualities to the powdered material. In tablet formulation, they ensure that the tablet remains intact after compression. They improve free flow qualities to formulation of granules of desired hardness and size.

Examples: Starch, **gelatin**, **sucrose**, **glucose**, **dextrose**, and **lactose** are frequently used as binders. Natural and synthetic gums that have been used include **acacia**, **sodium alginate**, **panwar gum** , **ghatti gum** , CMC, **veegum**, etc. **Starch paste** in varying concentration (10-20%) is used as a binder. **HPMC** which is more soluble in cold water as compared to hot water is also used in special cases.

Excessive use of binder in the tablet may lead to prolong disintegration time which is not desired. Therefore, they are used in prescribed concentration to overcome the same.

2.1.6.3. Lubricants

Lubricants prevent adhesion of the tablet material to the surface of dies and punches, reduce inter-particle friction, facilitate an easy ejection of tablets from the die cavity, and improve the flow rate of tablet granules.

Examples: Commonly used lubricants are **talc**, **magnesium stearate**, **calcium stearate**, **stearic acid**, **hydrogenated vegetable oil**, and **PEG** (Polyethylene Glycol). The method of adding lubricant is an important factor for satisfactory results.

The **quantity of lubricant** significantly varies from 0.1-5%. The addition of lubricant to granules in the form of emulsion or suspension is used to reduce the processing time. The problem in the preparation of water soluble tablet is the selection of satisfactory lubricant. **Soluble lubricants** include **sodium benzoate**, **sodium acetate**, **sodium chloride**, and **carbowax 4000**.

2.1.6.4. Glidants and Anti-Adherents

Glidants improve the flow characteristics of a powder mixture. They are always added in the dry state just prior to compression. The most commonly used glidants are **colloidal silicon dioxide** and **asbestos free talc**. They are used in concentration less than 1%.**Talc** is also used and may serve the dual purpose of lubricant/glidantAnti-adherents are added to a formulation prone to sticking to the die surface (or picking). Water-insoluble lubricants such as **magnesium stearate** can be used as anti-adherents, as can **talc** and **starch**.

2.1.6.5. Disintegrants

Disintegrants are added to a tablet to facilitate its break down or disintegration after administration. These are added to a formulation to overcome the cohesive strength imparted during compression, thus, facilitating break down of the formulation in the body and increasing the surface area for dissolution.

Examples: **Starches**, **clays**, **cellulose**, and **cross linked polymers** are the most commonly used disintegrants. The oldest and still the most popular disintegrants are **corn** and **potato starch**. Other ingredients like **veegum**, **methyl cellulose**, **agar**, **bentonite**, **cellulose**, **citrus pulp**, and **CMC** are also used. They are mostly added into two portions, one part is added prior to granulation and the remainder is mixed with the lubricant and finally both are mixed just before the compression.

2.1.6.6. Superdisintegrants

Compared to the more traditional starch, newer disintegrants are effective at much lower levels and comprise three groups, i.e., **modified starches**, **modified cellulose**, and **cross-linked povidone**. The mechanism of action of superdisintegrants is combination of proposed theories including water wicking, swelling, deformation recovery, repulsion, and heat of wetting.

Examples: Superdisintegrants are required in relatively low levels (2-4% w/w). **Sodium starch glycollate** (Primojel, Explotab) is made by cross-linking potato starch and can swell up to 12-fold in less than 30 seconds. **Crospovidone** is completely insoluble in water, although it rapidly disperses and swells in water, but does not gel even after prolonged exposure.

It rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency to form gels and has a greater surface area-volume ratio compared to other disintegrants.

Micronised versions are available to improve uniformity of mix. **Croscarmellose sodium**, a cross-linked polymer of carboxymethyl cellulose sodium is also insoluble in water, although it rapidly swells to 4-8 times its original volume in contact with water.

2.1.6.7. Colouring Agents

Colours in a compressed tablet impart aesthetic appearance to the dosage form. Colour helps the manufacturer to control the product during its preparation, as well as it serves as a means of identification to the user. Colourants can be used in solution form or in suspension form. Proper distribution of suspended colourants in the coating solution requires the use of powdered colourants (<10 microns).

Examples: Most commonly used colourants are certified as **FD & C** or **D & C colourants**. These are **synthetic dyes** or **lakes**. Lakes are choice for sugar or film coating as they give reproducible results. The inorganic materials (**e.g.,** iron oxide) and the natural colouring materials (**e.g.,** anthocyanins, carotenoids, etc.) are also used to prepare the coating solution. Magenta red dye is non-absorbable in a biological system and resistant to degradation in the GIT.

Concentration of colourants in the coating solutions depends on the colour shade desired, the type of dye, and the concentration of opaquant-extenders. If very light shade is desired, concentration of less than 0.01% may be adequate; on the other hand if a dark colour is desired, a concentration of more than 2.0% may be required.

2.1.6.8. Flavouring and Sweetening Agents

Flavouring agents are usually limited to chewable tablets or other tablets intended to dissolve in the mouth. In general, water-soluble flavours have found little acceptance in manufacturing of tablets because of their poor stability. Flavouring agents do not affect the physical characteristics of tablet granulation.

Chewable tablets having a bitter API are added with sweetening agents. Ingredients in tablet are normally added with sweeteners to make them more palatable, **e.g.,** in chewable tablets such as antacid or liquids like cough syrup. Therefore, cough syrup abuse may result in tooth decay. Unpleasant taste and smell of drug can be masked through sugar.

2.2. GRANULATION METHODS

2.2.1. Introduction

Granulation may be defined as a **size enlargement process** which converts small particles into physically stronger and larger agglomerates. The **ideal characteristics of granules** include uniformity, good flow, and compactibility. These are usually accomplished through creation of increased density, spherical shape, narrow particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), and incorporation of binder, if necessary. Granulation method can be broadly classified as:

1) Wet granulation, and
2) Dry granulation.

Table 2.2 enlists the granulation method and processing techniques employed:

Table 2.2: Granulation Techniques and Processing

Granulation Techniques	Processes	Dryers
Wet Granulation	Low-shear mixer	Tray or fluid-bed dryer
	High-shear mixer	Tray or fluid-bed dryer
	High-shear mixer	Vacuum/gas stripping/microwave assist–one-pot
	Fluid bed granulator/dryer	Fluid bed granulator/dryer
	Spray dryer	Spray dryer
	Extrusion/spheronisation	Tray or fluid-bed dryer
	Continuous mixer granulator (mechanical)	Fluid bed (continuous or batch)
	Fluid bed granulator (continuous)	Fluid bed granulator (continuous)
Dry Granulation	Process	Further processing
	Direct compression	Blend and process further
	Slugging	Mill slugged tablets/blend/ recompress/process further
	Roller compactor	Compacts milled/blend/process further

2.2.2. Wet Granulation

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. This process simply involves wet massing of the powder blend with a granulating liquid, followed by wet sizing and drying.

Steps Involved in Wet Granulation

1) Mixing of the drug(s) and excipients,
2) Preparation of binder solution,

3) Mixing of binder solution with powder mixture to form a wet mass,
4) Coarse screening of wet mass using a suitable sieve (sieve no. 6-12),
5) Drying of moist granules,
6) Screening of dry granules through a suitable sieve (sieve no. 14-20),
7) Mixing of screened granules with disintegrant, glidant, and lubricant, and
8) Tablet compression.

2.2.2.1. Wet Granulation Processes

Discussed below are the different processes of wet granulation:

1) **High Shear Mixer:** The blending and granulation techniques involve an extensive use of high shear mixers in pharmaceutical industries. This type of instrumentation utilises a high speed (50-100 rpm) rotating impeller to set the particles into movement. It also utilises a chopper (1500-4000 rpm) to break down the large lumps into smaller fragments. This increases the uniform distribution of binder into the blend. Three characteristic **phases of wet agglomeration process** in a high shear mixer are:
   i) Dry powder mixing,
   ii) Liquid binder addition, and
   iii) Wet massing.

   Following **processes are required to produce dried grade particle size granules from the wet mass**:
   i) Wet sieving of granules,
   ii) Drying of granules, and
   iii) Dry sieving of granules.

   Liquid is added while mixing the previously dried materials. To achieve a narrow particle size distribution, the moist mass is kneaded into wet mass. Then the granules are wet sieved, dried, and sieved again. The amount of liquid is critical because over-wetting may result in uncontrollable agglomerate growth.

   Advantages
   i) Short processing time.
   ii) Less amount of liquid binders required.
   iii) Highly cohesive materials can be granulated.

   Disadvantages
   i) Fragile particles may undergo mechanical degradation.
   ii) Chemical degradation of thermolabile material may occur due to high temperature.
   iii) Large size lumps may form as a result of over-wetting of granules.

2) **Fluid Bed Granulation:** Fluidisation is the operation by which fine solids are transformed into a fluid-like state through contact with a gas. Fluid bed granulation is a process of producing granules in a single equipment utilising spraying of a binder solution against a fluidised powder bed. In this system, heated air is directed across the material to be processed. Afterwards, the heated air leaves through the voids of the material. This technique is known to produce fine, free flowing, and homogenous material.

   Air Handling Unit (AHU), product container, air distributor, spray nozzle, disengagement area, process filters, exhaust blower or fan, control system, and a solution delivery system are the components in a fluidised bed system.

Advantages

i) Improves housekeeping by reducing dust formation during processing.
ii) Product loss is reduced.
iii) Ensures safety of the worker.

Disadvantages

i) Cleaning of fluid bed is a labour-intensive and time consuming process.
ii) Reproducibility in manufactured product is not possible.

3) **Extrusion and Spheronisation:** It is a process requiring five multiple steps to produce spherical particles of uniform size:

i) Achieving homogeneous dispersion by dry mixing of powder,
ii) Formation of wet mass of the resulted mixture through wet granulation,
iii) Formation of rod-shaped particles from the wet mass by extrusion,
iv) Formation of round particles in spheroniser, and
v) Drying of particles.

Steps involved in the extrusion-spheronisation process are described in **figure 2.1**.

Advantages

i) Ability to incorporate higher levels of active components without producing excessively larger particles.
ii) Same unit is required to combine two or more active agents in any specific ratio.
iii) Manipulating the physical characteristics of active ingredients and excipients is possible.
iv) Particles with high bulk density, low hygroscopicity, high sphericity, dust free, narrow particle size distribution and smoother surface can be produced.

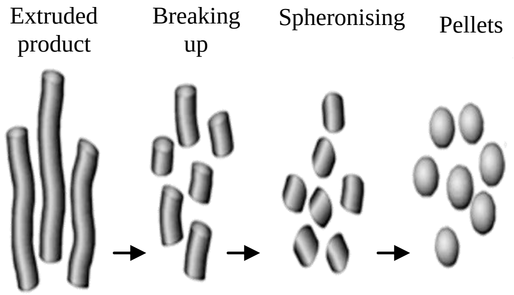


Figure 2.1: Steps Involved in Extrusion - Spheronisation Process

4) **Spray Drying Granulation:** Products like microcapsules, food ingredients, flavours, and various biotechnological preparations can be produced by this process. In comparison to the above mentioned methods, this process is a continuous process requiring solution or suspension (rather than the initially dried primary powder particles) to produce a dry granular product. The solution or suspension may be a complete formulation, a drug alone, or a mixture of different excipients. The dry powder continues to be produced simultaneously along with the feeding of suspension to the drying system.

The **three fundamental steps involved in spray drying process** are:

i) Fine droplets are produced by atomising the liquid feed.
ii) These spray droplets are mixed with a heated gas stream, resulting in the evaporation of liquid leaving behind the dried solid particles.
iii) The dried powder is separated from the gas stream.

Advantages

i) Rapid and continuous process.

ii) Avoids labour intensive drying and granulation steps, thus, making it more economical.

iii) OTC products are usually produced.

iv) Suitable for thermolabile substances.

2.2.2.2. Equipments

The equipments used for wet granulation are:

1) **High Shear Granulation**
   i) Littleford Lodige granulator,
   ii) Littleford MGT granulator,
   iii) Diosna granulator, and
   iv) Gral mixer.

2) **Granulators with Drying Facility**
   i) Fluidised bed granulator,
   ii) Double cone or twin shell processor,
   iii) Day nauta mixer processor, and
   iv) Topo granulator.

3) **Special Granulators**
   i) Roto granulator, and
   ii) Marumerizer.

The lists of equipments mentioned above are discussed in detail below:

Littleford Lodige Mixer/Granulator

This equipment utilises high shear powder blenders to blend pharmaceutical powders and wet massing within the same equipment. With some formulations, the agglomerated granular particles that are to be subjected to fluid bed or other drying methods can be produced using this equipment.

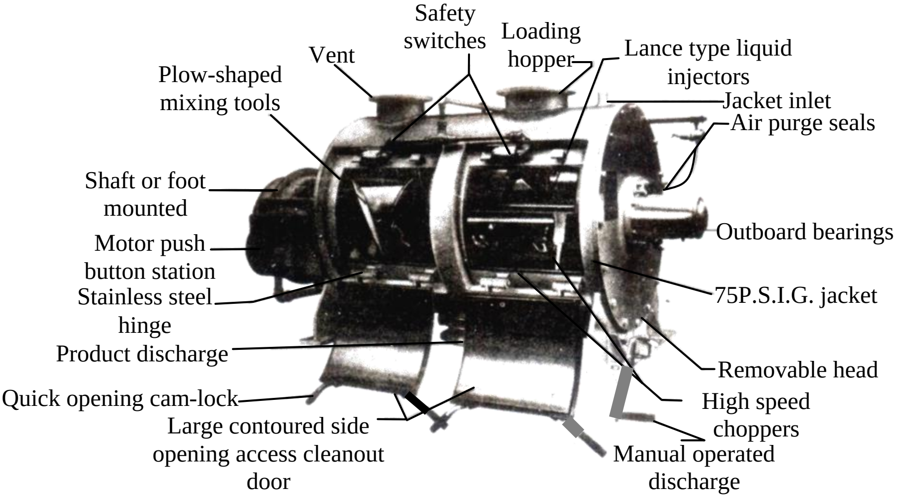


Figure 2.2: Littleford Lodige Mixer

Figure 2. 2 presents a traditional Lodige mixer and its various assemblies. The unit is provided with a **horizontal cylindrical shell** fitted with **plow-shaped mixing tools** arranged sequentially. One or more **high-speed blending chopper** assemblies are fixed

behind the mixer. Sieving is no longer an essential requirement in powder blending because the chopper blades result in uniform dispersion of powder lumps during dry mixing. Generally, **injection tubes** ending in one or more **spray nozzles** are required for adding liquids. The chopper assembly is located immediately below the spray nozzles.

This high-shear powder mixing equipment takes nearly 30-60 seconds to complete the mixing process. Continuation of dry blending process for 5-10 minutes increases the temperature up to 10-15°C. The use of high-speed, high-shear mixer (Littleford Lodige type) for wet granulation increases the wettability of powder mass which in turn increases the power consumption by the mixer. The end point for wet granulation can be assessed from the readings appearing on the **ammeter** or **wattmeter** mounted on the equipment.

Littleford MGT Mixer/Granulator

Figure 2.3 presents MGT mixer-granulator which specifically meets the granulation requirements. During a production operation, the high shear solids mixer should be mounted in a position that the bowl from a fluid bed dryer is placed under the mixer. This facilitates material transfer. Many fluid bed dryers are provided with wheel assemblies to facilitate transfer of materials to and from the fluid bed unit. The advantage of raising the equipment to an appropriate working height is that powder can be conveniently charged into the unit.

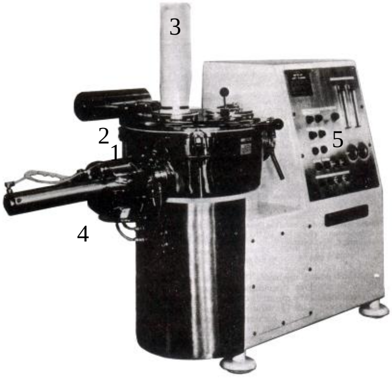


Figure 2.3: Littleford MGT Mixer-Granulator. (1) Bowl; (2) Lid with Counter Weight; (3) Exhaust Sleeve; (4) Discharge Port; (5) Control Panel.

Diosna Mixer/Granulator

Figure 2.4 presents Diosna mixer/granulator which is another type of high-speed powder mixer and processor. The **parts** of this equipment are:

1) A **bowl** is mounted vertically with a **high speed mixer blade**. The blade revolves around the bottom of the bowl. The blade fitted over a pin bar is powered by the bottom of mixing bowl. The blade is constructed so as to prevent the material from getting under it.
2) A **high-speed chopper blade** is also equipped within the mixer which breaks the lumps and agglomerates.
3) A **pneumatic discharge port** provides the unit with an automatic discharge.
4) A **lid** is also present and a counterweight is employed to raise or lower the lid of a larger mixer. The lid is provided with **three openings**:
    i) First to accommodate a spray nozzle,
    ii) A second larger opening for an air exhaust sleeve, and
    iii) The third opening for a viewing port.

5) The end point of granulation operations can be determined by using **ammeter** equipped on control panel of all the units.

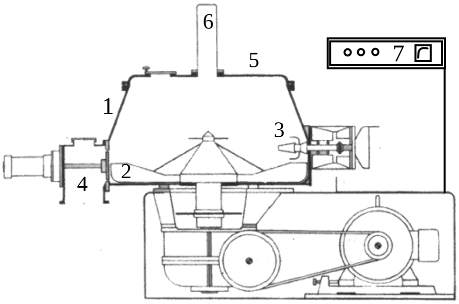


Figure 2.4: Schematic Diagram of the Diosna Mixer. (1) Mixer bowl; (2) High-speed mixer blade; (3) High-speed chopper blade; (4) Pneumatic discharge port; (5) Mixed lid; (6) Exhaust air sleeve; (7) Mixer control panel.

The **time sequences for operating Diosna mixer** are:

1) Mixing for 2 minutes or less,
2) Granulating for 8 minutes or less, and
3) Discharge in 1 minute (when the pneumatic discharge system is in place and capable of being predetermined).

Gral Mixer/Granulator

Figure 2.5 shows a Gral mixer which has been modified from the planetary mixers with the only difference that it contains two mixing devices.

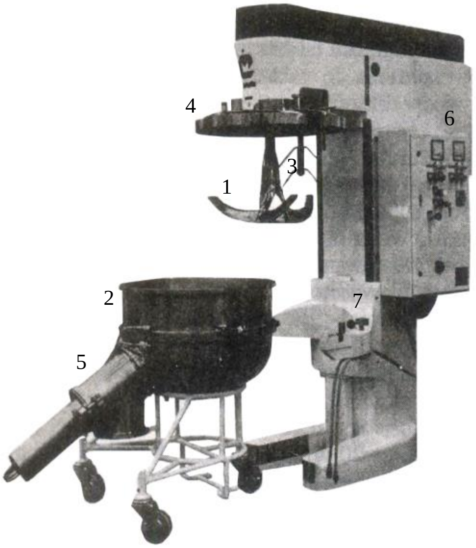


Figure 2.5: Gral Mixer-Granulator. (1) Mixing Arm; (2) Bowl; (3) Chopper Blade; (4) Bowl Cover; (5) Hydraulic Discharge Port; (6) Mixer Control Panel; (7) Bowl Elevator Cradle.

A **large mixing arm** is configured in a round shape to accommodate the bowl and provide large-scale mixing motion to the powder. A **small chopper blade** is located above the mixing arm and it enters off-centre from the mixing arm. The **mixing bowl** is initially present at the floor level, however while being operated a **hydraulic bowl elevator cradle** raises it to the mixing position.

Advantages

1) Even in the raised position the unit can be discharged by its hydraulic port, thus, providing adequate space for a container to be placed beneath the discharged port.
2) It is much easier to clean this unit, since the main mixing blade is not a part of the bowl.
3) The mixer bowl can be injected with fluid.
4) The equipment is provided with time control mechanism.

Fluid Bed Spray Granulator

Figure 2.6 presents a fluid bed spray granulator. The **suction fan** driven by an electric motor is mounted at the top portion of the unit providing necessary airflow for the fluidisation of powder. First the air is drawn through **pre-filters** to remove any impurity and then it is heated to the desired temperature by the **air heater**. The material to be processed is placed in the **material container** present just below the **spray inlet**.

The liquid granulating agent is pumped from its container and then sprayed as a fine mist onto the fluidised powder through a **spray head**. The particle-particle contact agglomerates the wetted particles. Dust and fine particles are retained by the **exhaust filters** present above the product retainer. The spray operation is discontinued after appropriate agglomeration is achieved, and the material is dried and discharged from the unit.

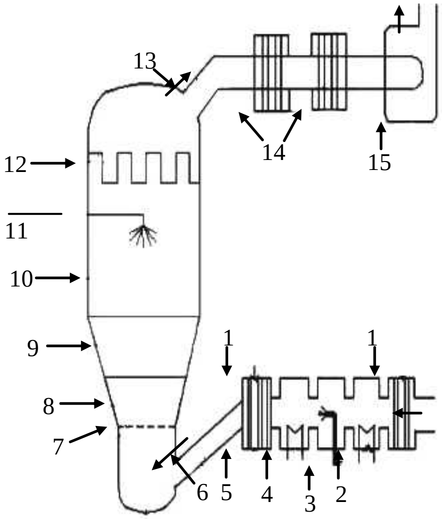


Figure 2.6: Schematic diagram of a fluid bed granulator dryer. (1) Inlet air filter; (2) Condenser; (3) Humidifier; (4) Inlet air heater; (5) HEPA filter; (6) Inlet air plenum; (7) Gas distributor plate; (8) Product container; (9) Conical expansion zone; (10) Filter housing; (11) Spray gun; (12) Product filter; (13) Outlet air; (14) HEPA filter; (15) Fan.

Advantages: There are various advantages of such rapid wet massing, agglomeration, and drying within one unit. Generally, the process gets completed within 60-90 minutes or less, excluding the cleaning of equipment.

Disadvantages

1) Powder components cannot be mixed properly through this system.
2) The processing of particles having uneven particle size or density may lead to de-mixing.

3) The granulating agent present on the particle surface may stick to the equipment filters, thus, reducing the effective surface area resulting in product loss and increasing clean-up difficulties.
4) The flammable solvents or dry materials that may develop static charges may cause dust explosion in a fluid bed dryer. Therefore, all production size fluid bed equipment should be provided with explosion relief panels.

Double-Cone Mixer-Dryer Processor

Equipment like double-cone (**figure 2.7**) and twin-shell blenders are modified to provide potential for proper orderly arrangement of processes like powder mixing, wet massing, agglomeration, and drying.

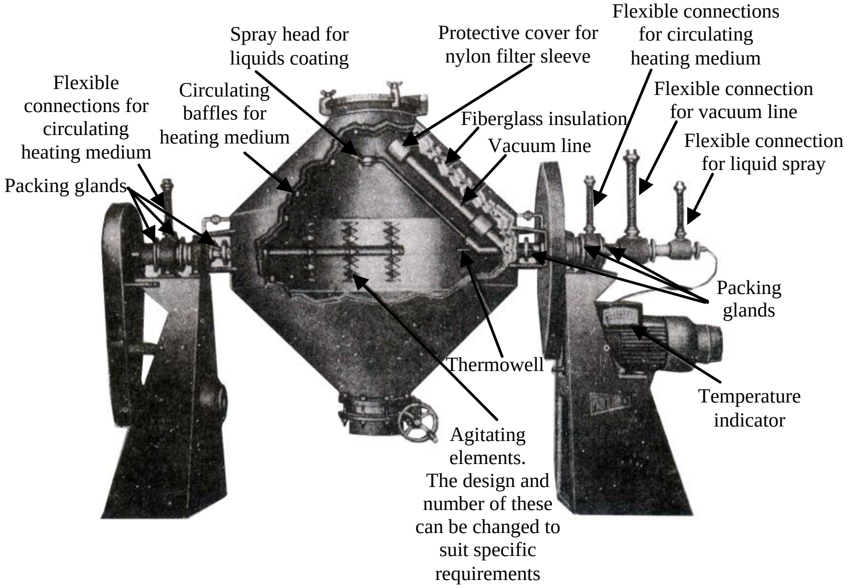


Figure 2.7: Cutaway View of a Double-Cone Mixer-Dryer Processor

This equipment utilises **trunnion mechanism** to include **liquid feed** leading to a **spray dispenser** present just above the axis of rotation of the unit. The same or the opposing trunnion provides a way for a **vacuum inlet** to a **vacuum intake port** covered by nylon or other appropriate fine-filter sleeve. This is also located above the axis of rotation and out of the direct path of powder motion. The blender utilises **agitating elements** capable of rotation within the powder mass contained in the blender. A **double wall construction** is provided within the blender to provide circulation of a heating medium; while in other cases the systems are operated at room temperature and vacuum pressure is the only source for liquid removal.

The equipment and drying costs are very high in vacuum-drying operation. Drying time is also much longer than that of the fluid bed granulator processor. However, the double-cone or twin-shell processors can be cleaned easily.

Day Nauta Mixer Processor

It is a vertical screw mixer (**figure 2.8**) which contains a **screw assembly** mounted in a **conical chamber**. The screw is utilised to lift the powder to be blended from the bottom to the top. For mixing the powder uniformly, the screw assembly circles around the conical chamber. The basic operations like incorporation of liquid-granulating agent, wet massing, and drying (passing hot dry air through the wet material) are involved in powder mixing. The hot air is passed through the material (kept in a state of motion by the orbiting screw material), dries the granules, and exits at the top of the processor.

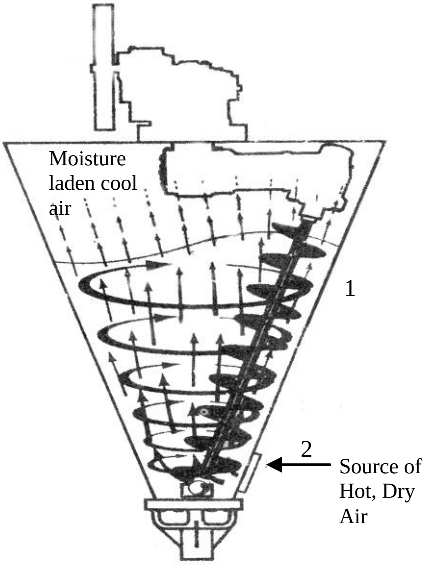


Figure 2.8: Schematic diagram of the Nauta processor. (1) Conical chamber. (2) Source of hot, dry air. Hot air moves up through the material (vertical arrows), which is kept in motion by the orbiting screw assembly (circular arrows).

Additional equipment like **lump breaker** (attached at the conical chamber bottom), **temperature monitor**, **nuclear**, **non-contact density gauge**, **ammeter** or **wattmeter**, **infrared moisture analyser**, and a **sampling system** are designed to monitor and control process operation.

Topo Granulator

Figure 2. 9 presents Topo granulator developed in Austria for preparing granules and coated particles under high vacuum. **Dust-free suction process** can be utilised to load materials to be granulated or coated inside the chamber. **Vacuum process** is used to load the material in granulating compartment, while the granulating fluid and other products (liquid or solid) are added by crushing the added ingredients against the components already in the chamber. The granulating agents are added to the chamber under vacuum. This increases the granulation forces enough to create the necessary compaction. The agglomerated particles thus produced are dried within the chamber under vacuum.

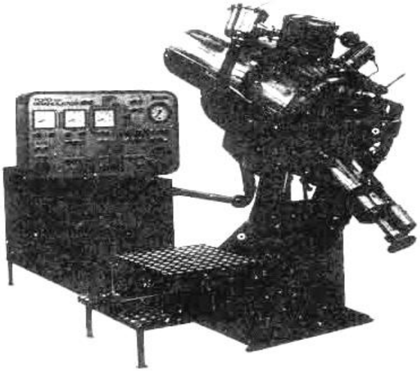


Figure 2.9: Topo Granulator

2.2.2.3. Advantages

The advantages of wet granulation technique are:

1) The agglomerates or granules formed improve the cohesiveness and compressibility of powders.
2) High dose drugs having a poor flow or compressibility properties can be prepared by wet granulation.
3) The soluble low dosage or potent drugs can attain uniform distribution and content by this process.
4) Colour distribution also occurs evenly in this process.
5) This process prevents the segregation or separation of components of a homogenous powder mix.
6) The dissolution rate of hydrophobic drugs is improved by this process.

2.2.2.4. Disadvantages

The disadvantages of wet granulation technique are:

1) It is an expensive process because of the labour, time, equipment, energy, and space requirements.
2) Loss of material occurs during various stages of processing.
3) Stability may be the major concern for moisture-sensitive drugs which degrade in the presence of water, moisture, or an aqueous environment.
4) Heat-sensitive drugs also cannot be processed as it involves drying steps.
5) Multiple processing steps add complexity and make validation and control difficult.
6) Any incompatibility or chemical reaction between the formulation components will be aggravated by the moisture used during granulation.

2.2.3. Dry Granulation

In dry granulation process, the powder mixture is compressed without the use of heat and solvent. The two basic procedures are to form a compact of the material by compression and to mill the compact to obtain granules.

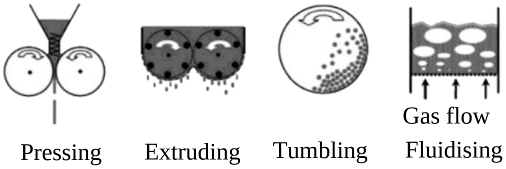


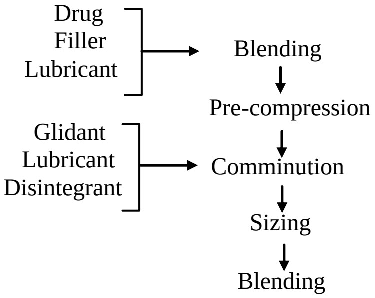
Figure 2.10: Typical Dry Granulation Methods

Some of the **dry granulation methods** (**figure 2.10**) are:

1) **Pressing:** Two methods involved are mechanical pressing and pneumatic pressing. One of the characteristic examples of mechanical pressing is roll compaction method.
2) **Extruding:** In this process, the fine powder is scrapped through a sieve or a perforated plate. It is an old but simple and easy granulation method which still finds its application in industries. But automation of equipment involved in this process is very difficult. The wide size distribution and rod-like shape of the product granules prevent much improvement in product flowability.
3) **Tumbling:** This granulation process is time-consuming. It is not applicable in case of spherical and small granules (less than 1mm).
4) **Fluidising:** Formation of agglomerates by fluidisation of fine cohesive particles is a difficult process.

Steps in Dry Granulation

1) Milling of drugs and excipients,
2) Mixing of milled powders,
3) Compression into large, hard tablets to make slug,
4) Screening of slugs,
5) Mixing with lubricant and disintegrating agent, and
6) Tablet compression.



2.2.3.1. Dry Granulation Processes

Discussed below are the different processes of dry granulation:

1) **Slugging Process:** Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity (large enough in diameter to fill quickly). The accuracy or condition of slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.

   Factors which determine how well a material may slug are:
   - i) Compressibility or cohesiveness of the matter,
   - ii) Compression ratio of powder,
   - iii) Density of the powder,
   - iv) Machine type,
   - v) Punch and die size,
   - vi) Slug thickness,
   - vii) Speed of compression, and
   - viii) Pressure used to produce slug.

2) **Roller Compaction:** The compaction of powder by means of pressure roll can also be accomplished by a machine called **chilsonator**. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules.

2.2.3.2. Equipment for Dry Granulation (Chilsonator Roller Compactor)

Roller compactor is a specially designed machine which is helpful in performing large scale compression granulation. **Figure 2.11** presents a roller compactor with two rollers revolving towards each other.

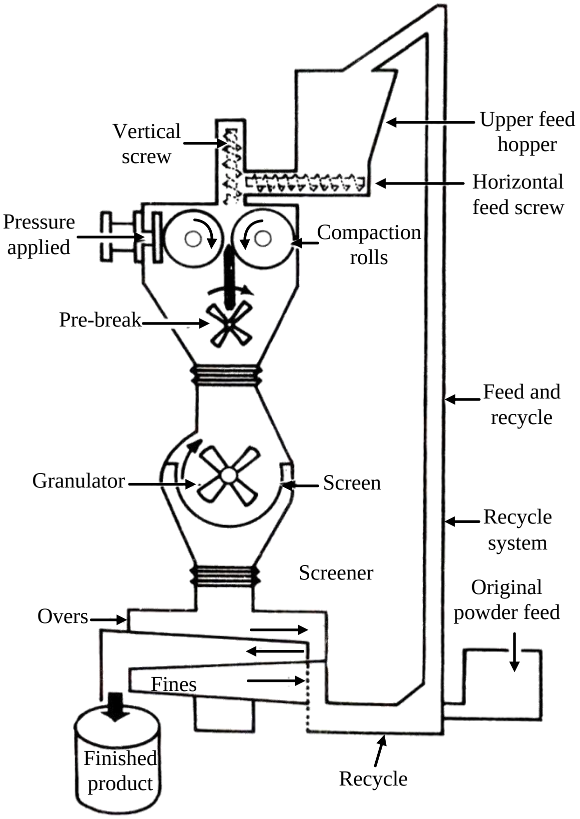


Figure 2.11: Schematic Diagram of a Chilsonator Roller Compactor in a Granulation Production System

A known fixed pressure is exerted on the powder material with a hydraulic ram forcing one of the rollers against the other. Under the influence of this pressure, the material flows between the rollers. A screw conveyor system is used to feed the powder material between the rollers. The compacted mass is passed through the rollers to produce a thin wide ribbon which breaks into large segments. These segments are similar to the slugs produced in the slugging process. Screening and milling of the segments are required to produce granules.

Variable-speed horizontal and **vertical screws** are the two types of feed screws present on most modern compactors. The horizontal screws are responsible for picking up the powder and transferring it continuously from hopper to the vertical screw. From the vertical screw the powder is delivered to the compaction rolls. The speed of vertical screw is critical for uniform compaction. The vertical screw speed is required to deaerate the powder and deliver it at a constant rate to the compaction rolls.

Roller compactors can be manufactured with various modifications. A complete range of designs from smooth to sign curves and serrated surfaces are available for roll designs. Also a wide range of designs are available for the shapes and sizes of screw feed assembly.

The liquid-cooled rolls and chambers are equipped within most of the compactors. Pilot plant facilities are provided in every manufacturing unit of roller compactors, which offer complete testing programmes. Trial runs are advisable to ensure that the compactor is suitable for the materials to be compacted.

2.2.3.3. Advantages

The advantages of dry granulation or slugging are:

1) It utilises less equipment and space.
2) It does not require binder solution and heavy mixing equipment.
3) The costly and time-consuming drying step required for wet granulation is also avoided.
4) It is suitable for moisture- and heat-sensitive materials.
5) Tablets with improved disintegration are produced as powder particles are not bonded together by a binder.
6) Solubility of the drug is also improved.

2.2.3.4. Disadvantages

Disadvantages of dry granulation are as follows:

1) It requires a specialised heavy duty tablet press to form the slug.
2) It does not permit uniform colour distribution.
3) It creates more dust than wet granulation, thus, increasing the potential contamination.

2.3. TABLET COMPRESSION

2.3.1. Introduction

Direct compression method of tablet production involves thorough mixing of dry ingredients followed by their compression into tablets. This process eliminates the drying steps involved in wet granulation method. This process is economical in comparison to wet granulation which includes increased equipment, labour, time, energy, and process validation.

Besides being efficient and economical, process of direct compression is also suitable for producing high quality tablets with adequate hardness, friability, and dissolution rates. Additionally, this process is also helpful in improving the physical and chemical stability of tablets as compared to wet granulation.

Crystalline substances like sodium chloride, sodium bromide, and potassium chloride may be compressed directly. Direct compression materials should possess good flowability and compressibility. They should be inert, tasteless, able to disintegrate, and inexpensive.

2.3.2. Stages of Compression

In order to consolidate a material into a single solid matrix, pharmaceutical tablet manufacturing involves compressing a suitable volume of granules within a die cavity, between an upper and lower punch. The solid matrix is ejected from the die cavity as an intact tablet.

The **stages involved in compression** are:

1) **Transitional Repacking:** The initial packing when the granulation movement occurs at lower pressure can be determined by the particle size distribution and shape of granules. The granules flow along each other and the finer particles enter the voids between the larger particles. This increases the bulk density of granules. Spherical particles undergo less particle rearrangement in comparison to irregular particles, since the spherical particles take up much closer initial packing arrangement.

Deformation at the Point of Contact: Application of further compression force at the contact point when all the granules are closely packed and the voids cannot be filled further results in deformation. It is of **two types**:

i) **Elastic Deformation:** It occurs when the deformation completely disappears and regains its original shape after the release of stress.

ii) **Plastic Deformation:** It occurs when the deformation does not recover completely even after the release of stress.

2) **Fragmentation and Deformation :** When the stress within the particles increases due to high pressure, cracks may occur, which gradually turn into fractures. Intrusion of smaller fragments into the void space may further increase the density. Since the stresses are released by plastic deformation, some materials do not undergo fragmentation. In plastic deformation, the group of particles slide to release the stress (visco-elastic flow) and also changes the particle shape. New clean surfaces are produced as potential areas during such deformation.

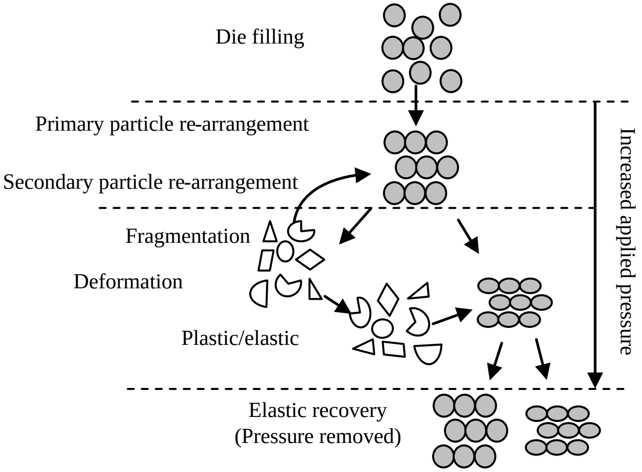


Figure 2.12: Schematic Illustration of the Powder Compression Cycle

3) **Bonding:** Different mechanisms of bonding are considered in the compression process, which are however not experimentally validated. Therefore, they are not useful in estimating the compressional properties of materials.

Three theories of bonding are:

i) The mechanical theory,
ii) The intermolecular theory, and
iii) The liquid surface film theory.

4) **Deformation of the Solid Body:** When the applied pressure is increased further, the bonded solid is confined to a limited density due to plastic and/or elastic deformation of the tablet within the die.

5) **Decomposition:** The stresses induced by elastic rebound and the associated deformation processes during decompression and ejection are responsible for the success or failure of producing an intact tablet. The radial pressure keeps the tablet in the die after the upper punch is withdrawn from the die cavity. Therefore, every dimensional change throughout decompression occurs in the axial direction.

6) **Ejection:** There is a continued residual die wall friction during the rising of lower punch and upward pushing of the tablet. On removing the tablet from the die, the lateral pressure is relieved. As a result, the tablet undergoes elastic recovery and increases the volume of the tablet portion removed from die.

2.3.3. Equipments

After the preparation of granules (in case of wet granulation) or sized slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to get the final product. The compression is done either by **single punch machine** (stamping press) or by **multi-station machine** (rotary press) (**figure 2.13**).

2.3.3.1. Single Station/Single Punch Press

Figure 2.13 presents a single punch press with one die and one pair of punches, i. e., a set of tableting tools.

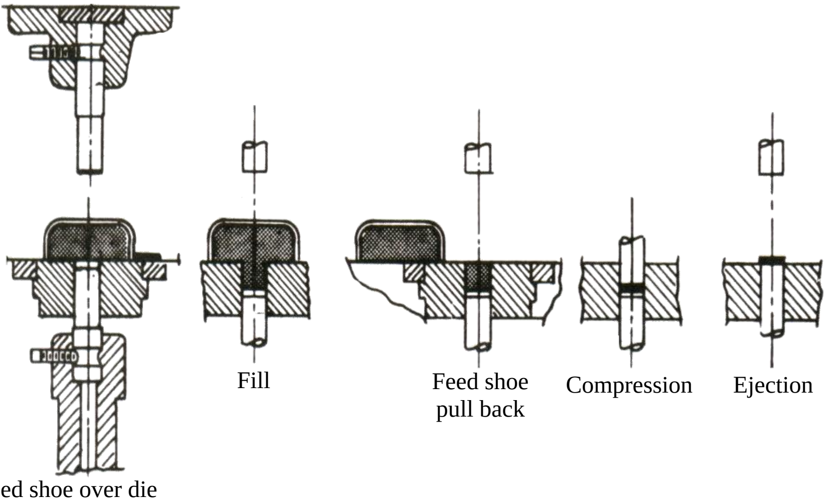


Figure 2.13: Compression Cycle of a Single Punch Tablet Press

The powder is kept within the hopper connected to a hopper shoe located at the die table. Either a rotational or a translational movement is performed by the hopper shoe moving to and fro over the die. Once the hopper shoe is positioned over the die, the powder is fed into the die by means of gravitational powder flow.

The position of the lower punch controls the quantity of powder filled into the die. The upper punch descends and compresses the powder when the hopper shoe is positioned near the die.

During compression, the lower punch remains stationary. Thus, the upper punch applies pressure which is controlled by the upper punch displacement. After ejection, the hopper shoe pushes away the tablet by moving back to the die for the next tablet. The output of 200 tablets per minute can be produced from a single punch press. Therefore, the main use of a single punch press is to produce small batches of tablets during formulation development and for clinical trials.

Components of a Single Station Press

The functional parts present in a single station press are given below and shown in **figure 2.31**:

1) **Hopper:** It is connected to the feed shoe and the granules/powder mixtures are poured into it prior to compression. Manual or mechanical techniques can be employed for filling the hopper for tableting process.
2) **Die Cavity:** Here the powder granules are compressed into tablets. The die is responsible for determining the diameter, size, and thickness of the tablet.

3) **Punches:** Tablets of various shapes can be manufactured by compressing the granules using upper and lower punches.
4) **Cam Truck:** The position and movement of the punches is guided by a cam truck.
5) **Tablet Adjuster:** It decides the tablet weight by adjusting the amount of powder to be compressed.
6) **Ejection Adjuster:** After compression the tablets are ejected from the die cavity utilising this part.

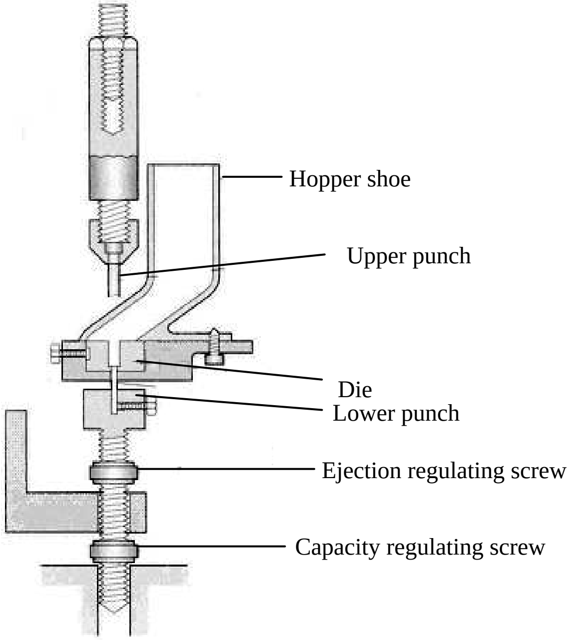


Figure 2.14: Single Punch Tablet Press

Advantages of a Single Station Press

1) The structure of a single punch is balanced and small.
2) It can be easily operated at a high utilisation ratio.
3) It can also produce odd-shaped products having a diameter of up to 20mm.
4) It is suitable for development of tablets and small batch production.
5) It reduces weight variations between tablets by utilising a high amount of pressure.
6) It also maintains a low noise level during operation.

2.3.3.2. Multi-Station/Rotary Press

Multi-station presses are also termed as **rotary presses** because the head of the tablet machine that holds the upper punches, dies, and lower punches in place, rotates. As the head rotates, the punches are guided up and down by fixed cam tracks, which control the sequence of filling, compression, and ejection. The head portions holding the upper and lower punches are called the **upper** and **lower turrets**, respectively, and the portion holding the dies is the **die table**. At the start of a compression cycle (**figure 2. 15**), granules stored in a hopper empties into the feed-frame (**A**) which has several interconnected compartments.

These compartments spread the granulation over a wide area to provide time for the dies (**B**) to fill. The pull-down cam (**C**) guides the lower punches to the bottom of their vertical travel, allowing the dies to overfill. The punches then pass over a weight-control cam (**E**) which reduces the fill in the dies to the desired amount. A wipe-off blade (**D**), at the end of the feed-frame removes the excess granules and directs it around the turret and back into the front of the feed-frame.

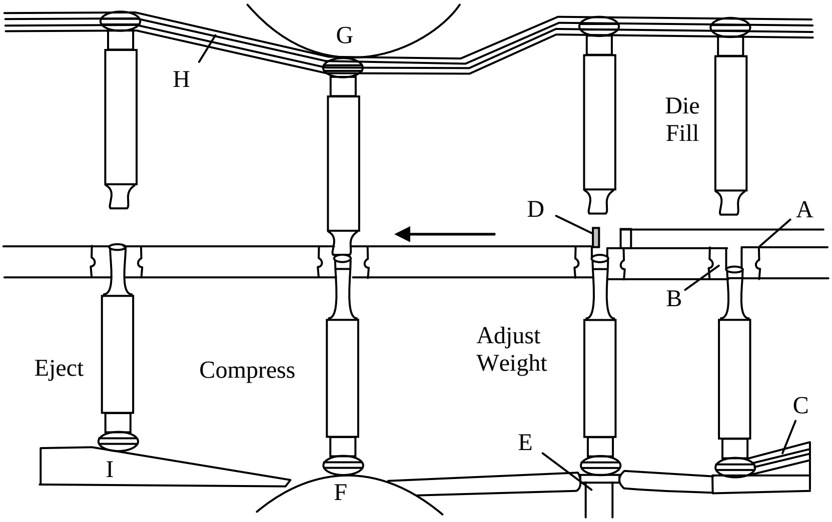
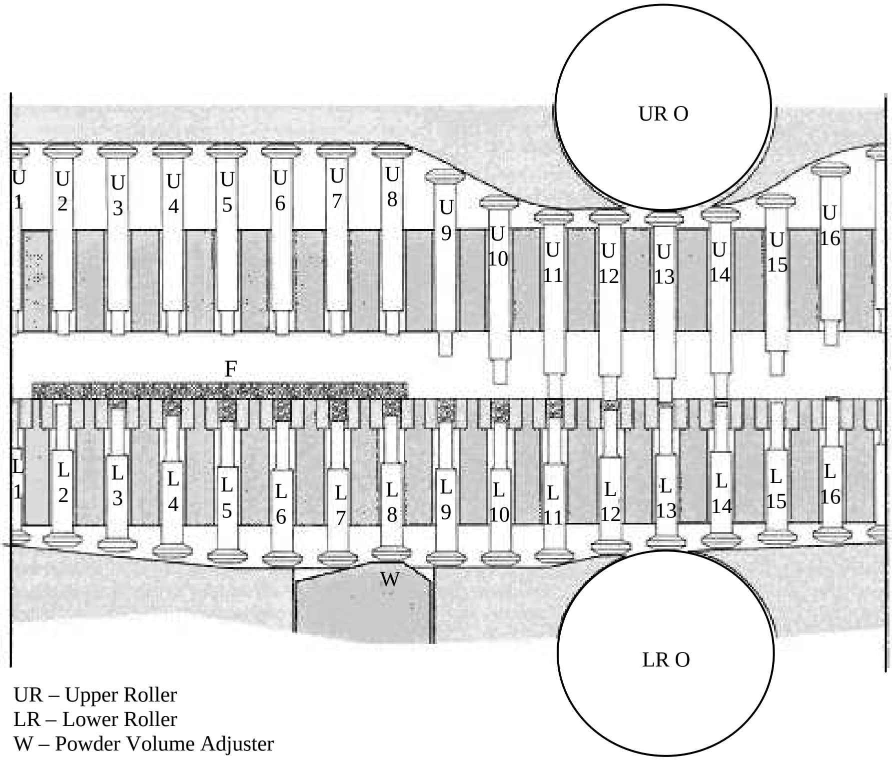


Figure 2.15: Compression Cycle of a Rotary Tablet Press

Components of a Multi-Station Press

1) **Hopper:** The granules or powder mixture containing API and excipients are poured into the hopper prior to compression or tableting.
2) **Die Cavity:** Here the powder granules are compressed into tablets. The die is responsible for determining the diameter, size, and thickness of the tablet.
3) **Feed Paddle:** This rotates at a fast speed to force the feed or granules into the dies.
4) **Punches:** These include the upper and lower punches which move within the die bore to compress granules into tablets.
5) **Lower Cam Track:** This allows accurate adjustment by permitting the overfilling of die bore by guiding the lower punch during the filling stage.
6) **Cam Truck:** This guides the position and movement of the punches.
7) **Department of Fill/Capacity Control:** This ensures that suitable quantity of granules fills the die prior to compression process by adjusting the lower punch track during the latter part of the fill stage.
8) **Recompression Rollers:** These provide an initial compression force to the granules for removing the excess air entrapped in the die.
9) **Main Compression:** This provides the final compression force required for the formation of tablets.
10) **Ejection Cam:** This is utilised to facilitate the ejection of tablet from the die cavity after compression.
11) **Take-off Blade:** This is fitted opposite to the feeder housing and deflects the tablet down the discharge chute.
12) **Discharge Chute:** After being deflected by the take-off blade, the tablet passes through the discharge chute for collection.



UR – Upper Roller
LR – Lower Roller
W – Powder Volume Adjuster
F – Feed Frame with Granules
U1 to U8 – Upper Punches in Raised Position
L1 – Lower Punch at Top Position, Tablet Ejected
L2 to L7 – Lower Punches Dropping to Lowest Position and Filling Die with Granules to an Overfill at L7
L8 – Lower Punch Raised to Expel Excess Granules Giving Correct Volume
U9 to U12 – Upper Punches Lowering to Enter Die at U12
L13 and U13 – Upper and Lower Punches Pass between Rollers and Granules are Compacted to a Tablet
U14 to U16 – Upper Punch Rising to Top Position
L14 to L16 – Lower Punch Rising to Eject Tablet

Figure 2.16: Diagram of Punch Tracks of a Rotary Tablet Press

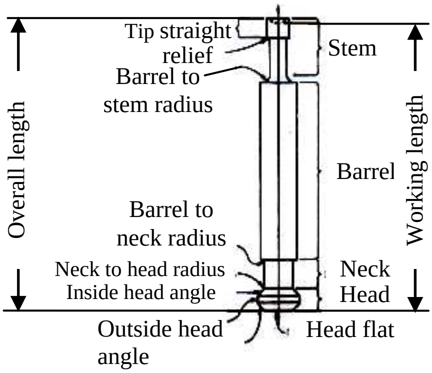
Advantages of a Multi-Station Press

1) This operation is cheaper, less labour intensive, and involves high productivity.
2) The process is time saving and is capable of meeting high demand of tablet dosage form. **For example**, rotary press has an output of 9000-234000tab/hour.
3) A moving feeder is required for managing the powder filled cavity automatically.
4) Rotary press involves minimum wastage of valuable formulation in non-specific tablets.
5) Both weight and hardness can be controlled independently by the rotary press.

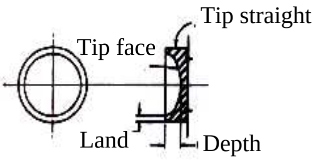
2.3.4. Tablet Tooling

Most commonly the tablets are manufactured in circular, oval, and oblong shape. However, they can also have triangular and diamond shapes. When viewed sideways, the tablets appear flat or convex and with or without bevelled edges. Break marks, symbols, or other markings may also be present on tablets. **Break marks** or **break lines** are provided so that tablets can be broken in a controlled manner to ensure reproducible doses. **Markings** which help in identifying a preparation are **embossed** (raised on the tablet surface) and **debossed** (indented into the tablet).

Punch body



Punch tip



Die

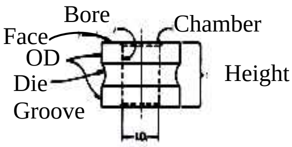


Figure 2.17: Tablet Press Tooling Nomenclature

The set of tools and tooling designs control the size, shape, and appearance of a tablet formed by powder compaction. Thus, the size, shape, and appearance of tablets vary widely. Precision tools like **punches** and **dies** should be handled and stored carefully. The quality of compression tooling may be associated with manufacturing problems. Therefore, the process involving development and production of tablets also utilises tooling inspection programmes.

2.3.4.1. Types of Tooling

A tooling set including the die and its connected punches are of two types:

1) **"B" Type:** A punch barrel having a diameter of 0.750 inches (19mm) is utilised in this configuration type. Two types of dies having different die sizes can be used in B type tooling:
    i) The "B" dies of 1.1875 inches (30.16mm) diameter are suitable for all tablet sizes up to the maximum for the "B" punches.
    ii) The smaller "BB" dies or small "B" die of 0.945 inches (24mm) diameter are suitable for tablets of 9-11mm diameter.

2) **"D" Type:** The minimum barrel diameter of this type is 1 inch (25.4mm) and a die diameter is 1.500 inches (38.10mm). Therefore, it is suitable for tablets having maximum diameter or maximum length of 25.4mm.

Two other types of tooling are also present:

1) "BB" type, and
2) "DB" type.

Table 2.3 shows different types of tooling, their dimensions, and maximum possible tablet sizes:

Table 2.3: Types of Tooling, their Dimensions, and Maximum Possible Tablet Sizes

Types of Tooling	Punch Diameter (in mm)	Die Diameter (mm)/(inch)	Punch Length (mm)/inch	Maximum Tablet Size (mm) Round/Capsule
'B'	19	30.15/1.187	133.60	16/19
'D'	25.4	38.1/1.50	133.60	25/25
'BB'	19	24/0.945	133.60	13/14
'DB'	25.4	30.15/1.187	133.60	19/19

Either "B" or "D" tooling (not both) can be used in tableting machines. The type of tooling affects the compression force obtainable in a machine. A compression force of up to 6.5 tonnes is exerted by machines with "B" type tooling, while those with "D" type exert compression force of 10 tonnes.

2.3.4.2. Tablet Tooling Terminology

The different terms used for tooling (punches and dyes) are defined below:

1) **Head:** It is the punch end guiding it through the cam track of tablet machine during rotation.
2) **Head Flat (Dwell Flat):** It is the flat area of the head receiving the compression force from rollers (in upper punches) and determining the weight and ejection height (in lower punches).
3) **Outside Head Angle:** It is the area in touch with the roller prior to head flat during compression.
4) **Inside Head Angle:** It is the area pulling down the lower punches after ejection and lifting the upper punches after compression.
5) **Neck:** It is the area between the head and barrel providing clearance for the cams.
6) **Barrel:** It is the area guiding the punches (while going up and down) with reference to turret guides.
7) **Stem:** It is the punch area lying opposite to the head, beginning at the tip and extending to the point where the full diameter of the barrel begins. If the chamber is present, the barrel usually reaches its full diameter just above the chamber.
8) **Tip:** It determines the size, shape, and profile of the tablet.
9) **Tip Face:** It is the punch area where the tablet is formed. Its surface should have a smooth finishing for yielding tablets of superior quality.
10) **Working Length:** It is the distance between the cup bottom and the head flat and determines the tablet weight and thickness.
11) **Overall Length:** It is the distance between the cup top and the head flat.
12) **Key Angle:** It is the relationship of the punch key to the tablet shape. Its position depends on the tablet shape, take-off angle, and turret rotation.
13) **Domed Head:** It increases the dwell time, thus, yielding tablets of adequate hardness.
14) **Dwell Time:** It is the time spent by the punches below the pressure roller while rotating in the machine.

2.3.5. Compression and Processing Problems & Remedies

Tablets undergo many defects which occur either apparently or later during storage (**e.g.,** capping occurs after storage). Therefore, it is important to perform appropriate tests at the beginning and during tablet production. The commonly occurring **tablet defects** are summarised below along with their **causes** and **remedies**:

1) **Binding in the Die :** During this problem tablet ejection becomes difficult and the process creates a characteristic 'grunting' noise. The tablets produced have rough edges. This problem may **occur due to conditions facilitating high die-wall friction** (**e.g.,** poor lubrication, under-dried granules and a dirty or blemished die). Another source is much **larger clearance between the lower punch and the die-bore** due to excessive wear. Much finer particles may seep through the gap and compact to form a tough film restricting the free movement of punches.

2) **Picking and Sticking:** This problem **occurs due to material adhesion to the punch faces**. If material adhesion is localised, some portions of the tablet surface are found to be missing and this defect is referred to as **picking**. If the entire tablet adheres to the punch face, the tablet appears rough and dull and this defect is referred to as **sticking**. Some causes and remedies of sticking of tablets are presented in **tables 2.4** and **2.5**:

Table 2.4: Causes and Remedies of Sticking of Tablets

Causes	Remedies
Granules are not dried properly.	Granules are properly dried and limits are evaluated by moisture analysis.
Lubrication is not done properly.	Lubricant is either increased in quantity or changed.
Binder is present excessively.	Binder is either decreased in quantity or changed.
Granular material is hygroscopic.	Granulation is modified and compressed under controlled humidity.
Materials are oily or waxy.	Mixing process is modified by adding an absorbent.
Granules are soft or weak.	Amount of binder and granulation technique is optimised.

Table 2.5: Causes and Remedies of Sticking Related to Machine (Dies, Punches, and Tablet Press)

Causes	Remedies
Concavity is deep for granulation.	Concavity is optimised.
Pressure is low.	Pressure is increased.
Compression speed is fast.	Speed is reduced.

3) **Cracking:** These appear as small, fine cracks on the upper and lower central surface of tablets, or on the sidewall. The causes and remedies of cracking are presented in **table 2.6**:

Table 2.6: Causes and Remedies of Cracking Related to Formulation (Granulation)

Causes	Remedies
Granules are large.	Granule size is reduced and fines are added.
Granules are dry.	Granules are moistened and proper amount of binder is added.
Tablets expand.	Granulation is improved& dry binders are added.
Granulation is too cold.	Tablets are compressed at room temperature.
Tablet expands on ejection due to air entrapment.	Tapered die is used.
Deep concavities cause cracking while removing tablets.	Special take off is used.

4) **Capping and Lamination: Capping** occurs before and during compression due to inadequate air removal from the granules in the die cavity. The air entrapped inhibits granule bonding while its expansion during ejection leads to the detachment of tablet top (cap). **Lamination** involves splitting of tablet into a number of layers or laminates. The causes and remedies of capping and lamination of tablets are presented in **tables 2.8-2.11**:

Table 2.7: Causes and Remedies of Capping Related to Formulation (Granulation)

Causes	Remedies
Granulation contains large amount of fines.	Some or all fines are removed by 100 -200 mesh screen.
Moisture content is very low.	Hygroscopic substance, **e.g.,** sorbitol, methyl-cellulose or PEG 4000, is added.
Granules are dry.	Granules are moistened.
Granules are improperly dried.	Granules are dried properly.
Binder is improper or the quantity is not sufficient.	Either a dry binder (**e.g.,** pre-gelatinised starch, gum acacia, powdered sorbitol, PVP, hydrophilic silica or powdered sugar) is used or quantity is increased.
Lubricant is improper or the quantity is not sufficient.	Either the lubricant is changed or quantity is increased.
Granular mass is too cold to compress firm.	Compression is carried out at room temperature.

Table 2.8: Causes and Remedies of Capping Related to Machine (Dies, Punches and Tablet Press)

Causes	Remedies
Finishing of dies is not proper.	Dies are properly finished.
Concavity of punches is deep or bevelled-edge faces of punches.	Flat punches are used.
Lower punch remains below the die face during ejection.	Lower punches are adjusted properly during ejection.
Sweep-off blade is not adjusted properly.	Sweep-off blade is adjusted correctly for proper ejection.
Turret speed is high.	Turret speed is reduced.

Table 2.9: Causes and Remedies of Lamination Related to Formulation (Granulation)

Causes	Remedies
Granules contain oily or waxy materials.	Mixing process is modified by adding adsorbent or absorbent.
Lubricant is hydrophobic (**e.g.,** magnesium stearate).	Either the lubricant is changed or quantity is reduced.

Table 2.10: Causes and Remedies of Lamination Related to Machine (Die, Punches and Tablet Press)

Causes	Remedies
Rapid relaxation of the peripheral regions of a tablet on ejection from a die.	Tapered dies are used, i.e., upper part of the die bore has an outward taper of 3° to 5°.
Decompression occurs rapidly.	Pre-compression step is involved; turret speed and final compression pressure are reduced.

5) **Excessive Weight Variation:** This involves **separation of granule constituents due to poor granular flow**. Weight variation occurs due to the presence of **under-dried granules**, **too large granules**, **too fine granules**, **large proportion of fines**, **improperly lubricated granules**, or **granules with variable densities or sizes**. A faulty rotary machine with a suitable granular flow indicates that one or more punches are of different length due to unintentional mixing of bottom punch sets.

6) **Fissured or Pitted Surface:** This problem **occurs due to the presence of uniformly sized granules which lack the fines required to fill up the voids**. The **remedy** for this problem is using granules of a broader size distribution. However, this should not result in problems like capping or lack of tablet weight uniformity.

7) **Soft Tablets:** Different reasons responsible for production of soft tablets are **very low compaction pressure**, **improperly dried granules**, **weak inter-granule bonds** (due to the presence of air in granule bed), or **high proportions of fatty lubricant** (magnesium stearate).

8) **Protracted Disintegration:** This process involves rapid breakdown of the tablet into larger particles that exist for a longer time, or produce fine particles. However, the total disintegration time is excessive. These faults may **occur due to**:
   i) Using a very strong adhesive granulating agent.
   ii) Inhibition of water penetration, high degree of compaction, hydrophobic tablet ingredients, excessive quantities of fatty lubricant, or gelling of the granulating agent.
   iii) Inefficient bursting due to insufficient or improper disintegrating agent.

   Surfactant in small amounts can be added in the tablet formulation if the granules are hydrophobic due to the use of a fatty lubricant. The surfactant added facilitates penetration by aqueous fluids. A hard polyethylene glycol can also be employed to provide soluble points in the tablet. On adding a disintegrant before the moistening or preliminary compression stages, a more efficient bursting action may occur. The disintegration time can be prolonged by applying a very low degree of compression.

9) **Mottling:** Uneven distribution of colour in tablets is termed **mottling** which **occurs due to discontinuous granule size distribution**. This is because the finer particles present a slightly different background against the larger particles present on the surface. This defect is commonly observed in coloured tablets due to migration of dye. The causes and remedies of mottling of tablets are presented in **table 2.11**:

Table 2.11: Causes and Remedies of Mottling

Causes	Remedies
Coloured drug is used along with colourless or white-coloured excipients.	Appropriate colourants are used.
Dye migrates to the granulation surface while drying.	Solvent and the binder system is changed; drying temperature is reduced; particles of small size are used.
Dye is improperly mixed, especially during direct compression.	Dye is mixed properly and its size is reduced to prevent segregation.
Coloured binder solution is improperly mixed.	Dry colour additive is added during powder blending followed by adding fine powdered adhesives (acacia and tragacanth) and mixing well; finally the granulating liquid is added.

10) **Variation of Medicament Content:** Standards are set for the drug content of individual tablets. If the content varies widely and the factors responsible for this variation can be eliminated, the most common sources of variation are **migration of solute**, **physical adsorption with separation** at some stage of the production, and **inefficient mixing**.

11) **Drug Instability:** Generally water is present and is also purposely added in various air-dried drugs and tablet excipients. This water may also be present even after the moist granulation process. To ensure drug stability and to comply with technical reasons associated with the physical processes of tablet production, it is necessary to **control the moisture content**.

2.4. TABLET COATING

2.4.1. Introduction

Coated tablets are defined as tablets covered with one or more layers of mixture of various substances such as natural or synthetic resins, gums, inactive and insoluble fillers, sugar, plasticisers, polyhydric alcohol, waxes, authorised colouring materials, and sometimes flavouring agents. Coating may also contain active ingredients. Substances used for coating are usually applied as solution or suspension under conditions in which the vehicle evaporates.

In tablet coating, the moving tablet bed is applied with coating solution along with the simultaneous use of heated air for rapid solvent evaporation. Coating of tablets is an essential step involved in manufacturing controlled and delayed release tablet dosage forms. There are many advantages associated with tablet coating like masking obnoxious odour, bitter taste, and unpleasant colour of the drug; protecting the drug from gastric environment; and also physically and chemically protecting the drug.

The tablet properties, coating process, and coating composition are the main constituents of tablet coating. Generally, a horizontal rotating pan is used for coating tablets by either spraying or pouring coating solution on them. A tablet's efficiency depends on the coating solution quantity on tablet surface. The latest advancements in tablet coating aims to eradicate the problems associated with solvent-based coating.

2.4.2. Advantages

The advantages provided by tablet coating are:

1) The tablet coating process prevents sticking of tablets.
2) It follows the fine contours of embossed characters or logos on tablets.
3) It maintains its stability and strength during tablet handling.
4) It provides a smoother finishing to tablets.
5) It aids in swallowing larger tablets.
6) It also conceals the unpleasant taste of certain drugs.
7) Tablet printing can also be accomplished by coating.

2.4.3. Disadvantages

The disadvantages of tablet coating are:

1) Other coating materials are preferred over sugar coating because it is an expensive technique and also requires prolonged time.
2) The tablet coating process is tiresome and requires prolonged time for completion.
3) It cannot be performed without the guidance of highly skilled technicians.

2.4.4. Types of Coating

The various types of tablet coating are:

1) **Sugar Coated Tablets (SCT):** These tablets are usually used for children to mask the unpleasant smell and taste of some drugs. In the process of sugar coating, sucrose-based coating formulations are applied successively onto the tablet cores in coating equipment. During the process , water evaporates from the syrup and a thick sugar layer is left around each tablet.

2) **Film Coated Tablets (FCT):** This type of coating is used to make the tablets attractive with various colours. Film coating protects the tablet to remain stable, and also masks the unpleasant taste and uneven colour of some drugs (such as the herbal extracts). In the process of film coating, a thin uniform film of a polymer formulation is deposited on the tablet by spraying method.

3) **Enteric Coated Tablets (ECT):** These tablets contain drugs that undergo best absorption in intestines (and not in gastric). Thus, they are coated such that they withstand the pH of stomach acid and slowly release the drug only in the small intestine.

4) **Compression Coating:** This type of coating is less popular; however it gained increased interest for creating modified-release products. In the process of compression coating, granular materials are compacted around a pre-formed tablet core using specially designed tableting equipment.

5) **Gelatin Coated Tablets:** These are capsule-shaped compressed tablets coated with gelatin layer.

2.4.5. Coating Materials and Formulation of Coating Composition

The formulation of coating solution includes:

1) Film forming materials (enteric or non-enteric),
2) Solvents,
3) Plasticisers,
4) Colourants,
5) Opaquants, and
6) Miscellaneous coating solution components.

Table 2.12 enlists some of the materials used for tablet coating process:

Table 2.12: Materials in Tablet Coating

Materials	Types	Examples
Film formers	Enteric, non-enteric	HPMC, ethyl cellulose, sodium CMC, polyethylene glycol, cellulose acetate phthalate, and HPMCP.
Solvent	–	IPA and methylene chloride.
Plasticisers	Internal and external plasticising	Castor oil, propylene glycol, glycerine, surfactants, and polysorbates.
Colourants	Inorganic and natural colourants.	FD and C colours, D and C colours, iron oxides, caramel, and turmeric.
Opacifiers	–	Titanium dioxide, talc, and aluminium silicate.

2.4.5.1. Film Forming Materials

The commonly used film formers are:

1) **Hydroxy Propyl Methyl Cellulose (HPMC) :** It is available in different viscosity grades. It is a polymer of choice for air suspension and pan spray coating systems because of solubility characteristic in gastric fluid, organic and aqueous solvent system. It has many **advantages** like it does not affect tablet disintegration and drug availability. Moreover, it is cheap, flexible and highly resistant to heat and moisture. It has no taste and odour; colour and other additives can be easily incorporated.

   However, when it is used alone, the polymer has the tendency to bridge or fill the debossed tablet surfaces. So mixture of HPMC with other polymers/plasticisers is recommended.

2) **Methyl Hydroxy Ethyl Cellulose (MHEC):** It is available in wide variety of viscosity grades. It is not frequently used as HPMC because of being soluble in fewer organic solvents.

3) **Ethyl Cellulose (EC):** Depending on the degree of ethoxy substitution, different viscosity grades are available. It is completely insoluble in water and gastric fluids. Hence, it is used in combination with water-soluble additives (like HPMC), and not alone. Unplasticised ethyl cellulose films are brittle and require film modifiers to obtain an acceptable film formulation. Aqua coat is aqueous polymeric dispersion utilising ethyl cellulose. These pseudolatex systems contain high solids, low viscosity compositions that have coating properties different from regular ethyl cellulose solution.

4) **Hydroxy Propyl Cellulose (HPC):** It is soluble in water below 40°C (insoluble above 45°C), gastric fluid, and many polar organic solvents. It is extremely sticky as it dries from solution system. It is used for sub-coat and not for colour or glass coat. It gives a very flexible film.

5) **Povidone:** Degree of polymerisation decides the molecular weight of material. It is available in four viscosity grades, i.e., K-15, K-30, K-60, and K-90 with their average molecular weight as 10000, 40000, 160000, and 360000, respectively. The grade K-30 is widely used as tablet binder and in tablet coating. It has excellent solubility in wide variety of organic solvents, water, gastric and intestinal fluids. Povidone can be cross-linked with other materials to produce films with enteric properties. It is used to improve dispersion of colourants in coating solution.

6) **Sodium Carboxy Methyl Cellulose:** It is available in medium, high and extra high viscosity grades. It is easily dispersed in water to form colloidal solutions but it is insoluble in most organic solvents and hence, not a material of choice for coating solution based on organic solvents. Films prepared by it are brittle but adhere well to tablets. Partially dried films are sticky, so coating compositions should be modified with additives.

7) **Polyethylene Glycols (PEG):** Low molecular weight PEGs (200-600) are liquid at room temperature and are used as plasticisers. High molecular weight PEGs (900-8000 series) are white, waxy solids at room temperature. Combination of PEG waxes with **Cellulose Acetate Phthalate** (CAP) give films soluble in gastric fluids.

2.4.5.2. Solvents

Solvents are used to dissolve or disperse the polymers and other additives and convey them to substrate surface. Mostly solvents are used either alone or in combination with **water**, **ethanol**, **methanol**, **isopropanol**, **chloroform**, **acetone**, **methylene chloride**, etc. Water is the most commonly used solvent. For drugs that readily hydrolyse in the presence of water, non-aqueous solvents are used.

2.4.5.3. Plasticisers

As solvent is removed, most polymeric materials tend to pack together in 3-D honey comb arrangement. **Internal** or **external plasticising technique** is used to modify the quality of film. Combination of plasticiser may be used to get the desired effect. Concentration of plasticiser is expressed in relation to the polymer being plasticised. Recommended levels of plasticisers range from 1-50% by weight of the film former.

Commonly used plasticisers are **castor oil**, **propylene glycol**, **glycerine**, **low molecular weight** (200-400 series) **PEG**, **surfactants**, etc. For aqueous coating, PEG and PG are mostly used, while castor oil and spans are primarily used for organic-solvent based coating solution. External plasticiser should be soluble in the solvent system used for dissolving the film former and plasticiser.

2.4.5.4. Colourants

Colourants can be used in solution form or in suspension form. To achieve proper distribution of suspended colourants in the coating solution, use of powdered colourants (<10 microns) is recommended.

Most common colourants in use are **certified FD and C**, or **D and C colourants**. These are synthetic dyes or lakes. **Lakes** are choice for sugar or film coating as they give reproducible results. Concentration of colourants in the coating solutions depend on the desired colour shade, the type of dye, and the concentration of opaquant-extenders. If very light shade is desired, concentration of less than 0.01% may be adequate; on the other hand, if a dark colour is desired a concentration of more than 2% may be required. The inorganic materials (**e.g.,** iron oxide) and the natural colouring materials (**e.g.,** anthocyanins, carotenoids, etc.) are also used to prepare coating solution. **Magenta red dye** is non-absorbable in biological system and resistant to degradation in the GIT (opaque colour concentrate for film coating).

2.4.5.5. Opacifiers/Opaquant-Extenders

Opacifiers are very fine inorganic powder used to provide more pastel colours and increase film coverage. These inorganic materials provide white coat or mask the colour of tablet core. They are cheap. In presence of opacifiers, the amount of colourants required decreases. Most commonly used opacifiers are **titanium dioxide**, **silicate** (talc and aluminium silicates), **carbonates** (magnesium carbonates), **oxides** (magnesium oxide), and **hydroxides** (aluminium hydroxides). Pigments were investigated in the production of opaque films and it was found that they have good hiding power and film-coated tablets have highlighted intagliations (carvings).

2.4.5.6. Miscellaneous Coating Solution Components

Flavours, sweeteners, surfactants, antioxidants, antimicrobials, etc. may be incorporated into the coating solution. **Polymers used for enteric coating** are:

1) **Cellulose Acetate Phthalate (CAP):** It is widely used in industries. Aquateric is reconstituted colloidal dispersion of latex particles. It is composed of solid or semisolid polymer spheres of CAP, ranging in size from 0.05-3 microns. Cellulose Acetate Trimellitate (CAT) developed as an ammoniated aqueous formulation showed faster dissolution than a similar formulation of CAP.

   Disadvantages

   i) It dissolves only at pH above 6.
   ii) It delays drug absorption.
   iii) It is hygroscopic.

  - iv) It is permeable to moisture in comparison to other enteric polymer.
  - v) It is susceptible to hydrolytic removal of phthalic and acetic acid changing film properties.
  - vi) CAP films are brittle and are usually used with other hydrophobic film forming materials.

2) **Acrylate Polymers:** **Eudragit L** and **S** are two forms of commercially available enteric acrylic resins. Both of them produce films resistant to gastric fluid. Eudragit L and S are soluble in intestinal fluid at pH 6 and 7, respectively. Eudragit L is available as an organic solution (isopropanol), solid or aqueous dispersion. Eudragit S is available only as an organic solution (isopropanol) and solid.

3) **Hydroxy Propyl Methyl Cellulose Phthalate:** HPMCP 50, 55 and 55-s (also called HP-50, HP-55 and HP-55-s) are widely used. HP-55 is recommended for general enteric preparation, while HP-50 and HP-55-s are required for special cases. These polymers dissolve at a pH 5-5.5.

4) **Polyvinyl Acetate Phthalate:** It is similar to HP-55 in stability and pH dependent solubility.

2.5. METHODS OF COATING

2.5.1. Introduction

Tablet coating processes are of the following two types:

1) Sugar coating, and
2) Film coating.

2.5.2. Sugar Coating

Compressed tablets may be coated with coloured or uncoloured sugar layer. The coating is water-soluble and quickly dissolves after swallowing. Sugar coat protects the enclosed drug from the environment and provides a barrier to objectionable taste or order. The sugar coat also enhances the appearance of compressed tablet and permits imprinting manufacturer's information. Sugar coating provides a combination of insulation, taste masking, tablet core smoothening, colouring, and modifying drug release.

The **disadvantages** of sugar coating are the time and expertise required in the coating process, and thus, increases size, weight, and shipping costs.

Sugar coating process involves five separate operations:

1) **Sealing/Water Proofing** It provides a moisture barrier and hardens the tablet surface.
2) **Sub-Coating:** It causes a rapid build-up to round off the tablet edges.
3) **Grossing/Smoothing:** It smoothens the sub-coated surface and increases the tablet size to predetermined dimension.
4) **Colouring:** It provides the desired colour to tablets.
5) **Polishing:** It produces the characteristic gloss.
6) **Printing:** It utilises edible inks for tablet characterisation.

2.5.2.1. Sealing/Water Proofing

Prior to applying any sugar/water syrup, the tablet cores should be sealed, thoroughly dried, and freed of all residual solvents. The seal coat provides a moisture barrier and hardens the tablet to minimise attrition effects.

The sealants are generally water-insoluble polymers/film formers applied from an organic solvent solution. The quantities of material applied as a sealing coat depends primarily on tablet porosity. Since, highly porous tablets soak up the first applied solution, their uniform spreading across the surface of every tablet in the batch is hindered. Hence, one or more further application of resin solution may be required to ensure that the tablet cores are sealed effectively.

Common materials used as a sealant include **shellac**, **zinc**, **cellulose acetate phthalate**, **polyvinyl acetate phthalate**, **hydroxypropyl cellulose**, **hydroxypropylmethyl cellulose**, etc.

2.5.2.2. Sub-Coating

Sub-coating is the step from where the actual sugar coating process begins. This step provides rapid build-up necessary to round up the tablet edges. It also acts as the foundation for the smoothing and colour coating.

Generally **two methods are used for sub-coating**:

1) **Application of gum-based solution** followed by dusting with powder and drying. This step is repeated until the desired shape is achieved.
2) **Application of a suspension of dry powder** in gum/sucrose solution followed by drying.

Thus, sub-coating is a sandwich of alternate layer of gum and powder. It is necessary to remove the bulk water after each application of coating syrup.

The **table** below enlists the formulation of a typical **binder solution** for sub-coating:

Ingredients	%w/w
Gelatin	6
Gum acacia (powdered)	8
Sucrose (powdered)	45
Distilled water	Up to 100

The **table** below enlists the formulation of a typical **dusting powder** for sub-coating:

Ingredients	%w/w
Calcium carbonate	40.0
Titanium dioxide	5.0
Talc (asbestos free)	25.0
Sucrose (powdered)	28.0
Gum acacia (powdered)	2.0

The **table** below enlists the formulation of a typical **suspension solution** for sub-coating:

Ingredients	%w/w
Sucrose	40.0
Calcium carbonate	20.0
Talc (asbestos free)	12.0
Gum acacia (powdered)	2.0
Titanium dioxide	1.0
Distilled water	25.0

2.5.2.3. Grossing/Smoothing

The grossing/smoothing process is specifically for smoothing and filing the irregularity on the tablet surface (generated during sub-coating). It also increases the tablet size to a predetermined dimension. If the sub-coating is rough with high amount of irregularities, the use of grossing syrup containing suspended solids will provide more rapid build-up and better filling qualities. Smoothing usually can be accomplished by application of a simple syrup solution (approximately, 60-70% sugar solid).

This syrup generally contains pigments, starch, gelatin, acacia, or opacifier (if required). Small quantities of colour suspension can be applied to impart a tint of the desired colour when there are irregularities in coating.

2.5.2.4. Colouring

This stage is often critical in the successful completion of a sugar coating process and involves the multiple application of syrup solution (60-70% sugar solid) containing the requisite colouring matter. Initially, soluble dyes were used in the sugar coating to achieve the desired colour as they migrate to the surface during drying. But nowadays, the insoluble certified lakes have virtually replaced the soluble dyes in pharmaceutical tablet coating. The most efficient process for colour coating involves the use of a pre-dispersed opacified lake suspension.

2.5.2.5. Polishing

After the colouring step, the tablet surfaces tend to be smooth but somewhat dull in appearance. To achieve a glossy finish, final stage involving application of waxes (beeswax or carnauba wax) is employed.

Several problems can be encountered during the polishing stage. One common problem is to attempt to polish the tablets which are not smooth. Under these conditions, wax will collect in the depressions on the tablet surface and remain as tiny white spots at the end of the process.

2.5.2.6. Printing

Different tablets could be identified by the manufacturer’s logo, product name, dosage strength, or any other appropriate code. For sugar coated tablets, such identification could be only achieved by printing process using special **edible inks**.

2.5.3. Film Coating

Film coating involves deposition of a thin film of polymer surrounding the tablet core. Conventional pan equipment may be used, but nowadays more sophisticated equipments are employed to have a high degree of automation and coating time. The polymer is solubilised into solvent, other additives (like plasticisers and pigments) are added, and the resulting solution is sprayed onto a rotated tablet bed. The drying conditions cause removal of the solvent, giving thin deposition of coating material around each tablet core.

Usually spray process is employed in the preparation of film coated tablets. Accela Cota is the prototype of perforated cylindrical drum providing high drying air capacity. Fluidised bed equipment has made considerable impact where tablets are moving in a stream of air passing through the perforated bottom of a cylindrical column. With a smaller cylindrical insert, the stream of cores is rising in the centre of the device together with a spray mist applied in the middle of the bottom. For fluidised bed coating, very hard tablets have to be used.

2.5.3.1. Characteristics of Film Coating

Film coating process has the following characteristic features:

1) It results in minimum weight gain (2-3%) of tablets.
2) The film coat affects tablet disintegration to a lesser extent.
3) It is a single stage process, thus, quick.
4) It is easy to automate (less reliance on skilled operator/easier to meet GMP requirements of SOPs, validation, etc.).
5) It maintains the original shape of core and allows embossing.
6) It requires expensive equipment and the plant requires a large space.
7) It demands high installation and energy costs.

2.5.3.2. Film Coating Materials

The **ideal requirements** for film coating materials are:

1) They should be soluble in the solvent selected for coating preparation.
2) They should dissolve freely in water, possess low water solubility, or show pH-dependent solubility depending on their use.
3) They should be capable of creating products having graceful appearance.
4) They should be stable against heat, light, moisture, air, and the substrate being coated.
5) They should not take over any colour, taste, or odour during the process.
6) They should be compatible with other excipients in the coating solution.
7) They should be non-toxic and possess no pharmacological activity.
8) They should be resistant against cracking.
9) They should not provide bridging or filling appearance to de-bossed tablets.
10) They should be compatible with printing methods involved in the process.

Table 2.13 presents the different materials required in film coating process:

Table 2.13: Film Coating Materials

Materials	Types	Uses	Examples
Film Formers	Enteric and non-enteric	Regulate drug release.	Hydroxy Propyl Methyl Cellulose (HPMC) and Methyl Hydroxy Ethyl Cellulose (MHEC).
Solvents	–	Required for dissolving and dispersing polymers.	IPA and methylene chloride.
Plasticisers	Internal plasticising	Affect the chemical alterations within the basic polymer, which cause change in polymer's physical properties.	Glycerol, propylene glycol, and PEG 200-6000 grades.
	External plasticising	Added along with the primary polymeric film former which may affect the flexibility, tensile strength, or adhesion properties of the resulting film.	Diethyl Phthalate (DEP), Dibutyl Phthalate (DBP), and Tributyl Citrate (TBC).
Colourants	Inorganic materials	Added in concentration less than 0.01% to produce a light shade.	Iron oxides
	Natural colouring materials	Added in concentration more than 2.0% to produce a dark shade.	Anthocyanins, caramel, and carotenoids.
Opaquant-extenders		Provide a light coloured appearance and enhanced film exposure.	Titanium dioxide, silicates (talc and aluminium silicates), and carbonates (magnesium carbonates).

2.5.3.3. Development of Film Coating Formulations

Colour, shape, and size of the final coated tablet are important for marketing and these properties have a significant influence on the marketing strategies. An experienced formulator usually takes the practical approach and develops a coating formulation ’s modification of one that has performed well in the past. **Spraying** or **casting films** can preliminarily screen film formulations. Cast films cab is prepared by spreading the coating composition on teflon, glass, or aluminium foil surface using a spreading bar to get a uniform film thickness. Sprayed films can be obtained by mounting a plastic -coated surface in a spray hood or coating pan.

2.5.4. Comparison between Film and Sugar Coating

Table 2.14 enlists the differential features between film and sugar coating:

Table 2.14: Comparison between Film and Sugar Coating

Features	Film Coating	Sugar Coating
Tablet		
1) Appearance	1) Retains contour of original core. Not as shiny as sugar coat.	1) Rounded with high degree of polish
2) Weight increase due to coating material	2) 2-3%	2) 30-50%
3) Logo or break lines	3) Possible	3) Not possible
Process		
1) Operator training required	1) Automated process and easy training of operator	1) Considerable
2) Adaptability to GMP	2) High	2) Difficulty may arise
3) Process stages	3) Single stage process	3) Multistage process
4) Functional coatings	4) Easily adaptable for controlled release	4) Not usually possible apart from enteric coating

2.5.5. Equipment Employed in Coating

Most coating processes use one of the three general types of equipment:

1) **Standard coating pan**
   - i) Pellegrini pan system,
   - ii) Immersion sword system, and
   - iii) Immersion tube system.

2) **Perforated coating pan**
   - i) Accela cota system,
   - ii) Hi-coater system,
   - iii) Glatt coater system, and
   - iv) Driacoated system.

3) **Fluidised bed (air suspension) coater**

The general trend has been toward energy-efficient, automated systems to shorten the total coating time and reduce operator participation in the coating process.

2.5.5.1. Standard Coating Pan System

The standard coating pan system **(figure 2.18)** consists of a **circular metal pan** mounted somewhat angularly on a stand. The pan is 8 -60 inches in diameter and is rotated on its horizontal axis by a motor. Heated air is directed into the pan and onto the tablet bed surface, and is exhausted by means of ducts positioned through the front of the pan.

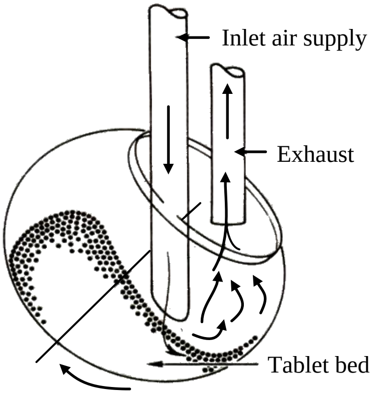


Figure 2.18: Standard Coating Pan

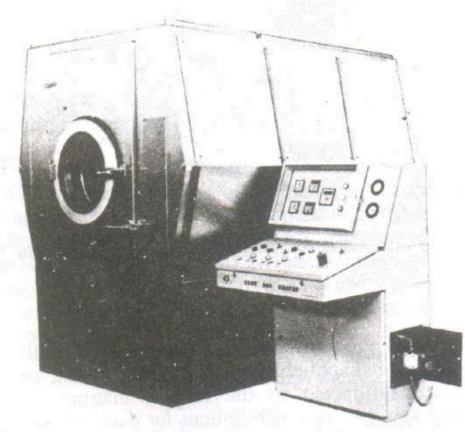


Figure 2.19: Pellegrini Pan (Enclosed) System

The **Pellegrini pan (figure 2.19)**, the **Glatt immersion-sword (figure 2.20)**, and the **immersion-tube systems (figure 2.21)** modify the drying efficiency of the standard coating pan.

Pellegrini Pan System

This system is equipped with a **baffled pan** and a **diffuser** for even circulation of drying air over the tablet bed surface. The newly developed models provide enhanced drying efficiency and automated control.

Glatt Immersion-Sword System

In this system, a **perforated metal sword device** (submerged in the tablet bed) is required to introduce the drying air. This sword device allows upward flow of drying air through the tablet bed. An effective drying environment is provided since the drying air and the wetted tablets undergo a close interaction. An **atomised spray system** is required for direct application of coating solutions to the surface of the rotating tablet bed.

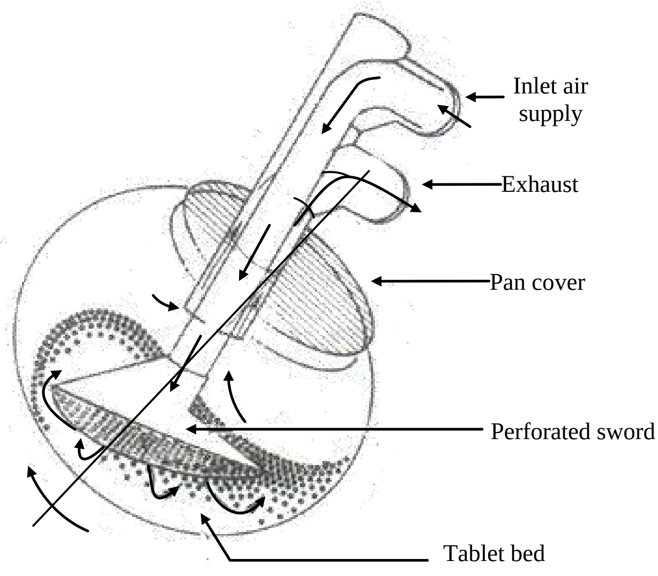


Figure 2.20: Glatt Immersion-Sword System

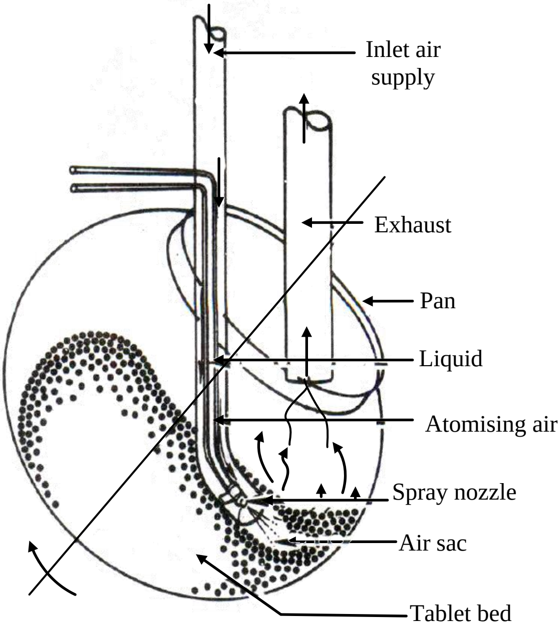


Figure 2.21: Immersion-Tube System

Immersion-Tube System

In this system, a **tube** (immersed within the tablet bed) is utilised to deliver the heated air. A **spray nozzle** is present at the tip of this tube. This process involves simultaneous application of the coating solution and the drying air (released from the immersed tube). The drying air flows upward through the tablet bed and is exhausted by a conventional duct. This technique performs both film and sugar coating operations within relatively lesser processing time.

Glatt Coater

Figure 2.22 presents the latest perforated pan coater to be introduced in the industry. In this coater, the drying air is directed from inside the **drum** through the tablet bed and out an **exhaust duct**. An alternative method is to use a **split-chambered plenum** for partial fluidisation of the tablet bed by allowing the reverse flow of drying air through the drum perforations. Different airflow patterns are possible with this coater. These coaters provide an efficient drying system with high coating capacity. They can utilise fully automated procedures for both sugar coating and film coating.

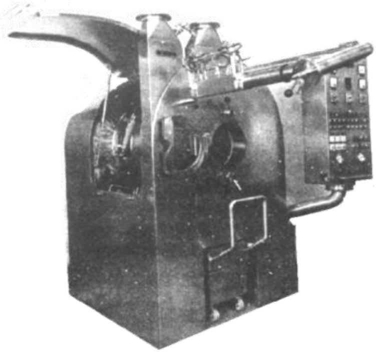


Figure 2.22: Glatt Coater

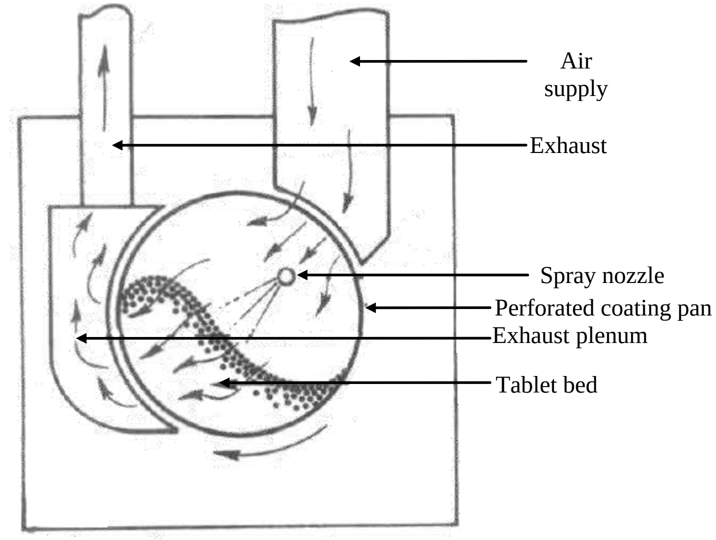


Figure 2.23: Accela-Cota System

2.5.5.2. Perforated Coating Pan

In general, all equipment of this type consists of a perforated or partially perforated drum that is rotated on its horizontal axis in an enclosed housing. In the **Accela-cota** (**figure 2.23**) and **Hi-coater** (**figure 2.24**) systems, drying air is directed into the drum, then passed through the tablet bed, and finally exhausted through perforations in the drum.

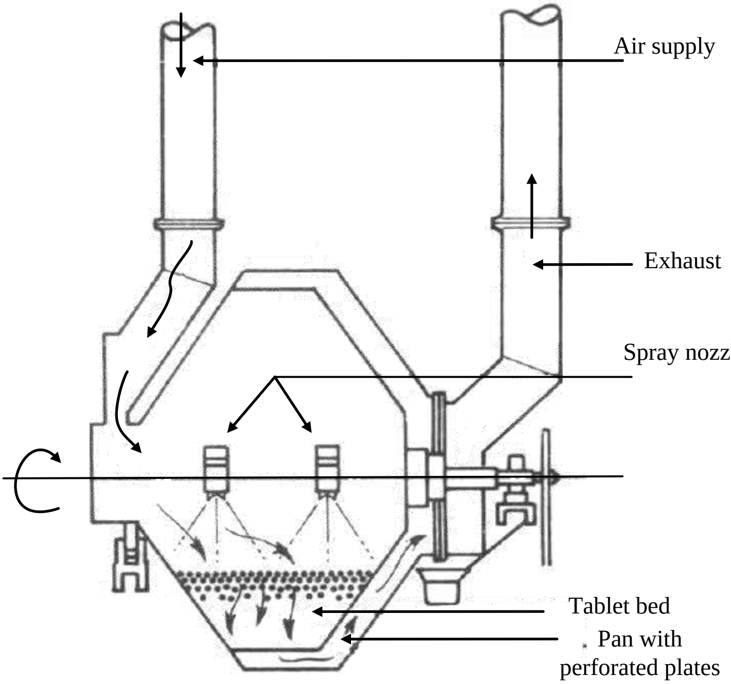


Figure 2.24: Hi-Coater System

The **Driacoater (figure 2.25)** introduces drying air through hollow perforated ribs located on the inside periphery of the drum.

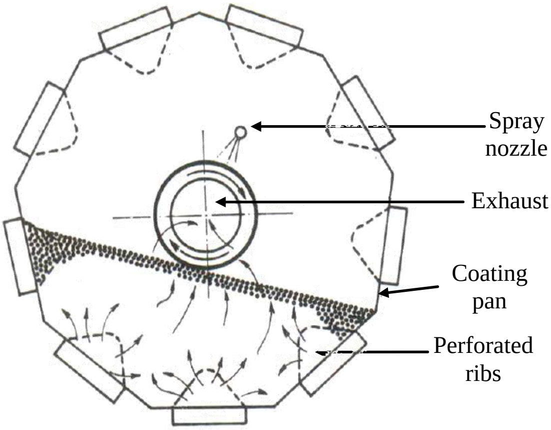


Figure 2.25: Driacoater Pan

2.5.5.3. Fluidised Bed (Air Suspension) Coater

Fluidised bed coaters (**figure 2.26**) are also highly efficient drying systems. Fluidisation of the tablet mass is achieved in a columnar chamber by the upward flow of drying air. The airflow is controlled so that more air enters the centre of the column, causing the tablets to rise in the centre. The movement of tablets is upward through the centre of the chamber. Then they fall towards the chamber wall and move downwards to re-enter the air stream at the chamber bottom.

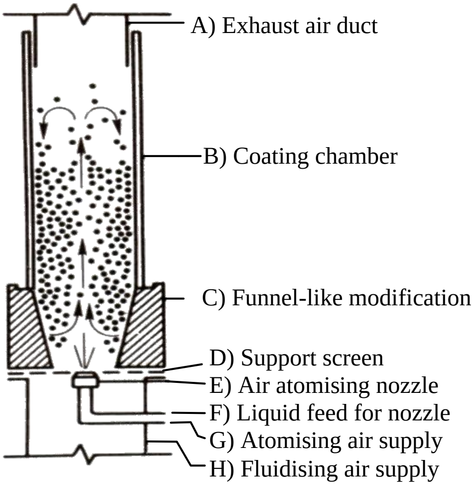


Figure 2.26: Fluidised Bed Coater

Important Processing Parameters for Fluidised Bed Coating

1) Inlet and bed temperature,
2) Relative humidity,
3) Atomisation air pressure,
4) Liquid spray rate,
5) Droplet size, and
6) Drying time.

2.5.6. Defects in Coating

Table 2.15 enlists the defects commonly found in coated tablets along with their causes and remedies:

Table 2.15: Tablet Coating Defects, Causes, and Remedies

Tablet Defects	Causes	Remedies
Blistering	Due to entrapment of gases in films as a result of overheating during spraying or at the end of the coating run.	Coating is carried out under mild drying conditions and moderate temperature.
Bridging	Due to improper application of coating solution, poor design of tablet embossing, high coating viscosity, high percentage of solids in solution, or improper atomisation pressure.	The parameters mentioned are modified and improved.
Capping	Due to improper tablet compression. This defect is revealed unless the coating process is initiated.	The tablets are not excessively dried in the pre-heating stage as excessive heating will make the tablets brittle and initiate capping.
Erosion	Due to soft tablets, over-wetted tablet surface, inadequate drying, or lack of tablet surface strength.	The parameters mentioned are modified and improved.
Peeling and Frosting	When the peeling solution does not lock with the tablet surface due to a defect in coating solution, over-wetting, or high moisture content in the tablet core.	The parameters mentioned are modified and improved.
Chipping	Due to decrease in fluidising air or rotation speed of the drum in pan coating. It may also occur due to a poor polymer or coating solution.	The film hardness is increased by adjusting the proportion of plasticiser in the coating solution or selecting a polymer with a higher molecular weight.
Picking	Due to over-wetting of tablets by the polymer solution making the adjacent tablets stick together and break apart.	The die liquid application rate is reduced or the drying air temperature and air volume is increased.
Twinning	Associated with capsule-shaped tablets.	The pan speed is increased and spray rate is reduced to overcome this problem without affecting the tablet shape. Sometimes, the tooling design is modified by slightly changing the radius.
Pitting	When the tablet core becomes hotter than the melting point of the materials used in its preparation.	The temperature of tablet core is regulated during the formulation.
Cratering	Due to penetration of tablet surface by the coating solution. The coating solution generally penetrates the more porous surface (i.e., at the crown) resulting in core disintegration and coating disruption.	The efficiency of drying process is checked and the drying conditions are optimised.
Blooming	As a result of using too much plasticiser or a low molecular weight plasticiser. The tablet colour can become dull as a result of changes in the composition of the surface film.	The concentration of plasticiser in the polymer is reduced and its molecular weight is increased.

Blushing	Due to precipitation of polymer particles (as hazy or white specks) on the film. Precipitation occurs due to high coating temperature, or by gelation of the polymer when combined with other materials.	The drying temperature is decreased to avoid polymer precipitation. Use of sorbitol with polymers such as hydroxy propyl cellulose, hydroxy methyl cellulose, methyl cellulose and cellulose ethers is avoided.
Colour variation	Due to poor mixing, uneven spray patterns of the machinery, insufficient coating, migration of soluble dyes-plasticisers and other additives during drying.	Even geometric mixing, reformulating with different plasticisers and additives, and/or using mild drying conditions is recommended.
Cracking or Splitting	When the internal stress of the film exceeds its tensile strength. This commonly occurs in higher molecular weight polymers or polymeric blends.	Low molecular weight polymers or polymeric blends are used. The plasticiser type and concentration are also increased.
Infilling	When the polymer solution sprayed on the tablet surface fails to disperse. When sprayed with air, bubbles can form in the solution leading to foam which accumulates within the intagliations instead of dispersing over the tablet. As a result the liquid droplets concentrate in the intagliations, thus, increasing the polymer concentration within the intagliations. If the droplets build-up, they coat the whole pellet giving rise to an uneven polymer film.	Alcohol is added to the polymer solution to improve dispersion, or a spray nozzle capable of finer atomisation is used.
Orange peel or Roughness	Due to soft tablets having poor composition. It can also be caused by too high a spray pressure combined with a fast spray rate, leading to uneven tablet coating.	Mild drying conditions or additional solvents are used to decrease the viscosity of polymer solution so that spraying rate can be reduced. This defect can also be corrected by reducing the degree of atomisation by moving the nozzle closer to the tablet bed.
Mottling	Due to incorporation of excipients having different colours in the coating solution, or if the degradation product of the tablet is also coloured.	The coating solution is prepared properly in appropriate quantity.

2.6. QUALITY CONTROL TESTS

2.6.1. Introduction

The quality of product manufactured by pharmaceutical industry should comply with the Pharmacopoeial specifications. It is also necessary to control any error occurring during the production process. The suitability of the goods or service to the determined qualifications is termed **quality**, and **quality control** involves product testing for defects and timely reporting to management making decision whether to investigate or deny the release.

The overall product quality can be ensured by the **in-process** and **finished product quality control tests** which involves making the product free of flaws before being marketed. The tests performed during the manufacturing process are termed **in-process tests**, thus, the **In-Process Controls** (IPC) involve measures to be taken during the manufacturing process. They are performed periodically during a process or at the end. To attain quality control and process control are the main objectives of in-process controls.

Finished Product Controls (FPC) are performed after a product is manufactured. These checks are related to qualitative and quantitative characteristics, test procedures, and acceptance limits of the product, with which the finished product should comply throughout its valid shelf-life.

2.6.2. In-Process Tests

In-Process Quality Controls (IPQC) are conducted during the manufacturing process. The in-process controls involve monitoring and adapting the manufacturing process (to ensure that it complies with the specifications), controlling manufacturing equipment and environment. In-process materials are tested for identity, strength, quality, and purity by the QC unit for being either approved or rejected during the production process. The in-process materials which are rejected are isolated and kept under a quarantine system to avoid their use in manufacturing.

Written procedures involving the following in-process controls and tests should be established and followed:

1) Drug content determination,
2) Moisture contents of granules,
3) Assay of active ingredients,
4) Hardness test, and
5) Disintegration test.

2.6.2.1. Drug Content Determination

It may be possible that a physically sound tablet may not produce the desired effects. To determine the effectiveness of a tablet, the measure of its ability to release drug and the amount of drug in each tablet should be monitored from tablet to tablet and batch to batch.

2.6.2.2. Moisture Content of Granules

The granules will bear normal handling and mixing processes without breaking down into smaller particles or producing large amounts of fine powder, only if they are of sufficient strength. In contrast, some size reduction during tablet compaction is necessary to expose the areas of clean surface and facilitate optimal bonding. Thus, moisture content plays an important role in producing a good pharmaceutical product.

2.6.2.3. Assay of Active Ingredients

Active Pharmaceutical Ingredient (API) is a therapeutically active ingredient present in a tablet. It is necessary to perform an assay of API before the preparation of tablet to produce a product of good quality.

2.6.2.4. Hardness Test

The tablets facing bioavailability problems related to alternation in dissolution profiles because of the employed compressive force should be monitored for their hardness. Monsanto hardness tester is one of the earliest testers used for evaluating tablet hardness.

2.6.2.5. Disintegration Test

A drug in solution form is readily available to the body. Disintegration is the first important step involving the breakdown of tablet into smaller particles or granules. The **USP disintegration device** utilises 3 inches long 6 glass tubes which are open at the top and held against a 10 mesh screen at the bottom end of the basket rack assembly. Disintegration test involves placing a tablet in each tube, and keeping the basket rack in a beaker filled with 1 L of water or simulated gastric fluid maintained at 37 ±2°C temperature. On moving upward the tablet should remain 2.5cm below the liquid surface and on downward movement it should remain 2.5cm above the bottom of the beaker. The basket assembly is moved up and down (using a standard motor) through a distance of 5-6cm at a frequency of 28-32 cycles per minute.

2.6.3. Finished Product Tests

The following standards or quality control tests are carried out on finished tablets:

1) Diameter size and shape,
2) Weight variation,
3) Thickness,
4) Hardness,
5) Friability,
6) Content uniformity,
7) Disintegration rate, and
8) Dissolution test.

2.6.3.1. Diameter Size and Shape

The tablet diameter size and shape depends on the die and punches selected for making the tablets. The tablets of various sizes and shapes are prepared but generally they are circular with either flat or biconvex faces. It can be dimensionally described and controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micrometre or by other device. Tablet thickness should be controlled within a ±5% variation of standard value.

2.6.3.2. Weight Variation

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, it should fall within the prescribed limits.

Tablet weight is mainly affected by factors, such as tooling of the compression machine, head pressure, machine speed, and powder flow. In consistent powder or granulate, density and particle size distribution are common sources of weight variation during compression. Variation between tablet with respect to dose and weight should be reduced to a minimum.

Test Procedure: 20 randomly selected tablets are individually weighed and the average weight is calculated. Not more than two of the individual weights should deviate from the average weight by more than the percentage given in the Pharmacopoeia and none deviates by more than twice that percentage. IP/BP and USP limits for tablet weight variation are given below:

IP/BP	Limit	USP
80 mg or less	10%	130mg or less
More than 80mg or Less than 250mg	7.5%	130mg to 324mg
250mg or more	5%	More than 324mg

2.6.3.3. Thickness

The tablet thickness can vary without any change in its weight. This is generally due to the difference in density of granules, pressure applied for compression, and the compression speed. The tablet thickness can be determined with the help of micrometre callipers. The thickness variation limits allowed are ±5% of the tablet size. The variation in thickness leads to counting and packing problems.

2.6.3.4. Hardness

The hardness of tablet depends on the weight of the material used, space between the upper and lower punches at the time of compression and pressure applied during compression. The hardness also depends on the nature and quantity of excipients used during formulation.

Following testers can be used for testing the hardness of tablets:

1) **Monsanto Hardness Tester (Figure 2. 27):** It is a small, portable hardness tester which was manufactured and introduced by Monsanto Chemical Company. It consists of a spring which can be compressed by moving the screw knob forward.

   The tablet to be tested is held between a fixed and a moving jaw and reading of the indicator is adjusted to zero. The force applied to the tablet edge is gradually increased by moving the screw knob forward until the tablet breaks. The reading is noted from the scale which indicates the pressure required in kg or lb to break the tablet. Hardness of **4kg** is **considered suitable** for handling the tablets. Hardness of **6kg or more** will produce **tablets of highly compact nature**.

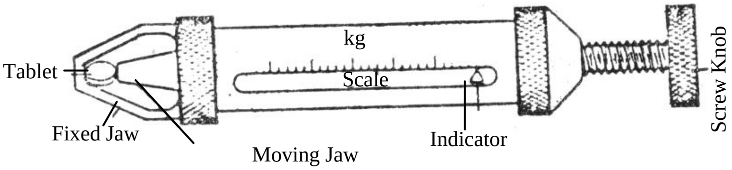


Figure 2.27: Monsanto Tablet Hardness Tester

2) **Pfizer Tablet Hardness Tester (Figure 2. 28):** It is another instrument used for testing the hardness of a tablet. It works on the principle of a plier and is also similar in shape. It is fitted with a dial. The tablet under test is held vertically in between the jaws which are pressed with hand, until the tablet breaks. The reading is noted from the needle of the pressure dial which may be expressed in kg or lb of force.

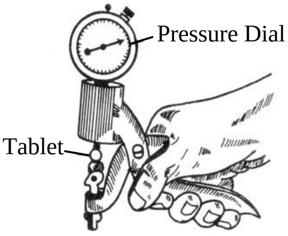


Figure 2.28: Pfizer Tablet Hardness Tester

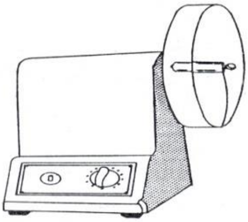


Figure 2.29: Roche Friabilator

2.6.3.5. Friability

Friability test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling, and transporting. The instrument used for this test is known as **friability test apparatus** or **friabilator**. Friability of a tablet can be determined in laboratory by Roche Friabilator (**figure 2. 29**). This consists of a plastic chamber that revolves at 25rpm, dropping the tablets through a distance of 6 inches in the friabilator, which is then operated for 100 revolutions. The tablets are re-weighed and friability (F) is calculated as:

$$F = \frac{W_{intial} - W_{final}}{W_{intial}} \times 100$$

Tablets that lose **less than 0.1-0.5%** of their weight are considered acceptable.

2.6.3.6. Content Uniformity

The test for content uniformity is performed to ensure that every coated or uncoated tablet contains the stated amount of medicaments within the prescribed limits. A number of tablets from a batch are selected randomly and assay procedures are carried out according to the monographs in the official books.

Randomly 30 tablets are selected and 10 of these are assayed individually. The tablets pass the test if 9 of the 10 tablets contain **85-115%** of the labelled drug content; and the 10th tablet contains **75-125%** of the labelled content. If these conditions are not met, the remaining 20 tablets are assayed individually, none of which should fall outside the 85-115% range.

2.6.3.7. Disintegration Rate

The disintegration test is performed to find out that within how much time a tablet disintegrates. This test is very important and necessary for all the coated or uncoated tablets to be swallowed because the dissolution rate depends upon the disintegration time which ultimately affects the absorption rate of drugs.

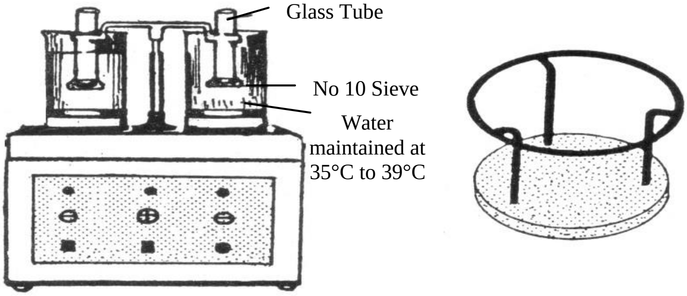


Figure 2.30: Tablet Disintegration Test Apparatus

The USP device to test disintegration (**figure 2.30**) uses 3 inches long 6 glass tubes that are open at the top and held against a 10 mesh screen at the bottom end. To test for disintegration time, a tablet is placed in each tube and the basket rack is placed in a beaker containing 1L of water, simulated gastric fluid or simulated intestinal fluid maintained at 37±2°C temperature.

On moving upward the tablet should remain 2.5cm below the liquid surface and on downward movement it should remain 2.5cm above the bottom of the beaker. The basket containing the tablets is moved up and down through a distance of 5-6cm at a frequency of 28-32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet.

According to the test, the tablet should disintegrate and all the particles should pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass.

Disintegration Time
For Uncoated Tablets: 5-30 minutes.
For Coated Tablets: 1-2 hours.

Table 2.16: BP Limits for Disintegration Time of Tablets

Categories of Tablets	Disintegration Time (min)
Uncoated tablets	15
Coated tablets	60
Effervescent tablets	5
Soluble tablets	3
Dispersible tablets	3
Orodispersible tables	3
Gastro-resistant tablets	60
Oral lyophilisates	3

2.6.3.8. Dissolution Test

The dissolution rate of a solid drug plays an important role in the absorption and physiological availability of the drug in the blood stream. Therefore, determination of dissolution rate of any solid drug is very necessary.

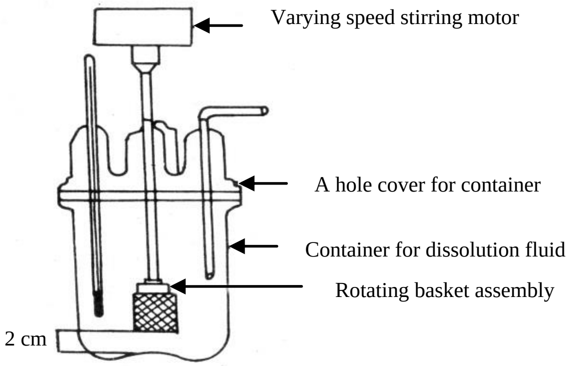


Figure 2.31: Dissolution Test Apparatus

The apparatus for dissolution test (**figure 2.31**) consists of:

1) A cylindrical stainless steel basket attached to the end of the stirrer shaft.
2) A 1000ml vessel made up of glass or other inert, transparent material fitted with a cover having 4 holes; one for the shaft of the stirrer, second for placing the thermometer, and remaining two for removing the samples.
3) A variable speed motor driven stirrer which rotates at a speed of 25 -150 revolutions per minute.
4) A suitable thermostatically controlled water bath to maintain the temperature of the dissolution medium maintained at 37±0.5°C temperature.

For performing the test, a suitable volume of dissolution medium like distilled water, hydrochloric acid, or phosphate buffer at 7.3 pH (as stated in the individual monograph), is filled in the glass vessel which is submerged in the water bath maintained at 37°C temperature. The tablet or capsule to be tested is introduced in the basket and fitted in position. The motor is started and its revolutions are adjusted according to monograph.

The samples are withdrawn at specified intervals and filtered immediately through a suitable filter medium. Generally, 5ml sample is withdrawn each time, which is replaced with 5ml of medium maintained at 37°C temperature to maintain a constant volume in the vessel. The samples are tested by chemical analysis for the proportion of drug dissolved which should meet the requirements as stated in the monograph.

Apparatus

i) **Apparatus-1 (Basket Type):** A single tablet is placed in a small wire mesh basket attached to the bottom of the shaft connected to a variable speed motor. The basket is immersed in a dissolution medium (as specified in monograph) contained in a 1000ml cylindrical flask with a hemispherical bottom.

The flask is maintained at 37±0.5°C temperature by a constant temperature bath. The motor is adjusted to turn the shaft at the specified speed and sample of the fluid are withdrawn at specified intervals to determine the amount of drug in the solution.

ii) **Apparatus-2 (Paddle Type):** It is same as the apparatus-1, except that the basket is replaced with a paddle. The dosage form is allowed to sink to the bottom of the flask before stirring. For dissolution test, U.S.P. specifies the dissolution test medium and volume, type of apparatus to be used, rpm of the shaft, time limit of the test, and the assay procedure.

Table 2.17: BP, USP, PhEur, JP and PhInt Acceptance Criteria for Dissolution Test of Tablet

Stages	No. of Tablets Tested	Acceptance Criteria
S1	6	Each unit is not less than Q + 5%.
S2	6	Average of 12 units (S1 + S2) is equal to or greater than Q, and no unit is less than Q –15%.
S3	12	Average of 24 units (S1 + S2 + S3) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%.

2.7. SUMMARY

The details given in the chapter can be summarised as follows:

1) Tablets are solid unit dosage form of medicaments with or without suitable diluents and prepared either by moulding or compression.
2) According to the **Indian Pharmacopoeia**, pharmaceutical tablets are solid, flat or biconvex discs, unit dosage form, prepared by compressing drugs or a mixture of drugs, with or without diluents.
3) Substances other than the active ingredients are commonly referred to as **excipients** or **additives**.
4) **Fillers** (or diluents) are inert substances added to increase the bulk to make the tablet of a practical size for compression.
5) **Binders** impart cohesive qualities to the powdered material.
6) **Lubricants** prevent adhesion of the tablet material to the surface of dies and punches, reduce inter-particle friction, facilitate an easy ejection of tablets from the die cavity, and improve the flow rate of tablet granules.

7) **Glidants** improve the flow characteristics of a powder mixture. They are always added in the dry state just prior to compression.

8) Disintegrants are added to a tablet to facilitate its break down or disintegration after administration.

9) Granulation may be defined as a **size enlargement process** which converts small particles into physically stronger and larger agglomerates.

10) The **ideal characteristics of granules** include uniformity, good flow, and compactibility.

11) **Wet granulation** process simply involves wet massing of the powder blend with a granulating liquid, followed by wet sizing and drying.

12) Fluid bed granulation is a process of producing granules in a single equipment utilising spraying of a binder solution against a fluidised powder bed.

13) In dry granulation process, the powder mixture is compressed without the use of heat and solvent.

14) Direct compression method of tablet production involves thorough mixing of dry ingredients followed by their compression into tablets.

15) **Multi-station presses** are also termed as **rotary presses** because the head of the tablet machine that holds the upper punches, dies, and lower punches in place, rotates.

16) **Break marks** or **break lines** are provided so that tablets can be broken in a controlled manner to ensure reproducible doses.

17) **Markings** which help in identifying a preparation are **embossed** (raised on the tablet surface) and **debossed** (indented into the tablet).

18) **Binding in the die** occurs due to conditions facilitating high die-wall friction (**e.g.,** poor lubrication, under-dried granules and a dirty or blemished die).

19) **Picking and Sticking** occurs due to material adhesion to the punch faces.

20) **Capping** occurs before and during compression due to inadequate air removal from the granules in the die cavity.

21) **Lamination** involves splitting of tablet into a number of layers or laminates.

22) Uneven distribution of colour in tablets is termed **mottling** which occurs due to discontinuous granule size distribution.

23) **Coated tablets** are defined as tablets covered with one or more layers of mixture of various substances such as natural or synthetic resins, gums, inactive and insoluble fillers, sugar, plasticisers, polyhydric alcohol, waxes, authorised colouring materials, and sometimes flavouring agents.

24) Opacifiers are very fine inorganic powder used to provide more pastel colours and increase film coverage.

25) Film coating involves deposition of a thin film of polymer surrounding the tablet core.

26) The suitability of the goods or service to the determined qualifications is termed **quality**.

27) **Quality control** involves product testing for defects and timely reporting to management making decision whether to investigate or deny the release.

28) **In-Process Controls** (IPC) involves measures to be taken during the manufacturing process.

29) **Finished Product Controls** (FPC) are performed after a product is manufactured.

2.8. EXERCISE

2.8.1. True or False

1) Sugar coating involves deposition of a thin film of polymer surrounding the tablet core.
2) Sublingual tablets are placed over the tongue and swallowed with water or any other suitable liquid.
3) Substances other than the active ingredients are known as excipients.
4) Film coated tablets contain drugs that undergo best absorption in intestines (and not in gastric).
5) Blistering occurs due to entrapment of gases in films.
6) Blooming occurs as a result of using too much plasticiser or a low molecular weight plasticiser.

2.8.2. Fill in the Blanks

7) __________ tablets are chewed before ingestion.
8) __________ tablets disintegrate in the intestines.
9) __________ test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling, and transporting.
10) ___________ involves splitting of tablet into a number of layers or laminates.
11) __________ occurs due to improper tablet compression.

Answers

1) False
2) False
3) True
4) False
5) True
6) True
7) Chewable
8) Enteric coated
9) Friability
10) Lamination
11) Capping

2.8.3. Very Short Answer Type Questions

1) Write a short note on tablets.
2) Discuss the ideal characteristics of tablets.
3) Discuss binders and lubricants.
4) What is tablet tooling? Discuss its types.
5) Write a short note on tablet coating.
6) Discuss friability.

2.8.4. Short Answer Type Questions

1) Discuss the advantages and disadvantages of tablets.
2) Discuss the hardness test for tablets.
3) Write a short note on dissolution tests.
4) Classify tablets.
5) Write a short note on defects in coating.

2.8.5. Long Answer Type Questions

1) Give a detailed explanation on finished product tests.
2) Write a short note on sugar coating.
3) Discuss compression and processing problems of tablets.
4) Briefly discuss the coating materials used in manufacturing tablets.

CHAPTER 3

Liquid Orals

3.1. LIQUID DOSAGE FORMS

3.1.1. Introduction

Solutions, syrups, suspensions, elixirs, and concentrates are oral liquid dosage forms, which offer exclusive advantages to numerous patients. **For example,** in patients facing problems in swallowing oral solid dosage forms, liquids offer better compliance for the patients and also provide enhanced dosage control against a fixed dose of tablet.

3.1.2. Advantages

The advantages of liquid dosage forms are enlisted below:

1) It is easier to swallow liquids than solids, thus, these dosage forms are more satisfactory and suitable for paediatrics and geriatrics.
2) Solutions get absorbed easily, thus, producing therapeutic response at a faster rate than the solids (which first disintegrates and then dissolves for getting absorbed from the gastrointestinal fluid).
3) In case a drug precipitates from the solution form under acidic conditions of the stomach, it will become moist and will divide into fine particles, allowing rapid absorption.
4) The drug in solutions is uniformly distributed. Whereas, in suspensions or emulsions dose variation may occur resulting from phase separation during storage.
5) If a drug is administered in solution form, gastric irritation is reduced as it immediately gets diluted by the contents present in the gastric area.

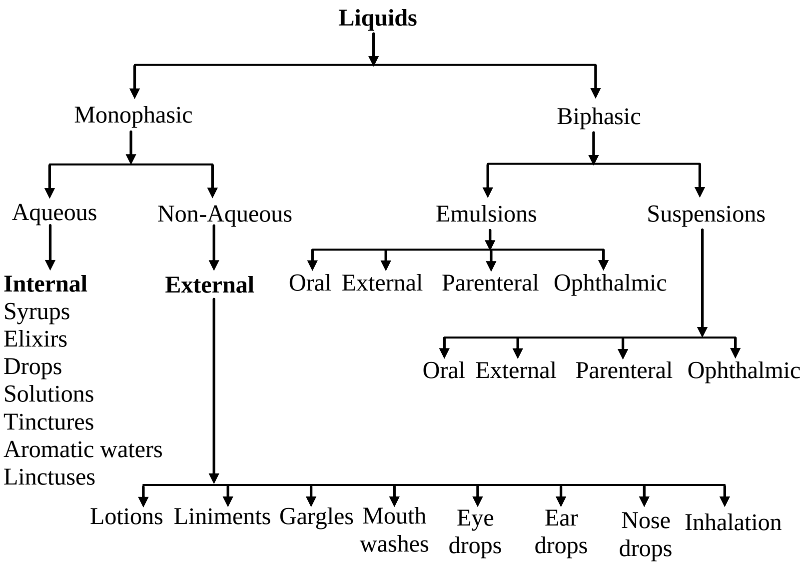
3.1.3. Disadvantages

There are several disadvantages of liquid dosage forms, such as:

1) The transportation and storage of liquids is problematic, as they are bulky. If any container breakage occurs during transportation, the whole formulated product is lost.
2) The ingredients in liquids are liable to deteriorate and lose their potency, thus, they have limited stability. This is the reason why liquid dosage forms have shorter shelf-life.
3) Growth of microorganisms is supported by liquid media, thus, the preparation needs a preservative to be incorporated within it.
4) Dose inaccuracy may occur if a patient takes a dose using household devices, like a teaspoon, etc.
5) These dosage forms also have flavouring and sweetening properties.
6) The dissolved substances in the liquids may result in incompatible interactions.

3.1.4. Classification

Liquid dosage forms on the **basis of their phases** are classified into:



3.1.5. Syrups

Simple syrup is a saturated solution of sucrose formed in purified water with the concentration of 66% w/w sugar. These preparations are viscous and sweet in taste.

Due to the following reasons the syrups are frequently used:

1) It gets hydrolysed partially in reducing sugars, like laevulose and dextrose, thus, retards oxidation.
2) Bacterial growth, fungal growth and growth of molds are the main reasons of decomposition of vegetable material in solution form. Such contaminations are prevented by syrups due to its high osmotic pressure, which prevent decomposition of many vegetable substances.
3) It is advantageous to incorporate syrups in nauseous preparations as the sweetness of sugar makes the preparation palatable.

Syrups are sweet, viscous, concentrated aqueous solutions of sucrose or other sugars. Syrups containing therapeutic or medicinal agents are **medicated syrups**, while syrups with flavours but no medicinal agents are **flavouring** or **flavoured** or **non-medicated syrups**.

3.1.5.1. Formulation

Syrups are formulated using the following components:

1) **Sugar (Sucrose) or Sugar Substitutes (Artificial Sweeteners):** Conventionally, syrups are made using sucrose (in 60-80% concentration) and purified water. Preservatives are not required to be added due to high concentration of sucrose and associated unavailability of water (termed low water activity). But when the sucrose concentration is reduced from the upper limit (**e.g.** through dilution), preservatives need to be added. In some other formulations, non-sucrose bases may replace the traditional syrup.

   Recently, many products have been formulated as medicated sugar-free syrups due to the glycogenetic and cariogenic properties of sucrose. Syrup substitutes should therefore provide an equivalent sweetness, viscosity and preservation to the original syrups. These properties can be achieved with artificial sweeteners (**e.g.,** saccharin sodium and aspartame), non-glycogenetic viscosity modifiers (**e.g.,** methylcellulose and hydroxyethylcellulose), and preservatives (**e.g.,** sodium benzoate, benzoic acid, and parahydroxybenzoate esters).

2) **Preservatives:** As already said, traditional syrups, containing sucrose in high concentrations, does not require preservatives. On the other hand, traditional syrups containing lower concentrations of sucrose and sugar-free syrups in which sucrose has been partially substituted with polyhydric alcohol require preservatives.

   Mixtures of **parahydroxybenzoate esters** (usually methyl hydroxybenzoate and propyl hydroxybenzoate in a ratio of 9:1) are **examples** of commonly used preservatives. The concentration range in which preservatives are used is 0.1-0.2% w/v. The preservative efficacy of these preservatives decreases in the presence of hydrophilic polymers (used to enhance viscosity), due to an interaction of the preservative with the polymer. This effect is annulled by increasing the overall preservative concentration. **Benzoic acid** (0.1-0.2%) and **sodium benzoate** (0.1-0.2%) are some other preservatives used.

3) **Flavours:** These are used when the unpalatable taste of a therapeutic agent is apparent, even if sweetening agents have been added. The flavours are of natural origin (**e.g.,** peppermint, lemon, herbs, and spices) and are available as oils, extracts, spirits, or aqueous solutions. A wide range of synthetic flavours are also available that are advantageous over the natural ones in terms of purity, availability, stability, and solubility.

   Some flavours also have a mild therapeutic activity; **for example**, some antacids contain mint due to its carminative properties. Some flavours offer a taste-masking effect by producing a mild local anaesthetic effect on the taste receptors; **examples** include peppermint oil, chloroform, and menthol.

4) **Colours:** These are natural or synthetic water-soluble, photo-stable ingredients selected according to the flavour of the preparation. **For example**, mint-flavoured formulations are green coloured; banana-flavoured formulations are yellow coloured. Such ingredients should not interact chemically or physically with other components of the formulation.

3.1.5.2. Manufacturing

Specific methods adopted for the preparation of any product depends on the physiochemical properties of the substance to be used in the formulation. The preparative methods for syrups are:

1) **Hot Process:** This method is not suitable for heat-labile or volatile active ingredients. In this method, firstly, sucrose is accurately weighed in a tarred dish and then dissolved in purified water. The solution is further heated on a water bath to completely dissolve the sucrose in water. The obtained product is strained completely and added with the desired quantity of boiling purified water to make up the required volume of the product. During the formulation of syrup, precautions should be taken while heating because overheating can cause sucrose inversion. An instrument known as **saccharometer** is used for determining the specific gravity of the syrup. Syrups prepared by this method include syrup I.P., acacia syrup NF, cocoa syrup NF, and tolu syrup I.P.

2) **Percolation (Cold Process):** For preparing U.S.P. syrup, this method is used. In this process, sucrose is placed in a percolator and an aqueous solution or purified water is allowed to pass over this sucrose slowly. Loosely compressed cotton is placed and packed upon the percolator neck. The dissolution rate of sucrose is dependent on the

percolation rate. To dissolve the sucrose completely, the percolate is returned back to the percolator. With the aid of water, the percolator is washed from with in and the cotton plug is also washed. Then the final volume of the preparation is made up as needed.

3) **Addition of Medicating or Flavouring Liquid to Syrup:** This method is used for preparing syrups containing fluid extracts, tinctures, or other liquids. These liquids contain alcohol to facilitate the dissolution of resinous and oleo resinous substances; but when added to the syrup, these liquids may precipitate the substances soluble in alcohol as they get diluted with water. This alcohol also functions as a preservative in these syrups.

4) **Agitation without Heat:** This preparative method is used when the active constituent is a heat-labile substance. In this method, sucrose and other required ingredients are solubilised in purified water in a bottle having the volume twice than that required for the syrup to facilitate thorough shaking. The bottle is closed by the stopper to avoid any contamination and water loss through evaporation. When not being agitated the bottle is rested on its side. For the formulation of syrups by this method on a large scale, glass lined tanks fitted with mechanical agitators are used. An **example** of syrup prepared by this method includes ferrous sulphate syrup U.S.P.

3.1.6. Elixirs

Elixirs are clear, sweetened, aromatic, hydroalcoholic liquids intended for oral use. They provide a palatable means of administering potent or nauseous drugs. They are less sweet and viscous than syrups and may contain less or no sucrose.

Generally, some substances are not stable in the form of mixtures, thus, are needed to be prepared instantaneously before administering to the patient by adding a suitable solvent to the dry granule form of the drugs. These drugs are generally potent and nauseous. In the form of elixirs, these drugs are flavoured satisfyingly and coloured pleasantly. Basically, elixirs are clear preparations and drugs in liquid form to be administered orally.

3.1.6.1. Formulation

Elixirs are formulated using the following components:

1) **Alcohol:** It is used as a co-solvent to ensure the solubility of all ingredients. The concentration of alcohol to be added depends on the formulation. Generally, its concentration is greater than 10% v/v; however, in some preparations, its concentration may be greater than 40% v/v.

2) **Polyol Co-Solvents:** Propylene glycol and glycerol are the polyol co-solvents used in elixirs to enhance the solubility of the therapeutic agent and related excipients. These ingredients allow the concentration of alcohol to be reduced. The concentration of co-solvents depends on the concentration of alcohol added, the type of co-solvent used, and the solubility of other ingredients in the alcohol/co-solvent blend.

3) **Sweetening Agents:** The sucrose concentration in elixirs is less than that in syrups; thus sweetening agents are required to be added in elixirs. The types of sweetening agents used are similar to those used in syrups, **e.g.,** sorbitol solution and artificial sweeteners such as saccharin sodium. However, the high concentration of alcohol forbids the addition of high concentration of sucrose due to the limited solubility of this sweetening agent in the elixir vehicle. To prevent this problem, saccharin sodium is used in the elixir in small quantities to exhibit the required solubility profile.

4) **Flavours and Colours:** These are added to pharmaceutical elixirs for increasing the palatability and enhancing the visual qualities of the formulation. Alcohol added in the formulation allows the use of flavours and colours that exhibit inappropriate solubility in aqueous solution.
5) **Preservatives:** Pharmaceutical elixirs containing alcohol in concentration greater than 12% v/v are not added with preservatives, as alcohol already possesses antimicrobial properties.
6) **Viscosity-Enhancing Agents:** Hydrophilic polymers may be added to optimise the rheological properties of elixirs.

Since some of the components of elixirs are volatile in nature, they should be packed in tight containers and stored at low temperatures.

3.1.6.2. Manufacturing

The preparation method for elixirs is the **simple dissolution method** involving the following steps:

1) In this method, either an admixture of two or more liquid components is used or the components are dissolved by agitation.
2) The ingredients are dissolved in the respective solvents, **for example**, water is used as a solvent for the water-soluble ingredients, and alcohol is used as a solvent for the alcohol-soluble ingredients.
3) **Always the aqueous solution is added to the alcoholic solution** for maintaining the ideal alcoholic strength and preventing the separation of alcohol-soluble ingredients.
4) The desired volume is adjusted using the vehicle or solvent specified in the formulation.
5) At this point, reduction in alcoholic strength is noted which leads to the separation of a few flavouring agents, thus, the product may not be found clear.
6) In such a case, the elixir preparation is kept aside for some time so that the hydroalcoholic solvent saturates resulting in the cluster of globules.
7) Filtration facilitates the removal of these globules.
8) To absorb the excess oil and removing it from the elixir solution, up to 3% of talc is used.
9) Filtration yields a bright and clear product.

3.1.7. Suspensions

Suspensions are biphasic liquid preparations containing finely divided 0.5-5.0 micron solid drug particles (**discontinuous phase**) dispersed or suspended throughout a liquid or semi-solid vehicle (**continuous phase**). Suspensions are intended for oral administration, external application, or parenteral use. The palatability of oral suspensions of certain drugs (like chloramphenicol palmitate) can be enhanced using the drug derivative.

A pharmaceutical suspension is a coarse dispersion in which insoluble solids are suspended in a liquid medium. In suspensions, water or water-based vehicles are normally used as a liquid medium, in which the insoluble solids (size ranging from 10-1000µm) are suspended.

3.1.7.1. Formulation

Suspensions are formulated using the following components:

1) **Wetting Agents:** These agents are surfactants that decrease the solid-liquid interfacial tension and contact angle between the solid particles and the liquid vehicle. The best range for wetting and spreading by surfactants is between a

Hydrophilic-Lipophilic Balance (HLB) value of 7-10; although surfactants with values higher than 10 are often used for this purpose. Polyoxyalkyl ethers, polyoxyalkyl phenyl ethers, polyoxy hydrogenate castor oil, sorbitan esters, polyoxy sorbitan esters, docusate sodium, and sodium lauryl sulphate are the **examples** of some surfactants commonly used as wetting agents.

2) **Deflocculants and Dispersing Agents:** These agents are used to produce deflocculated suspensions. **KCl** (an electrolyte) or **sodium hexametaphosphate** (a polyelectrolyte) creates a strong mutual repulsion between the suspended particles and act as a dispersing agent. Also **gelatin** (a strongly hydrated hydrophilic protective colloid) acts as a dispersing agent by getting adsorbed on the surface of the suspended particles and increasing the affinity for water compared to mutual attraction of adjacent particles for each other. A **non-ionic polymer or surfactant** aids the dispersion of insoluble phase by creating steric hindrance and preventing the adjacent suspended particles from joining with each other. Tween, spans, carbowaxes, and pluronics are the **examples** of commonly used dispersing agents.

3) **Flocculation Agents:** These agents are neutral electrolytes that can reduce the zeta potential of suspended charged particles to zero. Monovalent ions (**e.g.,** sodium or potassium chloride) in small concentrations (0.01-1%) induce flocculation of weakly charged, water-insoluble, organic non-electrolytes. Water-soluble divalent or trivalent ions (**e.g.,** calcium salts, aluminium chloride, sulphates, citrates and potassium biphosphate) are used in similar concentrations (i.e., 0.01%) for insoluble, highly charged, polyelectrolyte species.

4) **Suspending Agents:** These agents act as an energy barrier that minimises the inter-particle attraction, thus delays the settling and agglomeration of particles. The general choice of suspending agents includes protective colloids and viscosity-inducing agents. Protective colloids are different from surfactants as they do not reduce the interfacial tension. Their solutions have different viscosity and are used in concentrations higher than the surfactants. They are also different from other agents as their effect is due to their ability to increase the zeta potential and also their ability to form a mechanical barrier or sheath around the particles. There are many agents which act as protective colloids in low concentration (<0.1%) and as viscosity builders in higher concentrations (>0.1%). **Examples** of some commonly used suspending agents in pharmaceutical suspension are:

   i) **Modified Cellulose Polymers:** Anionic sodium carboxymethylcellulose, non-ionic methylcellulose, and hydroxypropylmethylcellulose are the **examples** of some widely used modified cellular polymers. Sodium carboxymethylcellulose in parenteral preparations is used in concentrations of 0.5% and in oral formulations is used in higher concentrations. It is incompatible with many electrolytes and complexes with some surfactants. Methylcellulose and hydroxypropylmethylcellulose turns into gels when heated and get affected by electrolytes. Polyacrylic acid (a synthetic polymer) is used in external lotions and gel preparations. It is highly sensitive to electrolytes, but is used in both aqueous and non-aqueous systems.

   ii) **Clays:** These agents hydrate in water to a high degree and form colloidal dispersions with high viscosities. Clays should always be added to the water with high shear to effect uniform dispersion and maximum hydration. The pH of aqueous clay dispersions lies in the range of 8.5-9.5; therefore, they also have some acid-neutralising capacity. The viscosity of aqueous dispersions of these agents depends on the type and amount of solids dispersed. Clays in 5-10% concentrations form firm opaque gels.

5) **Organoleptic Agents:** These agents include the preservative, colour, smell and flavour; they may materially affect the characteristics of the suspension system. Most colours are used in small quantities and are compatible. Flavours and smells are used similarly and are also compatible with the vehicle. Clay suspensions and gels are the best media for mold and bacterial growth, and should be preserved with non-ionic antimicrobial preservatives. The paraben esters and benzoates are useful, but cationic quaternary preservatives are ineffective.

3.1.7.2. Manufacturing

There are two ways of preparing suspensions:

1) Small scale preparation, and
2) Large scale preparation.

Small Scale Preparation

Step 1: The insoluble materials and a vehicle with the wetting agent are grinded or levigated together in a mortar to form a smooth paste.

Step 2: The soluble ingredients are dissolved in small quantity of the vehicle before being blended with the smooth paste obtained in step 1 to form slurry.

Step 3: The slurry obtained is moved to a graduated cylinder and the mortar is washed with succeeding fractions of the vehicle.

Step 4: The solid particles present are carefully observed for:

1) If they are suspended in a structured vehicle, or
2) If they are flocculated, or
3) If they are flocculated before being suspended.

Step 5: Finally, the volume of the dispersion is made up to the desired volume.

Large Scale Preparation

In large scale preparation, the steps are performed in the same sequence as in small scale. However, the processes involved in these steps are performed using more advanced equipment like dough mixer, pony mixers, etc. Equipment like micropulveriser, fluid energy grinding, or controlled precipitation can be employed in **dry milling process for reducing the particle size** prior to suspension. Homogeniser or colloid mills are generally employed in **wet milling process**. The quantity and quality of suspending agents play an important role since the equipment selection is based on the flow characteristics of the suspension. The suspending agent is either mixed with dry powder or suspended in a vehicle before adding to the preparation.

In large scale preparations, the **steps** involved are:

1) The fine drug particles are soaked in a small fraction of water (containing the wetting agent).
2) These particles are then left undisturbed for several hours to discharge the trapped air.
3) The suspending agent should be simultaneously dissolved or dispersed in the main fraction of the external phase and left undisturbed until it gets completely hydrated.
4) The wetted drug particles are then slowly transferred to the major fraction of the dissolved suspending agent.
5) In order to avoid any alteration in the particle charge, excipients like electrolytes or buffers should be added carefully.
6) Preservatives, flavouring and colouring agents are later included in the preparation.
7) Once all the ingredients are added, the mixture is subjected to homogenisers or ultrasonic devices for reducing the size of agglomerated particles.

3.1.8. Emulsions

A pharmaceutical emulsion is a biphasic liquid preparation containing two immiscible liquids, one of which is dispersed as minute globules into the other. The liquid in the form of minute globules is the **dispersed phase**, while the liquid containing the dispersed globules is the **continuous phase**.

An emulsifying agent is added to disperse two immiscible liquids for a prolonged time period. This agent covers the globules to scatter them indefinitely in the continuous phase, resulting in a stable emulsion.

The diameter of globules in an emulsion lies in the range of 0.25-25µm. The **coarse emulsions** have large-sized globules, whereas **fine emulsions** have mean diameter below 5µm. The **micro-emulsions** have globules of diameter as small as 10nm, and are milky and transparent in appearance.

3.1.8.1. Formulation

Following ingredients are included in the formulation of emulsion:

1) **Oil Phase:** This phase (medicament or vehicle) is made up of fixed oil, mineral oil, volatile oil, or oleo resin type that is used for preparation of emulsion. For preparing primary emulsion, the ratio of oil, water and emulgent to be used depends on the origin.
2) **Aqueous Phase:** Due to increased risk of microbial contamination, freshly boiled and cooled purified water is used.
3) **Antioxidants:** These agents prevent the oil from getting oxidised during its shelf-life; hence enhance the stability of oil phase in the emulsion. Butylated hydroxyanisole (BHA), Butylated hydroxytoluene (BHT), and tocopherol are the **examples** of antioxidants used in emulsions.
4) **Flavouring Agents:** These agents enhance the palatability of the final product. Pineapple, orange, chocolate, and mint flavours are commonly used.
5) **Colouring Agents:** These agents are used for identifying the preparation, and enhancing its aesthetic appeal. Erythrosine, tartrazine, etc. colours approved by the Food, Drug and Cosmetic Act are used as colouring agents.
6) **Perfumes:** These agents are added in preparations meant for external use, like creams.
7) **Preservatives:** Following are some characteristics of preservatives appropriate for use in emulsions:
    i) They should show a wide spectrum of activity against all bacteria, yeast, and moulds.
    ii) They should exhibit bactericidal activity instead of bacteriostatic.
    iii) They should be free from toxic, irritant, and sensitising activity.
    iv) They should be highly soluble in water. Since microorganisms grow in the aqueous phase, they should have a low o/w partition coefficient. The difficulty to preserve a product increases with the polarity of oil phase.
    v) They should be compatible with other ingredients of the preparation and also with the container.
    vi) They should be stable and effective over a wide range of pH and temperature.
    vii) They should be free from colour and odour.
    viii) They should retain their activity even in the presence of large number of microorganisms.

Benzoic acid (0.1-0.2%), methyl and propyl paraben (0.1-0.2%), chloroform (0.25%), chlorocresol (0.1%), and phenyl mercuric nitrate (0.004-0.01%) are the **examples** of preservatives used in emulsions.

8) **Emulsifying Agents (Emulgents):** Stable emulsions can be produced by using emulsifying agents. These agents reduce the interfacial tension between the two phases and then separate the globules by creating a barrier at the interface.

Surfactants are mainly used as emulsifying agents. The solubility of emulsifying agent determines the kind of emulsion to be prepared. By using water-soluble hydrophilic emulsifying agents, where water is the continuous phase, an o/w emulsion is prepared. In contrast by using more oil-soluble emulsifying agents, where oil is the continuous phase, w/o emulsion is prepared.

The phenomenon in which any added substance modifies the solubility of the emulsifying agent and change the emulsion type is known as **phase inversion**.

Usually, an ideal emulsifying agent is **colourless**, **odourless**, **tasteless**, **non-toxic**, **non-irritant**, and is capable of producing **stable emulsions at low concentrations**.

The efficient emulsifying agents can be grouped into **three categories**:

i) **Naturally Occurring Emulsifying Agents:** These agents are obtained from vegetables or animals. Since these agents are prone to microbial contamination and degradation, their quality differs from batch to batch. Some of the **examples** of naturally occurring emulsifying agents are:
   a) **Polysaccharides:** In the preparation of an oral emulsion, **acacia** is proven a best emulsifying agent due to its ability to form a thick film at the oil-water interface which provides a barrier against coalescence. But, acacia is too sticky to be used externally; thus, **tragacanth** is used as a viscosity enhancer which also prevents creaming. **Starch**, **pectin**, and **carrageenan** are some of the popularly used emulsifying agents in this category.

   b) **Sterol-Containing Substances:** Beeswax, wool fat, and wool alcohols are some of the **examples** of emulsifying agents of this category which form w/o emulsions.

ii) **Semisynthetic Polysaccharides:** Given below are the semisynthetic polysaccharides used:
   a) **Methyl cellulose** has a low viscosity, and can be used as emulgents and emulsion stabilisers. It is used in 2% concentration for emulsifying mineral and vegetable oils.

   b) **SCMC** has a medium viscosity, and is used in 0.5-1% concentration as an emulsion stabiliser.

iii) **Synthetic Surfactants:** These emulsifying agents are divided as follows on the basis of their ionic properties:
   a) **Anionic Surfactants:** The surface active anions present in these organic salts (i.e., anionic surfactants) provide them their surface-active properties. These may be non-compliant with some of the organic and inorganic cations, and with other large organic cations (like cetrimide). These are o/w emulsifying agents meant for topical applications, and are effective in ionised forms. Emulsions comprising anionic surfactants are more stable at alkaline pH.

Few popular **examples** of pharmaceutically used anionic surfactants are:

- Alkali metal and ammonium soaps, like sodium stearate (o/w).
- Soaps of divalent and trivalent metals, like calcium oleate (w/o).
- Amine soaps, like triethanolamine oleate (o/w).
- Alkyl sulphates, like sodium lauryl sulphate (o/w).

b) **Cationic Surfactants:** Since these quaternary ammonium compounds comprise of surface-active cations, they show sensitivity towards anionic surfactants and drugs. These are employed for preparing o/w emulsions intended for topical use. These surfactants are also more effective in their ionised forms and their emulsions are more stable at acidic pH. Few cationic surfactants like cetrimide and benzalkonium chloride possess antimicrobial activity.

c) **Non-Ionic Surfactants:** These synthetic agents, constituting the largest group of surfactants, are required for producing both o/w or w/o emulsions for external as well as internal applications. These surfactants are compliant with anionic and cationic substances. These remain unaffected to pH change. The emulsions formed depend on the balance between hydrophilic and lipophilic groups provided by the HLB number. Glycol esters, glycerol esters, macrogol ethers, sorbitan esters, and polysorbates are few of the popular **examples** of non-ionic surfactants.

iv) **Inorganic Agents:** These finely divided solids having balanced hydrophobic and hydrophilic properties get adsorbed at oil-water interface and form a coherent film which prevents the coalescence of dispersed globules. Formation of w/o emulsion occurs, when solid particles are wetted by the oil. Milk of magnesia (10-20%), magnesium oxide (5-10%), and magnesium aluminium silicate (1%) are the **examples** of inorganic agents.

v) **Alcohols:** Given below are the alcohols used in the preparation of emulsions:

a) **Carbowaxes:** These are used in ointment and cream preparation. The substances of molecular weight 200-700 are viscous, light-coloured, and hygroscopic liquids; while the substances having molecular weight more than 1000 are wax-like solids.

b) **Cholesterol:** It is used along with other emulsifying agents to form a stable emulsion.

c) Lecithin.

3.1.8.2. Manufacturing

Emulsions can be prepared by either of the two ways:

1) Small scale preparation, and
2) Large scale preparation.

Small Scale Preparation

The mortar and pestle is extensively used in the small scale preparation of emulsions. It provides a simple and economic means of preparing small quantities of emulsions. It is generally employed for batch process. Emulsifying agents like acacia and tragacanth are usually added to stabilise the small scale emulsions. Two simple **methods involved** in the preparation of emulsions using mortar and pestle are:

1) Dry gum/continental method, and
2) Wet gum method.

Dry Gum/Continental Method

This method is used when emulsions are to be prepared using dry gum emulgents (particularly, acacia). The amount of gum to be used is decided based on the oil nature. The formulae suitable for primary emulsions of different types of oils are given in the **table 3.1**:

Table 3.1: Formulae for Primary Emulsion

Types of Oils	Oil	Gum	Water
1) Fixed Oils (**e.g.,** liquid paraffin, castor oil, cod liver oil, olive oil, almond oil)	4	1	2
2) Volatile Oils (**e.g.,** turpentine oil, oil of cubebs, sandalwood oil)	2	1	2
3) Oleo-Resinous Substances (**e.g.,** balsam of Peru)	1	1	2

The **steps** involved in dry gum method are:

1) The oil to be used is measured and triturated with acacia using a mortar.
2) The aqueous vehicle in quantity twice that of the gum is added to the triturated mass and trituration is continued to obtain a thick mass.
3) This is the **primary emulsion** which gives a clicking sound on rapid trituration.
4) The remaining quantity of aqueous vehicle is added to this primary emulsion and triturated.
5) The emulsion so formed is transferred to a measure and volume is adjusted with the leftover content in the mortar. This is done by rinsing the mortar with aqueous vehicle.
6) Now the product obtained is stirred to make a uniform emulsion.
7) Since acacia may contain dust, the emulsion obtained should be clarified either by straining through muslin cloth or by allowing the impurities to settle so that the clear product can be decanted.

The dry gum method is much preferred due to its simplicity and it also does not require skilled pharmacist. This method is also quick and is suitable for dispensing purposes.

Wet Gum Method

This method involves the **same proportion of oil:gum:water** for primary emulsion as in the dry gum method. In this method, acacia is triturated with water till a mucilage is obtained. To this mucilage, oil is added at intervals with constant and rapid trituration which is continued even when all of the oil has been added. The emulsion is completed following the usual procedure.

The wet gum method is tedious and requires skilled pharmacists.

Large Scale Preparation

The large scale preparation of an emulsion is similar to the small scale preparation. The **steps** involved are:

1) The oil phase (containing hydrophobic constituents) and water phase (containing hydrophilic constituents) are heated separately in large tanks.
2) If waxes are present, both the phases are heated above the highest melting point of any component present.
3) Then, one phase is pumped into the tank containing the other phase.
4) Agitation is continued during the addition.
5) The emulsion is cooled and homogenised.

3.1.9. Formulation Considerations

The following factors should be taken into consideration while formulating a potent, stable, and appealing liquid formulation:

1) **Solubility:** On dissolving a solute in a solvent, two types of interactions occur; one is the **intramolecular force of attraction** between the solute molecules and the other is the **intermolecular force of attraction** between the solute and solvent molecules. When a solute dissolves, the cohesive force (intramolecular force) is overcome by the adhesive force (force of attraction between the solute and solvent molecules).

   Thus, the solute -solute forces and the solvent -solvent forces break to achieve the solute-solvent forces of attraction. Solubility of a drug in a solvent is the maximum concentration to which a solution should be prepared with that drug and solvent. The expression of solubility as per the I.P. is given in **table 3.2**:

Table 3.2: Expression of Solubility According to Indian Pharmacopoeia

Descriptive Phrase	Approximate Quantities of Solvent by Volume (ml) for 1 Part of Solute by Weight (1gm)
Very soluble	Less than 1 part
Freely soluble	From 1 to 10 parts
Soluble	From 10 to 30 parts
Sparingly soluble	From 30 to 100 parts
Slightly soluble	From 100 to 1000 parts
Very slightly soluble	From 1000 to 10,000 parts
Practically insoluble	More than 10,000 parts

2) **Preservatives:** These are added in pharmaceutical solutions to control its microbial bioburden. An ideal preservative should:
   i) Possess a broad spectrum of antimicrobial activity against gram -positive and gram-negative bacteria and fungi.
   ii) Remain chemically and physically stable throughout the product shelf-life.
   iii) Have low level of toxicity.

   Factors Affecting Preservative Efficacy in Oral Solutions

   The activity of a preservative in a formulation depends on the correct form of preservative added in required concentration to inhibit microbial growth. This is termed the **Minimum Inhibitory Concentration** (MIC). In many solution formulations, the preservative concentration is affected by the presence of other excipients and also by the formulation pH. Discussed below are the factors directly affecting the efficacy of preservatives in oral solutions:

   i) **Formulation pH:** In some aqueous formulations, the use of acidic preservatives, **e.g.,** benzoic acid, sorbic acid, should be avoided. The antimicrobial properties are the result of the unionised form of the preservative, the degree of ionisation being a function of the pH of the formulation. The activity of the unionised form of the acid is the result of its ability to diffuse across the outer membrane of the microorganism and then into the cytoplasm. The neutral conditions within the cytoplasm allow the preservative to dissociate, thereby resulting in acidification of the cytoplasm and inhibition of growth.

   ii) **Presence of Micelles:** In a preservative exhibiting lipophilic properties (**for example,** the unionised form of acidic preservatives, phenolics, parabens), these species get partitioned into micelle, thus the effective concentration of preservative in solution decreases. This problem can be overcome by increasing the preservative concentration so that the free concentration within the formulation is greater than or equal to the MIC of the preservative.

iii) **Presence of Hydrophilic Polymers:** The free concentration of preservative in oral solution formulations reduces in the presence of hydrophilic polymers, **e.g.,** polyvinylpyrrolidone, methylcellulose. This is due to the ability of the preservative to chemically interact with the dissolved polymer. As described above, this problem is addressed by increasing the preservative concentration in the formulation.

In some cases, the preservative may be incompatible with hydrophilic polymers in the formulation due to an electrostatic interaction. Therefore, cationic, hydrophilic polymers should not be used with acidic preservatives in oral solution formulations.

3) **Stability:** It is the extent to which a product retains its properties and characteristics (same as those it possessed at the time of manufacturing) within the specified limits and throughout its shelf-life (period of storage and use). Product stability is influenced by the factors like temperature, light, pH, humidity, and other factors related to manufacturing.

Table 3.3 enlists some of the conditions of physical instability for different dosage forms:

Table 3.3: Physical Instability for All Dosage Forms

Dosage Forms	Evidence of Physical Instability
Solid Dosage Forms	
Hard and soft gelatin capsules	Shell either hardens or softens; release of gas such as a distended paper seal.
Coated tablets	The coating becomes cracked, mottled, or tacky; the tablets become clumped.
Uncoated tablets	The tablets become cracked, mottled, swelled, discoloured, and fused.
Dry powders and granules	Cakes into hard masses; gets discoloured.
Effervescent tablets, granules or powders	The mass becomes swelled; gas pressure develops.
Liquid Dosage Forms	
Solutions, elixirs and syrups	Precipitation occurs; gases are formed; microbial growth occurs.
Emulsions	The oily phase separates; is not easily dispersed.
Suspensions	A caked solid phase is formed that cannot be re-suspended even after shaking; formation of large crystals.
Sterile liquids (parenteral solutions or ophthalmic solutions)	The colour changes; cloudiness appears; surface film is formed.
Tinctures	Precipitation occurs.

4) **Organoleptic Properties:** Some standards are available for a given formulation to select appropriate flavour and colour. **For example,** a sweet active ingredient should be flavoured in fruit or vanilla flavour and coloured red; a sour active ingredient should be flavoured in citrus flavour and coloured orange.

3.1.10. Manufacturing Considerations

The following factors should be taken into consideration while manufacturing an oral liquid formulation:

1) **Raw Materials:** Before the manufacturing process is started, the raw materials to be used should be tested for their identity, purity, uniformity, and freedom from microbial contamination. Also the processes of size reduction, milling or sterilisation are required before manufacturing. In case of oral liquids, the water used should meet the standards specified in the Pharmacopoeia, and the water should be obtained by distillation or ion exchange treatment.

2) **Equipment:** The following types of equipment should be used while manufacturing oral liquid solutions:
   i) Stainless steel mixing tanks and storage tanks fitted with an agitator.
   ii) Measuring devices for large and small volumes of solids and liquids.
   iii) A system for filtration.

   Tanks (made up of stainless steel) should be jacketed to allow heating or cooling of the contents. They are covered and equipped with transparent charging ports and illumination so that the contents can be easily observed. If a bulk liquid is to be compounded, tanks having an in-built agitation system are used. This compounded liquid is then transported to the filling line, either by filling manually into the portable transport tanks or by pumping through a liquid delivery unit.

   All the equipment and pipelines should be easy to disassemble, clean and sanitise. Before use, all the equipment should be thoroughly cleaned and sanitised with disinfectants, **e.g.,** dilute solutions of hydrogen peroxide, phenol derivatives, and peracetic acid. All the equipment should be sterilised with alcohol, boiling water, autoclaving, or steam or dry heat.

3) **Method of Manufacture:** Purified water is heated at 50-60°C temperature so that the solid solutes added to warm water dissolve easily by stirring. Additives are dissolved separately and then added to the bulk mixture. Large volume liquids (such as glycerol and sorbitol solution) are added and mixed until homogeneous. Colouring agents are first dissolved in a small amount of water and then added to the bulk mixture.

   Flavouring agents are added at low temperature (especially at the end), as the flavours are mostly volatile by nature. The flavouring agents are dissolved in a small amount of alcohol, propylene glycol or glycerine and then added to the bulk mixture. The final volume is made up with purified water up to the mark. The mixture is thoroughly agitated until homogeneity is obtained. Finally, the product is filtered to obtain a clear solution.

4) **Containers, Labelling, and Storage:** Glass or plastic bottles are used for holding the oral liquids. As the containers are in direct contact with the product, they should be cleaned before being filled. To maintain the stability of the formulation, the containers should not undergo any physical or chemical interaction with the product as it may alter the strength, quality, or purity of the product beyond the specified standards. The manufacturer takes into consideration all these concerns while selecting a suitable container.

   The product after filling into containers is shipped to pharmacies for dispensing. The shipping container is larger than the volume needed by the patient; this demands repackaging into proper containers for the patient by the pharmacist. At the current time, liquids are repackaged into plastic, light-resistant bottles. Packaging and dispensing should always be done as per the manufacturer's recommendation, since some of the products are required to be dispensed in glass bottles. The container caps should be tightly closed to avoid product loss or premature degradation of the drug or any other components.

The original container of the formulation (i.e., the one at the time of manufacturing) should bear an expiration date. The pharmacist should take necessary precautions to preserve the strength, quality, and purity of repackaged drugs. The pharmacist should place the beyond-use date on the label of the product container when it is dispensed to the patient.

If the product is repackaged and held in the pharmacy before being dispensed, the product should be stored in a humidity-controlled environment at the temperature specified by the manufacturer. While dispensing the product to the patient or care-giver, the pharmacist should instruct them to store the product under the same conditions. The product is best stored in a dark place away from direct sunlight. Drugs and all the toxic compounds should be stored in places beyond the reach of children and mentally impaired individuals.

5) **Quality Control/Quality Assurance:** Oral liquid dosage forms have specifications for drug substances and drug products, and these specifications should be followed by the manufacturers to establish batch to batch uniformity and to safeguard the product stability throughout the shelf-life. An established and validated stability-indicating assay method is the key for quality control or quality assurance.

   Content uniformity, viscosity, pH, colour, and odour are some parameters of liquid dosage forms being monitored regularly. The oral liquids are also added with a preservative, whose efficacy should also be monitored throughout the product shelf-life. In case of suspensions and emulsions, the flow properties and particle size and how they are affected by storage should be monitored.

3.1.11. Filling of Liquid Orals

Packaging of a product not only involves selection of a suitable container, but also it's filling into the container through further processing and handling procedures which may have an effect on the long-term stability of the product. For a small batch, filling is done manually; while for an industrial scale, filling is done with semi-automatic or automatic equipment containing thousands of product units. Such equipment are used for assembling the container, applying the closure, putting label, and if necessary placing the product into a carton.

Suspensions, especially those not containing a suspending agent are filled with much difficulty. If a product of the correct composition is to be packaged, the bulk should be continuously and thoroughly stirred throughout the filling operation. Special attention should be paid to the corners of the container where stirring is relatively ineffective and the solid may accumulate.

The transit time of the product from the bulk to the final container should be short to minimise sedimentation in the filling head. Accumulation of solid not only results in inaccurate composition of the filled product, but may also block the head mechanism. Filling of solutions also is a difficult task if the surface tension is low and the foam stability is high. The liquid jetting from the filling head into the product already in the bottle causes agitation and formation of a persistent froth. The vacuum line should suck off to the trap a large volume of froth before the liquid product is filled in the bottle. A variant of the standard head is being used to avoid this problem. In this variant, liquid jets onto the container wall and flows gently as a thin film without frothing. These types of head fill the container to a given distance below the rim of the neck, thus volumetric accuracy of filling depends on the observance of rigid tolerances during the manufacture of container. It is also not easy to vary the filling volume from the nominal value for the container.

If greater versatility is required, machine driven automatic syringes are used, particularly in large scale ampoule filling. The syringe size and plunger stroke determine the volume transferred to the container.

When the emulsions cool down completely, they are pumped into storage tanks, which can be transported and connected to filling lines. During the pumping process special care should be taken to avoid introducing air into the product.

Also, shear should be avoided as it might break the emulsion or change its viscosity or other physical characteristics. Emulsion products are filled by weight or volume into bottles or tubes. An over-aerated product will have too much volume to fit the correct amount into the container.

3.1.12. Packaging of Liquid Orals

Draughts, elixirs, emulsions, some types of gargles, oral gels, linctuses, mixtures, paediatric drops, and syrups are the **examples** of common liquid oral preparations. These products are mostly dispensed in the **metric medicine bottle** made as per the British Standard Specification. These bottles have the following **properties**:

1) They are made up of soda-lime glass.
2) They are ovoid in section but the back portion is flatter than the front; thus enables the bottle to rest steadily on the bench while fixing the label to the bowed front and wrapping the container.
3) They do not have any imprinted graduations as on some of the imperial bottles and also those which are not accurate enough for measuring dose volumes.
4) They have a special lip for ease of pouring.
5) They can be fitted with either of the two types of screw closure:
    i) **White moulded polypropylene** to contain within a crab's claw sealing ring that hides the irregularities in the bottle lip and does not require a wad or liner. Polypropylene due to its low permeability to gases and vapours is widely used as a closure material.
    ii) **Black thermosetting plastic** requires an insert with a flexible wad (of wood pulp) faced with an impervious liner (a plastic film or a resin-impregnated paper). The wad should be sufficiently stout to resist distortion or fracture when the cap is tightened repetitively.

    The bottles prior to use should be checked for the presence of chips or cracks on its neck, which if present will prevent the closure from making an impervious seal.
6) They are generally colourless.
7) Light-resistant, emulsion-type, or plastics bottles can be used or the label should have an instruction for the patient to store away from light, if the preparation contains light-sensitive ingredients.
8) They are available in six sizes, i.e., 50, 100, 150, 200, 300, and 500ml.

The packaging requirements for **suspensions** are:

1) The suspensions should be packed in wide-mouthed containers having sufficient airspace above the liquid so that it can be thoroughly mixed by shaking and can be easily poured.
2) Suspension should be shaken before each use so that the solid uniformly distributes in the vehicle, thus it provides uniform and correct dosage.

Emulsions meant for internal use are packed in flat amber medical bottles; whereas emulsions for external use such as creams are packed in collapsible tubes, and liniments and lotions are packed in fluted amber bottles (**table 3.4**). Pharmaceutical bottles are available in a variety of different sizes. Thus, it is necessary to select a container of accurate size for dispensing emulsions. Container should not be too large in size due to the reasons of cost and appearance. Bottles having enough space to allow the shaking of the emulsions before use should be selected.

Table 3.4: Summary of Packaging for Pharmaceutical Emulsions

Emulsion Type	Containers	Typical Sizes
Oral emulsions	Amber flat medical bottle (wide-mouthed)	50ml, 100ml, 150ml, 200ml, 300ml, and 500ml.
External emulsions (applications and lotions)	Amber fluted medical bottle (wide-mouthed)	50ml, 100ml, and 200ml.

3.1.13. Evaluation of Liquid Orals in Pharmacopoeia

After the oral liquid products are manufactured and packaged, their physicochemical properties should lie within the specified standards during the shelf-life period. Any deviation from these standards will invalidate the pharmaceutical claims of the product; therefore, an essential aspect of product manufacture is the assurance and control of quality. The quality of pharmaceutical products can be assured by following a thorough analysis of their physicochemical properties, after their manufacture as well as during their storage.

The types of analysis to be applied to the pharmaceutical products depend on the product nature; however, some physicochemical parameters are examined and quantified commonly in all the pharmaceutical products. All the pharmaceutical products have finished product specifications, i.e., specifications for the properties of the products after manufacture and throughout the storage period. These specifications are a range to allow some flexibility in manufacture and to ensure that the product is safe and efficacious to be used clinically.

3.1.13.1. Solutions

The pharmaceutical solutions are evaluated as follows:

1) **Concentration of Therapeutic Agent:** After the manufacture, the concentration of therapeutic agent should lie within **95-105%** of the nominal concentration. This range offers flexibility for the product to be successfully manufactured. Products with drug concentration outside this range cannot be released for market. Throughout the shelf-life of the product, the drug concentration should not be less than 90% of the nominal amount, or else the product is assumed as expired.

2) **Uniformity of Content:** The individual mass of the therapeutic agent in 10 units should be determined. The product is considered to pass the test if the content of each individual unit lie within the range of **85-115%** of the average content. The product is considered to fail the test if the mass of therapeutic agent in more than one unit lies outside the above mentioned range or if the mass of therapeutic agent in one unit lies outside the extended range of **75-125%** of the average content.

The drug content of 20 more units should be determined if the mass of therapeutic agent of one unit lies outside the range of 85-115% but within 75-125% of the average content.

In this case, the batch is considered to pass the test if not more than one of the individual contents of the 30 units lie outside the range of 85-115% and none lies outside the range of 75-125% of the average content.

3) **Uniformity of Mass:** After the product is manufactured, the contents of 20 units are decanted, weighed separately, and the average mass is determined. The batch is considered to pass the test, if the average mass of not more than two units deviate by more than **10%** and no units deviate by more than **20%** of the specified average mass.

   This evaluation can also be done by emptying the container and measuring the volume/mass. The product is considered to pass the test if the mass or volume is not less than the nominal volume/mass on the label.

4) **Uniformity of Dose of Oral Drops:** This test examines the reproducibility and accuracy of dosing of oral drop solutions. In this method, the prescribed quantity for one dose is dispensed and weighed; this process is repeated for another 9 doses, thus producing a total of 10 masses.

   Then the average mass is calculated. The batch is considered to pass the test if no single dose (mass) deviate by more than **10%** of the average mass and no single dose is greater than **20%** of the average mass.

5) **Concentration of Preservative:** After manufacture and also during the storage period, the concentration of therapeutic agent should lie within the range of **95-105%** of the nominal concentration.

6) **Preservative Efficacy Testing:** After manufacture and also during the storage period, the efficacy of preservatives added in the formulation should be assessed by evaluating the product resistance to microbial challenge.

7) **Appearance:** Pharmaceutical solutions should be clear and free of particles as the presence of particles would invalidate the claim of the product to be a solution. The specification may include a statement of the product colour and changes to its colour due to drug degradation on storage. This test should be performed after manufacture and also during storage. Also, the appearance of the product after its exposure to a series of cycles of freezing and thawing should be examined. This storage regimen examines the occurrence of precipitation of any formulation component.

8) **pH:** The product pH should be measured after manufacture and during the storage period. The measured pH is compared to the specified range, and any change is evidence of possible drug degradation.

9) **Viscosity:** The product viscosity should be measured and compared to the specified range after manufacture and also during storage.

3.1.13.2. Suspensions

The problems in suspension stability mainly arise when the suspended particles sediment, the particle size and shape changes, and the rheology and electro-kinetic properties of the suspension gets altered. Thus, the suspensions are evaluated by the following methods:

1) **Sedimentation Methods:** A major parameter for evaluating the stability of suspension is the sedimentation volume (F). It is defined as the ratio of the ultimate

height (H_u) of the sediment (after a suspension settles in a cylinder under standard conditions) to the initial height (H_0) of the total suspension. The value of F can be estimated by transferring a measured volume of suspension in a graduated cylinder and leaving it undisturbed for a specific time period. Then the values of H_u and H_0 are noted and their ratio is determined which alters with time. In order to obtain the sedimentation pattern at storage, a curve is obtained by plotting sedimentation volume against time. An ideal suspension gives a curve parallel to time axis.

Sedimentation rate can also be determined through an alternate simple test. It is generally accomplished by observing the sedimentation height (or the clear supernatant height) at specific time intervals and plotting a curve of sedimentation height against time.

The **degree of flocculation** is another evaluating parameter of sedimentation. The ultimate height of the sediment (H_∞) is comparatively smaller in an entirely deflocculated suspension. Thus:

$$F_\infty = H_\infty/H_0$$

Where, F_∞ = Sedimentation volume of the deflocculated suspension.

The ratio of F to F_∞ is used to define the **degree of flocculation** (β), which can be expressed as:

$$\beta = F/F\infty = \frac{H_u/H_0}{H_\infty/H_0} = \frac{H_u}{H_\infty}$$

$$\text{Thus,}\ \beta = \frac{\text{Ultimate sedimentation volume of flocculated suspension}}{\text{Ultimate sedimentation volume of deflocculated suspension}}$$

2) **Rheological Methods:** These methods are employed to evaluate the stability of suspensions. The suspensions possess non-Newtonian flow properties. A Brookfield viscometer with T-spindle is, therefore, employed to evaluate the different rheological aspects of a suspension at different depths in a sample. Sample data obtained at specific time intervals can provide essential information related to the suspension stability.

3) **Electrokinetic Methods:** These methods involve the evaluation of zeta potential for obtaining suspensions of high stability. At some specific zeta potentials, more stable suspensions are formed due to controlled flocculation. The electrophoretic methods measure the migration velocities of the particles which are used to calculate the zeta potential.

4) **Micromeritic Methods:** One of the major indications of suspension instability is the increase in particle size which may end up forming lumps or cakes. Therefore, a change in particle size at specific time intervals may provide essential data related to the suspension stability. Processes like coulter counter and micro scopy are generally employed to evaluate changes in particle size distribution and crystal habit.

5) **Degree of Air Entrapment:** This can be evaluated by measuring the specific gravity of suspensions.

6) **Efficiency of Preservative and Appropriateness of Formulation:** These parameters are evaluated by performing microbiological assay and ageing tests.

3.1.13.3. Emulsions

The evaluation tests carried out for emulsions are discussed below:

1) **Determination of Particle Size and Particle Count :** The emulsions are also evaluated for any changes in their average particle size or the size distribution of droplets. Processes like optical microscopy and Coulter counter method are employed to perform this operation.
2) **Determination of Viscosity :** The emulsions that are stored for longer time periods are checked for their viscosity using viscometers.
3) **Determination of Phase Separation :** It is a method for examining the emulsion stability by either observing visually or measuring the volumes of separated phases.
4) **Determination of Electrophoretic Properties:** Flocculation of emulsion can be evaluated by determining its electrophoretic properties like zeta potential, since electrical charge on particle surface affects the flocculation rate.

Following methods are used for **evaluating the physical stability of emulsions**:

1) **Dilution Test:** If the emulsion remains stable after dilution with water, it is o/w type; and if it breaks after dilution, it is w/o type. This test is based on the fact that more of the continuous phase can be added into an emulsion without causing stability problem.
2) **Dye Test:** In this test, scarlet red dye is mixed with the emulsion, and a drop of this emulsion is viewed under a microscope. If the globules are red and ground is colourless, the emulsion is w/o type.
3) **Conductivity Test:** In this test, a pair of electrodes is connected to a lamp and an electric source is dipped in the emulsion. If the lamp glows, the emulsion is o/w type; and if the lamp does not glow, it is w/o type.
4) **Fluorescence Test:** In this test, the emulsion is exposed to fluorescence light and viewed under a microscope. If the entire field fluoresces, the emulsion is w/o type; and if the emulsion is spotty, it is o/w type.
5) **Macroscopic Examination:** The physical stability of an emulsion is examined by its degree of creaming or coalescence occurring over a time period. This is carried out by calculating the ratio of volume of the creamed or separated part of the emulsion and the total volume, and then comparing these values for different products.
6) **Extent of Phase Separation:** Study of phase separation provides a proper understanding of practical and commercial features of stability. This study involves a quick method and is used to evaluate poorly formed and rapidly breaking emulsions. Even if the indications of instability (creaming and coalescence) occur at an early stage, phase separation occurs after a certain time period.
7) **Globule Size Distribution:** The appearance of bigger size globules is an earlier sign of instability. The small globules aggregate and coalesce on prolonged storage of emulsion, thus, leading to its instability. The globule size distribution of emulsions can be analysed microscopically for evaluating its physical stability. This method is almost similar to the optical microscopy method for particle size analysis in micromeritics.

   Figure 3.1 represents a graph plotted between the globule diameters (globule size in μm) on the x-axis and the frequency or number of globules of each size on the y-axis.

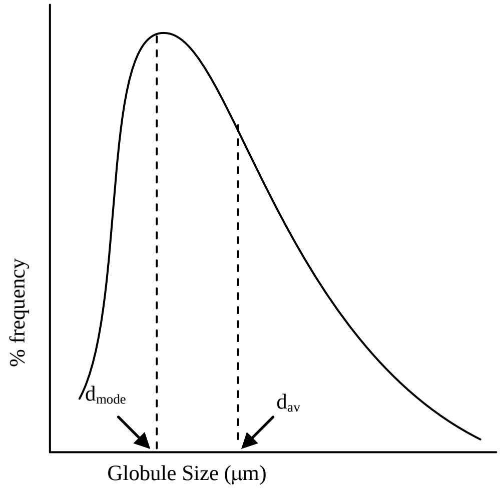


Figure 3.1: Size distribution of globules in an emulsion. The mode diameter is the highest point on the curve. The arithmetic diameter is found somewhat to the right of the mode in a right skewed distribution curve.

The surface area of globules is more associated with physical stability than the globule size distribution. After its manufacture, the emulsion immediately undergoes active coalescence for a time period, throughout which the emulsion becomes stable and independent of the strains induced in the preparation. After this time period, the emulsion remains stable on extended storage.

8) **Accelerated Stability Studies - Centrifugation:** Flocculation and creaming are slow processes which can be accelerated by using ultracentrifuge producing stress conditions within the system. At room temperature, the emulsions are exposed to diverse range of centrifugal speeds (2000-3000rpm) and the phase separation is examined at certain time intervals (**figure 3.2**).

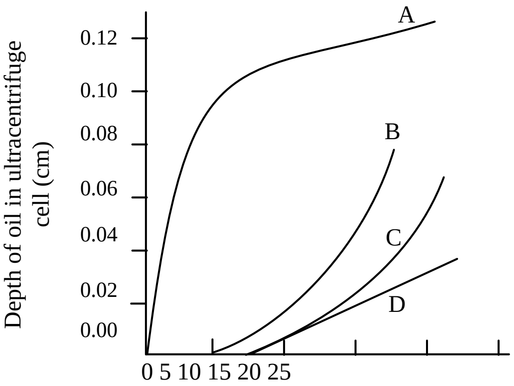


Figure 3.2: Oil coalescence-time profile of different emulsions (o/w type). Curve A is a bad emulsion, and B, C and D are good emulsions.

9) **Microwave Irradiation:** In this method, the emulsion is subjected to microwave radiations. Subsequently, its surface temperature increases and the temperature gradient existing between the surface and the bottom should be small enough to maintain the stability.

3.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) Liquids offer better compliance for the patients and also provide enhanced dosage control against a fixed dose of tablet.
2) **Simple syrup** is a saturated solution of sucrose formed in purified water with the concentration of 66% w/w sugar.
3) Syrups containing therapeutic or medicinal agents are **medicated syrups**, while syrups with flavours but no medicinal agents are **flavouring** or **flavoured** or **non-medicated syrups**.
4) An instrument known as **saccharometer** is used for determining the specific gravity of the syrup.
5) **Elixirs** are clear, sweetened, aromatic, hydroalcoholic liquids intended for oral use.
6) **Suspensions** are biphasic liquid preparations containing finely divided 0.5 -5.0 micron solid drug particles (**discontinuous phase**) dispersed or suspended throughout a liquid or semi-solid vehicle (**continuous phase**).
7) A **pharmaceutical emulsion** is a biphasic liquid preparation containing two immiscible liquids, one of which is dispersed as minute globules into the other.
8) In emulsions, the liquid in the form of minute globules is called **dispersed phase**.
9) In emulsions, the liquid containing the dispersed globules is the **continuous phase**.
10) The **coarse emulsions** have large-sized globules.
11) The **fine emulsions** have mean diameter below 5µm.
12) The **micro-emulsions** have globules of diameter as small as 10nm, and are milky and transparent in appearance.
13) Stable emulsions can be produced by using emulsifying agents.
14) **Surfactants** are mainly used as emulsifying agents.
15) The activity of a preservative in a formulation depends on the correct form of preservative added in required concentration to inhibit microbial growth. This is termed the **Minimum Inhibitory Concentration** (MIC).
16) If the emulsion remains stable after dilution with water, it is o/w type; and if it breaks after dilution, it is w/o type.

3.3. EXERCISE

3.3.1. True or False

1) The coarse emulsions have large-sized globules.
2) The fine emulsions have mean diameter below 7µm.
3) Surfactants are mainly used as emulsifying agents.
4) The specific gravity of the syrup is determined by saccharometer.
5) Stable emulsions can be produced by using emulsifying agents.

3.3.2. Fill in the Blanks

6) ___________ is a saturated solution of sucrose formed in purified water with concentration of 66% w/w sugar.
7) Syrups containing therapeutic or medicinal agents are _____________.

8) An instrument known as _______________ is used for determining the specific gravity of the syrup.
9) _____________ are mainly used as emulsifying agents.
10) If the emulsion remains stable after dilution with water, it is __________ type.

Answers

1)	True	2)	False	3)	True	4)	True
5)	True	6)	Simple syrup	7)	Medicated syrups	8)	Saccharometer
9)	Surfactants	10)	O/W				

3.3.3. Very Short Answer Type Questions

1) What are the advantages of liquid dosage forms?
2) Give the disadvantages of liquid dosage forms.
3) Discuss syrups.
4) Write a short note on elixirs.
5) Write a short note on emulsions.

3.3.4. Short Answer Type Questions

1) Classify liquid dosage forms. Give their disadvantages.
2) Discuss the formation of elixirs.
3) Write a short note on filling of liquid orals.
4) Discuss evaluation of emulsions.
5) Give evaluation procedure of solutions.

3.3.5. Long Answer Type Questions

1) Give a detailed account on manufacturing and formulation of syrups.
2) Briefly discuss the evaluation of liquid orals according to pharmacopoeia.
3) Discuss the formulation and manufacturing of emulsions.
4) Write a note on manufacturing considerations.

CHAPTER 4

Capsules - I

4.1. CAPSULES

4.1.1. Introduction

Capsules are solid dosage forms in which one or more medicinal and inert ingredients are enclosed in a small shell or container (usually of gelatin). They are of various shapes and sizes and contain a single dose of one or more active ingredients. They are intended for oral administration. Capsules are also defined as "**gelatin or methylcellulose shell designed to hold solids and liquids for oral administration**." There are two types of capsules, i.e., **hard** and **soft**. The hard capsule is also called **two piece** as it consists of two pieces in the form of small cylinders closed at one end. The shorter piece is called the **cap** which fits over the open end of the longer piece, called the **body**. Hard capsules are intended to contain solids. The soft gelatin capsule is also called as **one piece** and is intended to hold liquids.

Capsules are available in many sizes to provide dosing flexibility. Unpleasant drug tastes and odours can be masked by the tasteless gelatin shell. The administration of liquid and solid drugs enclosed in hard gelatin capsules is one of the most frequently utilised dosage forms. Capsules are solid preparations with hard and soft shells of various shapes and capacities, usually containing a single dose of active ingredients.

4.1.2. Types of Capsules

Generally, capsules can be categorised into:

1) **Hard Gelatin Capsules:** A base containing plasticiser and water is utilised to manufacture hard capsules. Preservatives, colours, flavours, and sugars may also be present in the base.
2) **Soft Gelatin Capsules:** A liquid gelatin is utilised to manufacture soft capsules or liquid gel caps. The liquid gelatin is later hardened in a humid environment. Generally, these capsules are a continuous piece of gelatin.

4.1.3. Advantages

The advantages of capsules are:

1) They are tasteless, odourless, and can be easily administered.
2) They are attractive in appearance.
3) The drugs having unpleasant odour and taste are enclosed in a tasteless shell.
4) They can be filled quickly and conveniently, therefore, the physician can change the dose and combination of drugs to suit the individual patient (this is an advantage over tablets).
5) The solubility of gelatin at gastric pH provides rapid release of medication in the stomach.
6) They are economical.
7) They are easy to handle and carry.
8) They require minimum excipients.
9) Little pressure is required to compact the material.

4.1.4. Disadvantages

The disadvantages of capsules are:

1) The hygroscopic drugs are not suitable for filling into capsules as they will absorb the water present in capsule shell, rendering the shell very brittle and ultimately leading it to crumble into pieces.
2) The concentrated solutions which require previous dilution are unsuitable for capsules because if administered as such it will lead to stomach irritation.
3) The capsules are not suitable for highly soluble substances like potassium chloride, potassium bromide, ammonium chloride, etc.
4) They are also not suitable for highly efflorescent or deliquescent materials.
5) They demand special storage conditions.

4.2. HARD GELATIN CAPSULES

4.2.1. Introduction

Hard capsules have a rigid shell in two separate pieces fitted together, hence are also called **two-piece capsules**. There was a time when two-piece capsules could be filled only with dry powders; but over the time, the manufacturers began filling capsules with pellets, granules, pastes, and liquids. Since hard capsules can be filled with substances in a variety of forms, they are believed to be more versatile than soft gels.

The **material types which can be filled into hard gelatin capsules** are:

1) **Dry Solids:** Powders, pellets, granules, or tablets.
2) **Semi-Solids:** Suspensions or pastes.
3) **Liquids:** Non-aqueous liquids.

4.2.2. Size of Capsules

Hard gelatin capsules are available in various sizes, designated by numbers from 000 to 5. Relative sizes of hard gelatin capsules are shown in the **table 4.1**. The exact capacity of any capsule varies according to the density and compressibility of the formulation. Relative amounts of water, aspirin, and sodium bicarbonate which can be filled in capsules of different sizes are compared in **table 4.1**:

Table 4.1: Capsule Sizes

Capsule Size	Water Volume (in ml)	Approximate Weight (mg)	
		Aspirin	Sodium Bicarbonate
000	1.37	1000	1430
00	0.95	650	975
0	0.68	500	715
1	0.50	320	510
2	0.37	250	390
3	0.30	200	325
4	0.21	150	260
5	0.13	100	130

For small scale preparation, manual filling machines are available in the capacities of 24, 36, 96, 100, and 144 capsules, **e.g.,** hand-operated capsule filling machine. The sizes of hard gelatin capsules intended for human consumption are shown in **figure 4.1**:

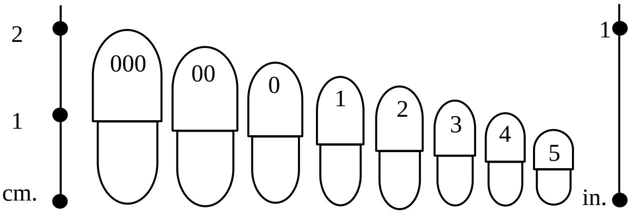


Figure 4.1: Relative Sizes of Hard Gelatin Capsules for Human Use

When necessary, particle size may be reduced by milling to produce particles ranging from 50-1000µm. Milled powders may be blended effectively for uniform distribution throughout a powder mix when the drug's dosage is 10mg or greater.

For drugs of lower dose or when smaller particles are required, micronisation is employed. Depending on the materials and equipment used, micronisation produces particles ranging from about 1-20µm.

On industrial scale preparation of capsules using high-speed automated equipment, the powder mix or granules should be free-flowing to allow steady passage of the capsule fill from the hopper through the encapsulating equipment and into the capsule shells. Addition of a lubricant or glidant (about 0.25-1%) to the powder mix enhances the flow properties.

Inserting tablets or small capsules into a capsule is sometimes useful in the commercial production of capsules and in a pharmacist's extemporaneous preparation of capsules (**figure 4.2**).

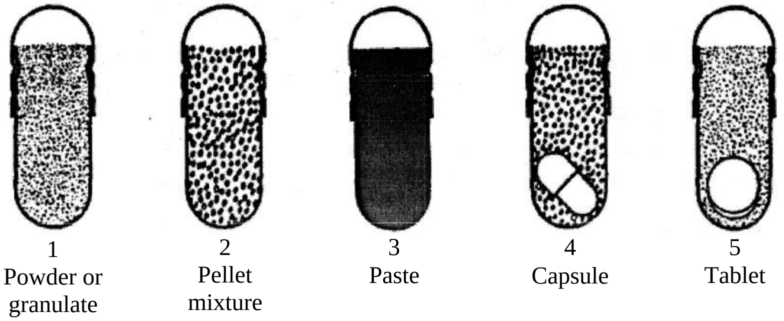


Figure 4.2: Examples of Fill in Hard Gelatin Capsules

This may be done to separate chemically incompatible agents or to add pre-measured amounts of potent drug substances. Rather than weighing a potent drug, a pharmacist may choose to insert a pre-fabricated tablet of the desired strength in each capsule. Other less potent agents and diluents may then be weighed and added.

Eutectic mixtures of drugs, or mixtures of agents having a tendency to liquefy when admixed, may be mixed with a diluent or absorbent (such as magnesium carbonate, kaolin, or light magnesium oxide) to separate the interacting agents and to absorb any liquefied material that may form. In large-scale capsule production, liquids are placed in soft gelatin capsules that are sealed during filling and manufacturing. Hard gelatin capsules are used to encapsulate about 65mg to 1gm of powdered material. The smallest capsule no. 5 may be expected to hold 65mg of powder or more, depending on the characteristics of the powder.

4.2.3. Preparation

The large-scale or small-scale preparation of filled hard gelatin capsules is divided into the following general steps:

1) Formulation development and selection of capsule size,
2) Production of hard gelatin capsule shells,
3) Filling of capsule shells,
4) Sealing of capsules (optional),
5) Cleaning and polishing of the filled capsules, and
6) Finishing.

4.2.3.1. Formulation Development

In developing a capsule formulation, the goal is to prepare a capsule with accurate dosage, good bioavailability, ease of filling and production, stability, and elegance. In dry formulations, the active and inactive components should be blended thoroughly to ensure a uniform powder mix for the fill. Care in blending is especially important for low dose drugs, since lack of homogeneity may result in significant therapeutic consequences.

The **raw materials used** are:

1) **Plasticisers:** The walls of hard gelatin capsules are firm and rigid, while those of soft gelatin capsules are more soft and flexible; it is turgid because it is manufactured and filled in one operation, which results in the pressure of the contents maintaining the capsule shape. The capsule is soft because it contains a large proportion of a plasticiser. The most frequently used plasticiser is **glycerol**; other plasticisers being used are **sorbitol**, **propylene glycol**, **sucrose**, and **acacia**.

2) **Colourants:** The colourants which are used can be of two types:
   i) Soluble dyes, or
   ii) Insoluble pigments.

   The soluble dyes are mainly synthetic in origin. Using **mixtures of dyes**, capsules can be made in all the colours of spectrum. The pigments used are of two types. The one which is used in the largest quantity is **titanium dioxide**. This is white and is used as an opacifying agent. The other class of pigments is the **oxides of iron** (black, red, and yellow).

3) **Preservatives:** These are sometimes added as an in-process aid to prevent microbiological contamination during manufacture. The manufacturers operate their plants following GMP guide lines to minimise this risk. In the finished capsules, the moisture levels are such that bacterial growth is not supported. Soft gelatin capsules sometimes have antifungal agents to prevent growth on their surfaces, when stored in non-protective packages. **Propyl parabens** and **methyl parabens** are mostly used as preservatives in capsule manufacturing.

4) **Diluents:** These are needed in certain cases where the medicament quantity is too small in bulk to get it filled in the smallest available capsule size. In such cases, diluent is added to attain the desired bulk of the medicament. The commonly used diluents are **lactose**, **mannitol**, **sorbitol**, **starch**, etc. The quantities of the diluent to be incorporated depend on the medicament dose and the capsule size.

5) **Absorbents:** Sometimes the medicaments are physically incompatible with each other, **e.g.,** eutectic substances or hygroscopic substances. In such cases, absorbents (such as **oxides** and **carbonates of magnesium and calcium** and **kaolin**) are added to the powdered drug. These inert materials act as a protective sorbent.

6) **Glidants:** To ensure a regular flow of powder into the automatic capsule machine, glidants are mixed with the medicaments. Various glidants used for this purpose are **talc**, **magnesium stearate**, and **calcium stearate**.
7) **Anti-Dusting Compounds:** During the process of capsule filling using an automatic filling machine, dust is generated in huge amount which is inhaled by the operator. It can pose a serious health hazard if allowed to be unchecked (especially, when the dust of potent drugs is inhaled). To avoid this, some anti-dusting components, like **inert edible oils**, are added to the formulation.
8) **Opacifiers:** The most commonly used opacifier is **titanium dioxide** which may be added to produce an opaque shell when the fill formulation is a suspension. It may also be added to prevent photo-degradation of light-sensitive fill ingredients. Concentration of opacifiers may be up to 0.5%.

4.2.3.2. Production of Hard Gelatin Capsule Shells

Currently, more advanced machineries are employed to manufacture capsule shells in **large scale industries**. The capsule shell machine is provided with several pairs of pins, each of which corresponds to the capsule body and cap.

The **preparation of gelatin solution** involves the following **steps**:
1) Demineralised hot water (maintained at 60-70°C) is utilised for preparing concentrated gelatin solution (35-40%) in jacketed pressure vessels.
2) The solution is stirred to achieve complete dissolution of gelatin.
3) Thereafter, the gelatin solution is subjected to vacuum for removing any trapped air bubbles.
4) Aliquots of this solution are poured into proper vessels, followed by the addition of required quantities of dye solutions and pigment suspensions.
5) Viscosity of the resultant solution is measured and adjusted to the required value by adding hot water. Viscosity of the solution is proportional to the thickness of capsule shell produced, i.e., higher the viscosity, thicker is the shell.
6) The final prepared mixture is shifted to a heated holding hopper of the manufacturing machine.

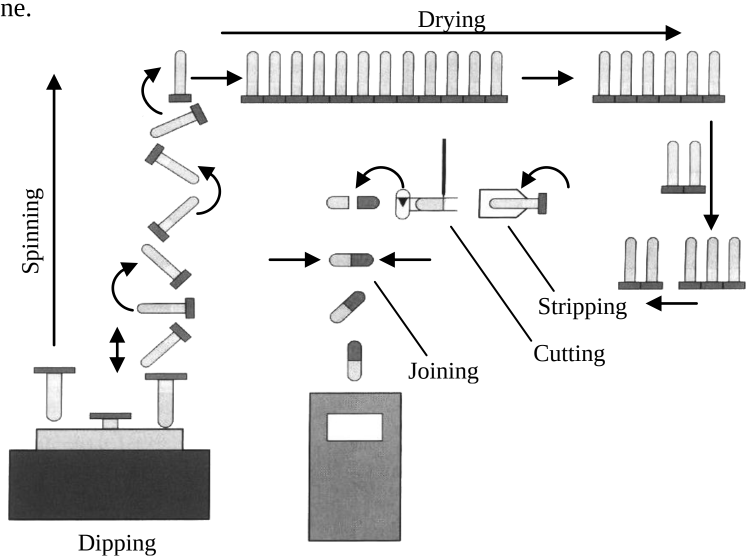


Figure 4.3: Manufacture of Two-Piece Hard Gelatin Capsule Shell

Figure 4.3 depicts the steps involved in the manufacturing of two-piece hard gelatin capsule shell. A hopper (also known as a **drip pan** or **pot** and located at the front end of the machine) is required to hold a fixed quantity of gelatin, maintained at a constant temperature of 45-55°C. The holding hopper maintains the solution level through automated mechanical feeding.

The **manufacturing process of capsules** involves the following **steps**:

1) The sets of moulds (maintained at 22°C) are dipped into the gelatin solution containing the necessary ingredients.
2) Gelling process initiates the formation of film on the surface of each mould.
3) The moulds are slowly withdrawn from the gelatin solution and shifted to the upper level of the machine with simultaneous rotation to obtain a film of uniform thickness.
4) The rotating pins are also subjected to cold air to promote firmness of the gelatin shells.
5) These pins are passed through a sequence of furnaces where they are subjected to controlled humidity air.
6) As soon as the pins reach the rear machine end, the bars are shifted back to the lower level and again passed through drying furnaces until they reach the front of the machine.
7) After drying, the dried films are removed from the moulds, the bodies and caps are separated from the pins through mechanical jaws and are cropped to suitable dimensions by rotating the blades.
8) The two parts are joined together to form a complete capsule.
9) Finally, the moulds are cleaned, lubricated and are prepared to start the next cycle.

The **manufacturing machines** involved are about 10m long, 2m wide, and 3m high. They are made up of two parts which are mirror images of each other; **one half of the machine produces the capsule cap**, while the **other half produces the capsule body**. The machines are also divided into an **upper** and a **lower level**.

The **moulds** or **pins** are made up of stainless steel and are mounted in sets on metal strips, also known as **bars**. Each machine carries nearly 50,000 mould pins. The machines are kept inside large rooms with strictly controlled humidity and temperature.

The machines run continuously on a 24-hour basis, 7 days per week. The operations are discontinued only during their maintenance. Each machine produces more than a million capsules per day. However, this yield depends on the capsule size; smaller the size, more will be the production.

4.2.3.3. Filling of Hard Gelatin Capsules

The filling machines used in pharmaceutical industries have in common the following operations (**figure 4.4**):

1) **Rectification:** The empty capsules are oriented so that all point in the same direction, i.e., body end downward. In general, the capsules pass one at a time through a channel wide enough to provide a frictional grip at the cap end. A specially designed blade pushes against the capsule by rotating about its cap end as a fulcrum. After two pushes (one horizontally and one vertically downward), the capsules arrange themselves with body end downward, regardless of which end entered the channel first.

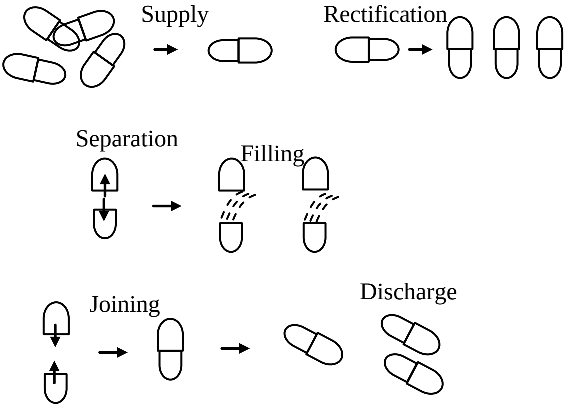


Figure 4.4: Capsule Filling Process

2) **Separation of Caps from Bodies:** This process depends on the difference in diameters between the cap and body portions. Here, the body ends of rectified capsules are delivered first into the upper portion of split bushings or split filling rings. A vacuum applied from below pulls the bodies down into the lower portion of the split bushing. The diameter of caps is too large to allow them to follow the bodies into the lower bushing portion. The split bushings are then separated to expose the bodies for filling.

3) **Dosing of Fill Material:** Various methods are employed for dosing, **e.g.,** Lilly capsule filling machine.

4) **Replacement of Caps and Ejection of Filled Capsules:** The cap and body portions are re-joined. Pins are used to push the filled bodies up into the caps for closure and to push the closed capsules out of the bushings. Compressed air may also be used to eject the capsules.

4.2.3.4. Hand-Operated, Semi-Automatic, and Automatic Equipments

The machines for capsule manufacturing may be hand-operated, semi-automatic, or automatic. The various machines used in manufacturing of hard gelatin capsules are:

1) **Hand-Operated Capsule Filling Equipment:** It consists of (**figure 4.5**):
    i) A bed having 200-300 holes,
    ii) A loading tray having 200-300 holes,
    iii) A powder tray,
    iv) A pin plate having 200-300 pins,
    v) A sealing plate having a rubber top,
    vi) A lever, and
    vii) A cam handle.

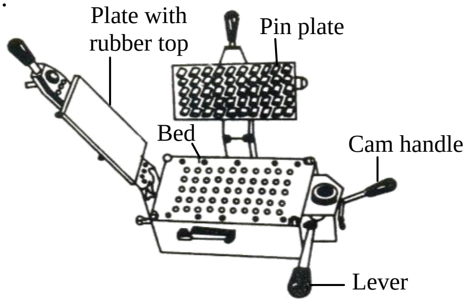


Figure 4.5: Capsules Filling Machine (Hand-Operated)

The **operating steps** are:

i) The empty capsules are filled in the loading tray and placed over the bed.

ii) The cam handle is operated to separate the capsule caps from their bodies.

iii) The powder tray is placed in a proper position and filled with an accurate quantity of powder with scraper.

iv) The excess of powder is collected on the platform of the powder tray.

v) The pin plate is lowered and the filled powder is pressed by moving the pin downwards.

vi) After pressing, the pin plate is raised and the remaining powder is filled into the capsule bodies.

vii) The plate with the rubber top is lowered and the lever is operated to lock the caps and bodies.

viii) The loading tray is then removed and the filled capsules are collected.

With a 200 hole machine, about 5000 capsules can be filled in one hour, whereas, in a machine having about 300 holes, about 7500 capsules can be filled in one hour.

2) **Semi-Automatic Capsule Filling Equipment:** The **operating steps** (**figure 4.6**) are:

i) The capsules are transferred to the perforated capsule filling ring which is rotated on a turntable.

ii) While rotating the ring is subjected to vacuum which pulls the bodies into the lower half of the ring, leaving the caps in the upper half.

iii) The upper and lower halves of the capsule filling ring are separated manually.

iv) The cap half of the ring is kept aside and the body half is transferred to another turntable rotated mechanically underneath a powder hopper.

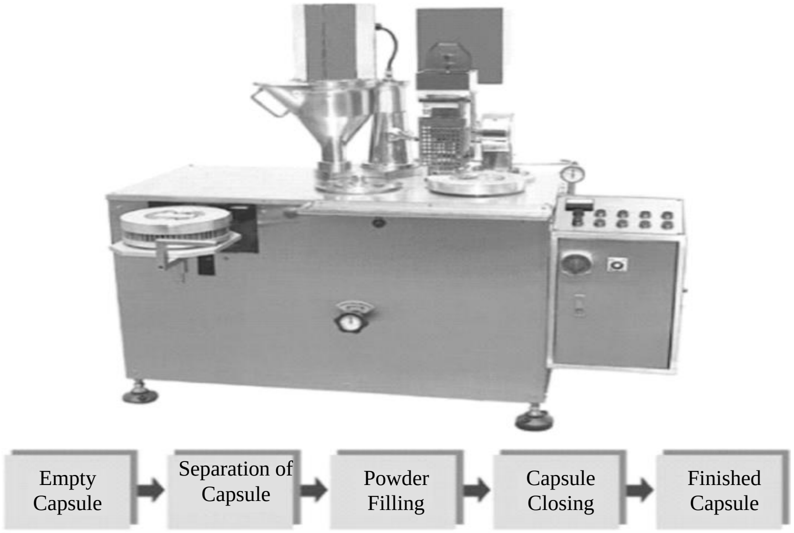


Figure 4.6: Semi-Automatic Capsule Filling Machine

v) This hopper contains a drill mechanism which is utilised to feed the powder into the capsule bodies.

vi) The capsule cap is detached and the empty capsule body is held between the thumb and forefinger and frequently pressed downward until it is fully filled.

vii) The cap is then replaced and the filled capsule is weighed using an empty capsule of the same size as a tare.

viii) After the filling of capsule bodies, the cap and body rings are joined together.

3) **Automatic Capsule Filling Equipment:** Machines developed for industrial use automatically separate the caps from empty capsules, fill the bodies, scrape off the excess powder, replace the caps, seal the capsules as desired, and clean the outside of the filled capsules at up to 1,65,000 capsules per hour. The formulation should be such that the filled body contains the accurate drug dosage. This is verified through the use of automated in-process sampling and analysis.

   The **automatic capsule filling process** normally involves **four simple steps**:
   i) Removal of caps,
   ii) Filling of the bodies,
   iii) Replacement of caps, and
   iv) Ejection of filled capsules.

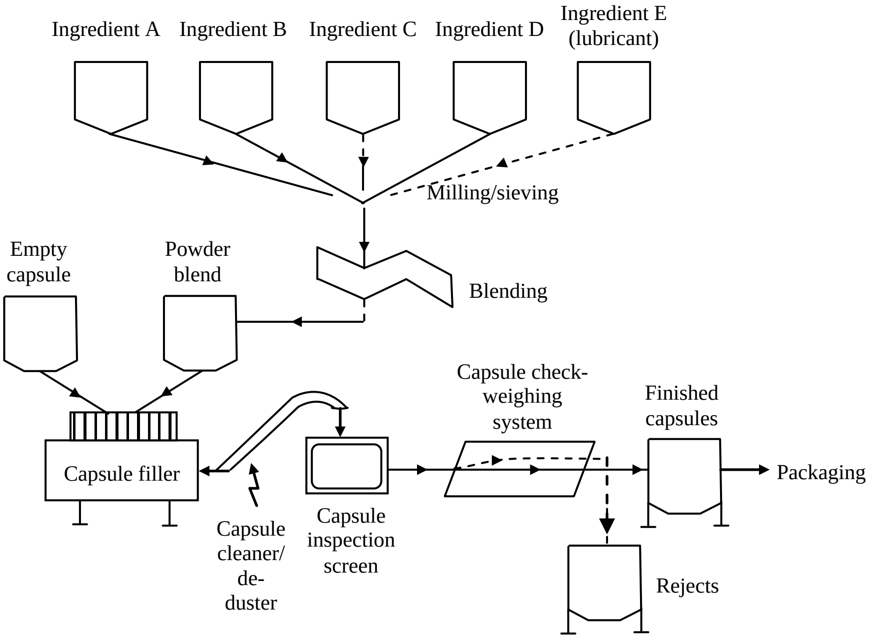


Figure 4.7: Filling of Capsule by Automated Method

4.2.3.5. Principles in Capsule Filling (Volumetric and Dosator)

Following are the principles employed in capsule filling:

1) **Bench-Scale Filling:** There is a requirement for filling small quantities of capsules, from 50-10,000, in hospital pharmacies or in industries for special prescriptions or trials. There are several simple pieces of equipment available for doing this, **e.g.,** the 'Feton' from Belgium or the 'Labocaps'. These consist of sets of plastic plates which have pre-drilled holes to carry 30-100 capsules of a specific size. Empty capsules are fed into the holes, either manually or using a simple loading device.

   The bodies are locked in their plate by means of a screw and the caps in their plate are removed. Powder is placed onto the surface of body plate and is spread with a spatula to fill the bodies. The uniformity of fill weight is dependent upon the powder flow properties.

   The cap plate is then repositioned over the body plate and the capsules are re-joined applying pressure manually. Stainless steel versions of these devices are now available, **e.g.,** Torpac Inc. which can be cleaned and autoclaved to comply with GMP requirements.

2) **Industrial-Scale Filling:** The machines for industrial-scale filling of hard gelatin capsules come in great variety of shapes and sizes, varying from semi- to fully-automatic and ranging in output from 5,000-1,50,000 capsules per hour. Automatic machines can be either continuous in motion, like a rotary tablet press, or intermittent, where the machine stops to perform a function and then indexes round to the next position to repeat the operation on a further set of capsules.

The **dosing systems** can be divided into two groups:

i) **Dependent Dosing Systems (Volumetric):** These dosing systems use the capsule body directly to measure the powder. Uniformity of fill weight can only be achieved if the capsule is completely filled.

Auger Filling Machine

Empty capsules are fed into a pair of ring holders (**figure 4.8**). The caps are retained in one half of the holder and the bodies in the other half. The body holder is placed on a turntable revolving in a variable-speed; the powder hopper is pulled over the top of this revolving plate. In the hopper, the revolving auger forces the powder down into the capsule bodies. The weight of powder filled in the body is dependent on the time the body is below the hopper during the revolution of the plate holder.

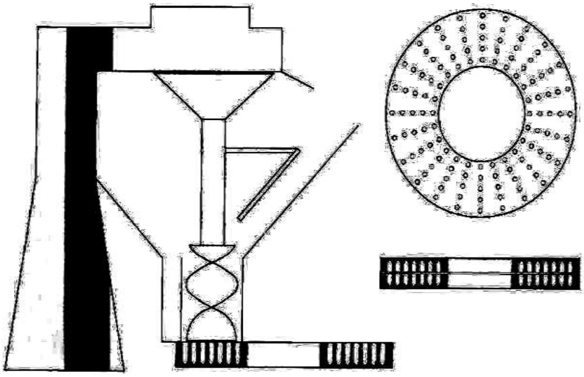


Figure 4.8: Auger Filling Machine Using the Ring System

These machines are semi-automatic in operation, and require an operator to transfer the capsule holders from one position to the other.

ii) **Independent Dosing Systems:** These dosing systems measure the powder independent of the body in a special measuring device. Weight uniformity is not dependent on filling the body completely.

There are two types of independent dosing system:

a) **Dosator or Dosing Tube:** This consists of a dosing tube inside which a movable spring-loaded piston is present, thus, forming a variable-volume chamber in the cylinder bottom (**figure 4.9**).

The tube is lowered into a powder bed, which enters the tube to fill the chamber and form a plug. This can be consolidated by applying a compression force with the piston. The assembly is then raised from the powder bed and positioned over the capsule body. The piston is lowered, ejecting the powder plug into the capsule body.

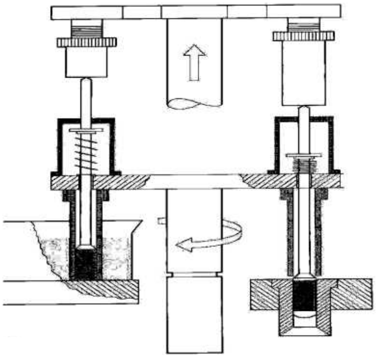


Figure 4.9: Dosing Tube or Dosator-Type Machine

The weight of powder filled can be adjusted by altering the position of the piston inside the tube, i.e., increasing or decreasing the volume, and by changing the depth of powder bed.

b) **Tamping Finger and Dosing Disc:** The dosing disc forms the bottom of a revolving powder hopper (**figure 4.10**). This disc has in a series of sets of accurately drilled holes in which powder plugs are formed by several sets of tamping fingers-stainless steel rods that are lowered into the powder bed. At each position, the fingers compress the material in the holes, building up a plug before they index on to the next position. As the disc rotates, material flows into the holes. At the last position, the finger pushes the plug through the disc into a capsule body. The powder fill weight can be varied by the amount of insertion of the fingers into the disc, by changing the thickness of the dosing disc, and by adjusting the amount of powder in the hopper.

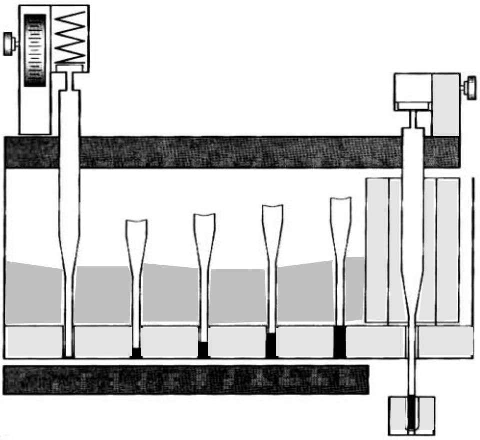


Figure 4.10: Dosing Disc and Tamping Finger Machine

4.2.3.6. Sealing of Capsules

Some manufacturers make tamper-evident capsules by sealing the joint between the two capsule parts. A manufacturer makes distinctive-looking capsules by sealing them with a coloured band of gelatin (**Kapseals**). If removed, the band cannot be restored without expert resealing with gelatin.

Capsules may also be sealed through a **heat welding process** that fuses the capsule cap to the body, through the double wall thickness at their juncture. The process results in a distinctive ring around the capsule where heat is welded.

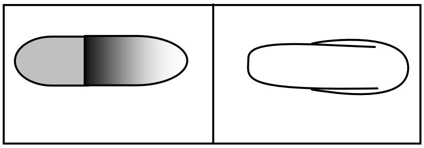


Figure 4.11: Z-Weld's Gelation Seal Fuses the Two Capsule Halves to Create a One-Piece Capsule, i.e., Tamper-Evident

Another process uses a **liquid wetting agent** that lowers the melting point in the contact areas of the capsule's cap and body and then thermally bonds the two parts at 40-45°C. Industrial capsule sealing machines are capable of producing 60000-150000 gelatin banded; heat welded, or thermally coupled capsules per hour. **Figure 4.11** depicts a sealed hard gelatin capsule.

Although it is difficult and tedious, extemporaneously prepared capsules may be sealed by lightly coating the inner surface of the cap with a warm gelatin solution immediately prior to the placement on the filled capsule body.

4.2.3.7. Cleaning and Polishing of Capsules

Small amounts of powder may adhere to the external surface of capsules after filling. The powder may be bitter or otherwise unpalatable and should be removed before packaging or dispensing.

On a small-scale, capsules may be cleaned individually or in small numbers by rubbing them with a clean gauze or cloth. On a large-scale, many capsule-filling machines are affixed with a cleaning vacuum for removing any extraneous material from the capsules as they exit the equipment.

4.2.3.8. Finishing

There are chances that small amounts of powder mixture may adhere to the external surfaces of finished capsules. Consequently, the finished capsules need to undergo dusting and polishing processes so that the powder can be removed from their surfaces. In small-scale industries, clean clothes or scientific cleaning wipes (**e.g.,** Kimwipes) are used for de-dusting the capsules. In large-scale industries, the following methods are utilised:

1) **Pan Polishing:** Accela-Cota pan coating machines lined with a polyurethane or cheese cloth are utilised.
2) **Cloth Dusting:** A cloth drenched with inert oil is used for rubbing the capsules.
3) **Brushing:** The finished capsules are introduced under rotating soft brushes to clean the dust from the surface. This process further requires application of a vacuum system for complete removal of dust.

4.2.4. Special Techniques of Formulation of Hard Gelatin Capsules

Some special techniques applied to the capsules are:

1) **Imprinting** on capsules provides information about the company and enables product identification. The filled capsules can be printed, yet imprinting on empty capsules is preferred to avoid any damage of capsules upon imprinting. Imprinting filled capsules cause contamination, poor print quality, and damage to the imprinting equipment.

Many firms, along with empty capsule suppliers provide custom imprinting services. Imprinting machines work on a rotogravure process, and many colours of edible inks (water-and solvent-based) are available commercially.

2) **Special purpose capsules** are given a special treatment to decrease their solubility. This may cause delayed absorption of the active ingredient, facilitating enteric properties. Some **examples** of such capsules are:
   i) The solubility of gelatin capsules can be enchased by formalin treatment. Exposure to formalin vapours or treatment with aqueous formalin lowers the solubility of gelatin film, due to cross-linkage of the gelatin molecule through aldehyde. This is important if the product to be filled bears aldehydic materials, or if the added flavourants are aldehydic in nature. Due to the nature of the reaction initiated likewise, the degree of insolubilisation is hard to manage, or even to prevent complete insolubility.
   ii) Different types of coatings (like salol, shellac, cellulose acetate phthalate, and certain resins applied through pan coating techniques) have been employed to modify the solubility characteristics.

   Gelatin capsules favour the delivery of pellets or granular material when delayed or prolonged release properties are required in the complete or some portions of the material to be filled.

3) Incompatible materials are separated through two-phase fill in the capsule. One phase may be a soft capsule, a smaller hard capsule, a pill, or a coated tablet filled in each capsule. For the second phase, a powder fill is incorporated in the usual manner. Employing this technique on commercial filling equipment, modifications need to be done in the filling cycle of machine. The minimum changes brought to machine facilitate material loading at two points during the filling cycle. In tamp type powder filling machines, the tamp cycle is disabled.

4) Recent advancements in the filling of typical two-piece gelatin capsules utilise liquids and semisolids. Earlier in the 1890s, hard gelatin capsules carried oils, ethereal extracts, and pill masses, but filling the capsules through semi-automatic and automatic equipment is a recent development. Usually, semisolids at ambient temperatures are filled after melting. Thixotropic formulations can be filled where shear developed in filling favours pumping, but upon decrease of shear its elevated viscosity prevents leakage after filling. Quantitative study of gastric emptying of hard gelatin capsules carrying thixotropic liquids is done through lag time before emptying, and the slope of the first order emptying curve. Results depict that the viscosity of fill has no effect on the emptying characteristics of the dosage forms.

4.2.5. Manufacturing Defects

Some difficulties which may arise during filling of capsules are:

1) **Deliquescent or Hygroscopic Powders:** A gelatin capsule contains water which is extracted or taken up by a hygroscopic drug. This renders the capsule brittle, which leads to its cracking. **Addition of an absorbent** (like magnesium carbonate, heavy or light magnesium oxide) overcomes this difficulty, provided the capsules are packed in tightly closed glass capsule vials.

2) **Eutectic Mixtures:** Certain substances when mixed together tend to liquefy or form a pasty mass due to the formation of a mixture having a melting point lower than the room temperature. For filling these types of substances each troublesome ingredient is mixed with an absorbent separately, then mixed together and filled in capsules.

The **absorbents** used are magnesium oxide and kaolin. Another method in dealing with such type of difficulty is that the substances are mixed together to form a eutectic mixture, then an absorbent is added.

3) **Addition of Inert Powders :** When quantity of the drug to be filled in capsules is very small, an inert substance or a diluent is added to increase the powder bulk, thus, facilitating easy filling of capsules.

4) **Use of Two Capsules:** Some manufacturers separate incompatible ingredients of the formulation by placing one of the ingredients in smaller capsule, and then placing this smaller capsule in a larger capsule containing the other ingredients of the formulation.

5) **Filling of Granular Powder :** Powders lacking adhesiveness and most of the granular powders are difficult to fill in the capsules by punch method. This is because they are not compressible and flow out of the capsule as soon as they are lifted from the powder pile into which they are punched. To overcome this difficulty the **non-adhesive powders should be moistened with alcohol** and the **granular powders should be reduced to powder** before filling into capsules.

6) **Improper Flow of the Powder Mixture during the Filling Operation:** Addition of suitable quantities of **glidants** or **lubricants** is helpful in improving the flow properties of the powder mixture.

7) **Segregation and Homogeneity:** Generally, semi-automatic or automatic machines performing capsule filling operation may face this error. The segregation and inhomogeneity of the particles may occur as a result of vibrations generated by these heavy-duty machines. Utilisation of **powder having uniform particle sizes and densities** overcome this defect.

8) **Incompatibility:** This defect may occur as a result of incompatibility among formulation ingredients, formulation components, and the capsule shell. A thorough understanding of physical and chemical properties of each ingredient is needed to prevent such defects. The **excipients generally used in the filling** of hard gelatin capsules are:
   i) **Diluents:** Lactose, corn starch, and microcrystalline cellulose are the diluents used to increase the powder bulk and thus to facilitate its easy and accurate handling during filling operations.
   ii) **Disintegrants:** Corn starch, microcrystalline cellulose, sodium starch glycolate, and croscarmellose are the disintegrants used for breaking down the powder bulk exposed to a liquid medium.
   iii) **Glidants:** Colloidal silicon and talc are the glidants used to improve the powder flow by reducing the inter-particle attraction and preventing agglomeration.
   iv) **Lubricants:** Magnesium and other metallic stearates are the lubricants used to minimise the contact between powder particles and components of the filling machine.
   v) **Surfactants:** Sodium lauryl sulphate is employed into the powder mixture to reduce the surface tension and promote powder wetting with the discharge medium containing greater quantities of hydrophobic constituents.

4.2.6. In-Process and Final Product Quality Control Tests

Physical parameters of pharmaceutical capsules like temperature, pressure, relative humidity, particle size, colour, fill weight, shell weight, and disintegration time are controlled by IPQC tests. While the QC tests for pharmaceutical capsules are like assay, fill weight, content uniformity, mass uniformity, mass variation, microbiological test, disintegration test, dissolution test, etc. Pharmacopoeia provides a list of IPQC and QC tests to be performed for pharmaceutical capsules:

1) Appearance,
2) Size and shape,
3) Unique identification markings,
4) Assay,
5) Content of active ingredients,
6) Content uniformity test,
7) Uniformity of mass,
8) Mass variation test,
9) Disintegration test,
10) Dissolution test, and
11) Moisture permeation test.

4.2.6.1. Appearance

It is essential for each and every capsule produced either on a small- or a large-scale to have an unvarying appearance. Visual or electronic detection is generally undertaken to detect any faults in the reliability and appearance of the capsule. Existence of any unrefined changes in appearance, including hardening, softening, cracking, swelling, mottling, printing mistake, or discolouration of the shell is an indication of physical instability of product. These flawed capsules are discarded.

4.2.6.2. Size and Shape

The hard capsules are available in a variety of sizes. Few commercially available capsules of standard sizes, for human consumption, range from 000 (the largest, 1.40ml) to 5 (the smallest, 0.13ml).

4.2.6.3. Unique Identification Markings

Capsule can easily be identified through symbols or other unique markings imprinted on their surfaces.

4.2.6.4. Assay

An active ingredient present in a capsule is known as Active Pharmaceutical Ingredient (API). Proper analytical methods are generally employed to perform capsule assays and produce a good finished product.

4.2.6.5. Content of Active Ingredients

The test for the assay of contents is described in individual monographs and calculates the API quantity in each capsule. In accordance with the IP, the monograph provides that not less than 20 capsules are required to perform this assay. In case of unavailability of 20 tablets, not less than 5 tablets can be utilised to perform this assay. **Table 4.2** presents wide range of tolerant values allowed for sampling errors:

Table 4.2: IP Limits for Content of Active Ingredients

Weight of API in each Capsule (gm)	Subtract from Lower Limit for Samples of			Add to the Upper Limit for Samples of		
0.12 or less	15	10	5	15	10	5
More than 0.12 but less than 0.3	0.2	0.7	1.5	0.3	0.8	1.8
0.3 or more	0.2	0.5	1.2	0.3	06	1.5

4.2.6.6. Content Uniformity Test

In accordance with the BP, 10 capsules are randomly selected for their content evaluation using a method described in monograph or other appropriate analytical method of equivalent accuracy and precision. The **Acceptance Value** (AV) for this test is calculated by using the following formula:

$$AV = |M - X| + KS$$

Where, M = Reference value.
X = Mean of individual content (x1, x2...., xn) expressed as percentage of the label claim.
K = Acceptability constant.
S = Sample standard deviation.

According to BP, capsules comply with this test if not more than one of the capsule is outside the limits of 85-115% of the average value and none is outside the limits of 75-125%. On the contrary, capsules fail to comply with the test if the contents of more than 3 capsules deviate from the range of 85-115% of the average content or if one or more capsule contents are outside the limits of 75 -125% of the average content. The process is performed again taking another 20 capsules, if the contents of 2 or 3 capsules lie outside the range of 85-115% of the average content. The capsules comply with this test if in a sample of 30 capsules, the contents of not more than 3 capsules lie outside the range of 85-115% and not a single capsule lie outside the range of 75-125% of the average content.

Table 4.3 presents the limits for content uniformity (CU) and mass variation (MV) tests of capsules as specified in IP, BP, USP, and PhEur. In accordance to IP, this test is not valid for multivitamins or trace elements containing capsules.

Table 4.3: IP, BP, USP and PhEur Limits for Content Uniformity (CU) and Mass Variation (MV) Tests

Capsules	**Dose and Ratio of Active Substance**	
	≥ 25 mg and ≥ 25 %	< 25 mg or < 25 %
Hard	MV	CU
Soft	CU	CU

4.2.6.7. Uniformity of Mass

In this test, a pre-weighed capsule is opened and its contents are completely removed without losing any part of the shell. The empty capsule shell is weighed. The difference between the weight of filled and empty capsule shell gives the weight of contents. This process is again performed using 19 capsules and their average mass is calculated.

In accordance with the standards mentioned in IP, BP, and PhEur, the content mass of not more than 2 capsules should deviate from the average mass by more than the percentage deviation listed in the **table 4.4** and none of the capsules should deviate by more than twice that percentage.

Table 4.4: IP, BP, and PhEur Limits for Uniformity of Mass

Average Mass (mg)	**Percentage Deviation (%)**
Less than 300	10
300 or more	7.5

4.2.6.8. Mass Variation Test

In accordance with BP, this test can be performed by individually weighing 10 capsules. The content of every capsule is removed using appropriate techniques. Each empty shell is accurately weighed. The content weight is obtained by subtracting the weight of empty capsule shell from that of the filled capsules. The active substance content in each capsule is estimated from the mass of contents removed from each capsule. The **Acceptance Value** (AV) is obtained by using the formula:

$$X_i = W_i \times A/W$$

Where, $x_1, x_2...., x_n$ = Individual estimated contents of the dosage units tested.
$w_1, w_2,..., wn$ = Individual masses of the dosage units tested.
W = Mean of individual weights ($w_1, w_2,....., w_n$).

In accordance with BP and USP, the AV of 10 capsules should be less than or equal to 15%. In case the AV is greater than 15%, the test is repeated with the next 20 capsules and their AV is calculated. In order to meet the acceptance criteria, the final AV of 30 capsules should be less than or equal to 15% and no individual content of the capsule should be less than (1 – 25 × 0.01) M or more than (1 + 25 × 0.01) M in calculation of acceptance value under mass variation or content uniformity.

4.2.6.9. Disintegration Test

The USP device to test disintegration uses 3 inches long 6 glass tubes that are open at the top and held against a 10 mesh screen at the bottom end. To test for disintegration time, a capsule is placed in each tube and the basket rack is placed in a beaker containing 1 lt. of water, simulated gastric fluid or simulated intestinal fluid maintained at 37±2 °C temperature.

On moving upward the capsule should remain 2.5cm below the liquid surface and on downward movement it should remain 2.5cm above the bottom of the beaker. The basket containing the capsule is moved up and down through a distance of 5 -6cm at a frequency of 28 -32 cycles per minute. Floating of the capsules can be prevented by placing perforated plastic discs on each capsule. These discs also impart an abrasive action. The apparatus is operated for the time specified.

The capsule should disintegrate and all the particles should pass through the 10 mesh screen within the time specified. Any remaining residues should have a soft mass with no firm core. In accordance with USP, this test is considered successful if all the capsules disintegrate completely. Just in case, if 1 or 2 capsule fail to disintegrate the test needs to be performed again using 12 extra capsules.

The required specifications are only achieved if 16 out of 18 tested capsules disintegrate. **Table 4.5** displays the disintegration time of various capsules according to IP, and **table 4.6** displays the disintegration time of various capsules according to BP:

Table 4.5: Disintegration Time of Various Capsules According to IP

Capsules	Disintegration Time (min)
Hard capsule	30
Soft capsule	60
Enteric capsule	60

Table 4.6: Disintegration Time of Various Capsules According to BP

Capsules	Disintegration Time (min)
Hard capsule	30
Soft capsule	30
Gastro resistance capsule	60
Rectal capsule	30
Vaginal capsule	30

As per the IP, disintegration test is not meant for modified-release capsules. The requirements for disintegration are not applicable to capsules whose dissolution requirements are included in their monographs.

4.2.6.10. Dissolution Test

This test utilises BP or USP dissolution apparatus (also known as **basket apparatus**) consisting of a cylindrical glass vessel with a hemispherical bottom (the vessel may be covered, made up of other inert, transparent material), a motor, a metallic drive shaft, and a cylindrical basket.

The vessel is partially immersed in a suitable water bath of any convenient size or provided with a heating jacket. The water bath or heating device maintains the temperature inside the vessel at 37±0.5°C during the test and keeps the bath fluid in constant, smooth motion.

In this test, a stated volume of the dissolution medium is placed inside the vessel. The parts of apparatus are assembled and the dissolution medium is maintained at 37±0.5°C temperature. A single capsule is placed in the apparatus, allowing exclusion of air bubbles from its surface. The apparatus is operated at a specified speed.

At definite time intervals, specimens are withdrawn from a midway zone between dissolution medium surface and the top of the rotating basket or blade, not less than 1cm from the vessel wall. At each withdrawal, same amount of fresh dissolution medium (maintained at 37°C temperature) is added.

The vessel is kept covered during the test and the temperature of dissolution medium is checked at specific times. The analysis is performed using a proper assay method as specified in the individual monographs.

The test is repeated with more capsules. In accordance with BP, USP, PhEur, PhInt, and JP, the specified requirements are met if the quantities of API dissolved from the tested capsules comply with the acceptance criteria presented in **table 4.7**:

Table 4.7: BP, USP, phEur, phInt and JP Acceptance Criteria for Dissolution Test of Capsule

S1	6	Each unit is not less than Q + 5%.
S2	6	Average of 12 units (S1 + S2) is equal to or greater than Q, and no unit is less than Q – 15%.
S3	12	Average of 24 units (S1 + S2 + S3) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%.

The capsules are continuously tested for 3 stages until the test results confirm at either S1 or S2. The quantity (Q) presents the definite quantity of dissolved API, stated as a percentage of the labelled content. The 5%, 15%, and 25% values in the capsule are percentages of the labelled content so that these values and Q are in the same terms.

4.2.6.11. Moisture Permeation Test

The suitability of capsule packaging can be ensured by determining the permeation characteristics of single-unit and unit dose in accordance with the specifications provided in USP. In this test, a unit dosage is packed with a colour revealing desiccant pellet and is exposed to known relative humidity for a specific period of time.

This pellet suffers colour change in the presence of moisture. Absorption of moisture can be indicated by a colour change. The quantity of moisture can be calculated by subtracting the pretest weight from the after test weight. This test is extremely useful for determining the degree and rate of moisture penetration.

4.3. SUMMARY

The details given in the chapter can be summarised as follows:

1) **Capsules** are solid dosage forms in which one or more medicinal and inert ingredients are enclosed in a small shell or container (usually of gelatin).
2) Capsules are also defined as "gelatin or methylcellulose shell designed to hold solids and liquids for oral administration".
3) There are two types of capsules, i.e., **hard** and **soft**.
4) The hard capsule is also called **two piece** as it consists of two pieces in the form of small cylinders closed at one end.
5) The soft gelatin capsule is also called as **one piece** and is intended to hold liquids.
6) A base containing plasticiser and water is utilised to manufacture hard capsules.
7) A liquid gelatin is utilised to manufacture soft capsules or liquid gel caps.
8) **Hard gelatin capsules** are available in various sizes, designated by numbers from 000 to 5.
9) To ensure a regular flow of powder into the automatic capsule machine, glidants are mixed with the medicaments.
10) The most commonly used opacifier is **titanium dioxide** which may be added to produce an opaque shell when the fill formulation is a suspension.
11) Capsules may be sealed through a **heat welding process** that fuses the capsule cap to the body, through the double wall thickness at their juncture.
12) **Imprinting** on capsules provides information about the company and enables product identification.
13) It is essential for each and every capsule produced either on a small- or a large-scale to have an unvarying appearance.
14) Capsule can easily be identified through symbols or other unique markings imprinted on their surfaces.
15) An active ingredient present in a capsule is known as Active Pharmaceutical Ingredient (API).

4.4. EXERCISE

4.4.1. True or False

1) There are two types of capsules, i.e., hard and soft.
2) Hard gelatin capsules are available in various sizes, designated by numbers from 000 to 5.
3) Polishing on capsules provides information about the company and enables product identification.
4) An active ingredient present in a capsule is known as Active Pharmaceutical Ingredient (API).
5) The soft gelatin capsule is also called as liquid capsule.
6) The hard capsule is also called two piece.

4.4.2. Fill in the Blanks

7) The soft gelatin capsule is also called as ___________.
8) ____________ are available in various sizes, designated by numbers from 000 to 5.
9) The hard capsule is also called ___________.
10) A __________ gelatin is utilised to manufacture soft capsules or liquid gel caps.
11) Colloidal silicon and talc are ________.

Answers

1) True
2) True
3) False
4) True
5) False
6) True
7) One piece
8) Hard gelatin capsules
9) Two piece
10) Liquid
11) Glidants

4.4.3. Very Short Answer Type Questions

1) Write a short note on capsules.
2) Discuss the types and advantages of capsules.
3) Write a short note on automatic capsule filling equipment.
4) Discuss bench scale filling.

4.4.4. Short Answer Type Questions

1) Discuss the size of capsules.
2) Discuss formulation development of capsules.
3) Write a short note on principles in capsule filling.
4) What are the special techniques of formulation of hard gelatin capsules.

4.4.5. Long Answer Type Questions

1) Discuss the manufacturing defects associated with capsules.
2) Give a detailed account on in-process and final product quality control tests.
3) Discuss production of hard gelatin capsule shells.

CHAPTER 5

Capsules - II

5.1. SOFT GELATIN CAPSULES

5.1.1. Introduction

Soft capsules or liquid gel caps are formed from liquid gelatin that is later hardened in a humid environment. Soft gel capsules are one continuous piece of gelatin. When pharmaceutical formulation scientists face the challenge of designing a solid oral dosage form for drug compounds, they have a number of choices. Over recent years, new drug molecules have tended to be more hydrophobic and therefore, less soluble in aqueous systems.

In case of drugs for oral administration, it is becoming more difficult to formulate poorly water-soluble drugs into products from which the drug is fully released and well absorbed. One of the best methods to overcome this problem is to make a liquid formulation containing the drug. In order to convert this liquid formulation into a solid dosage form, it may be encapsulated into soft gelatin capsules.

Soft capsules have thicker shells than hard capsules, and contain antimicrobial preservatives. The shells are available in various shapes and sizes. The contents of soft capsules are usually solutions or suspensions of the API(s) in non-aqueous liquids. Partial migration of the contents into the shell may occur (and *vice versa*) depending on the nature of materials used and the product in question.

5.1.2. Nature of Shell

The capsule shell is basically composed of gelatin, a plasticiser, and water; it may contain additional ingredients such as preservatives, colourants, and opacifying agents, flavours, sugars, acids, and medicaments to achieve the desired effects.

Bloom or Gel Strength

The bloom or gel strength of gelatin is a measure of the **cohesive strength of the cross-linking between gelatin molecules** and is proportional to the molecular weight of the gelatin. Bloom is determined by measuring the weight in grams required to move a plastic plunger that is 0.5 inches in diameter into a $6\,{}^{2}/_{3}\%$ gelatin gel that has been held at 10°C temperature for 17 hours. Bloom may vary with the requirements of the individual custom manufacturer but ranges from 150-250gm.

In general, with all the other factors being equal, the **higher the bloom strength of the gelatin** used, the **more physically stable is the resulting capsule shell**. The cost of gelatin is directly proportional to its bloom or gel strength and thus, is an important factor in the cost of soft capsules.

Consequently, the higher bloom gelatin is only used when necessary to improve the physical stability of a product or for large capsules (over 50 minims), which require greater structural strength during manufacture.

Viscosity

Viscosity of gelatin, determined on a 6 $^2/_3$% concentration of gelatin in water at 60°C temperature, is a measure of the molecular chain length and determines the manufacturing characteristics of the gelatin film. The desired film characteristics are usually based on standard gelatin formulations, which allow production at a set sealing temperature and definite drying conditions, and produce a firm, non-tacky, non-brittle, and pharmaceutically elegant product.

The **viscosity for gelatin** can range from **25-45 millipoise**, but the individual manufacturer sets a narrow range, **e.g.,** 38 ± 2 millipoise, for a particular type of gelatin, to make use of a standard formulation and thus conform to standard production conditions.

Low-viscosity (25-32 millipoise), **high-bloom** (180-250gm) **gelatin** are used in conjunction with the capsulation of hygroscopic vehicles or solids, and standard gelatin formulas can be modified so as to require up to 50% less water for satisfactory operation on the capsulation machine. These modified formulas afford less opportunity for the hygroscopic fill materials to attract water from the shell, thereby improving the ingredient and physical stability of the product.

The plasticisers used with gelatin in soft capsule manufacture are relatively few. Glycerine USP, sorbitol USP, pharmaceutical grade sorbitol special, and combinations of these are the most prevalent.

The ratio by weight of dry plasticiser to dry gelatin determines the **hardness of gelatin shell**, assuming that there is no effect from the capsulated material. Some **examples** of glycerine/gelatin ratios are shown in **table 5.1** along with their typical usage.

The ratio by weight of water to dry gelatin can vary from 0.7-1.3 (water) to 1.0 (dry gelatin) depending on the viscosity of gelatin being used. For most formulations, however, it is approximately 1 to 1.

Since only water is lost during the capsule drying process, the percentage of plasticiser and gelatin in the shell is increased, but the important plasticiser to gelatin ratio remains unchanged.

Table 5.1: Typical Shell "Hardness" Ratios and their Uses

Hardness	Ratio Dry Glycerine/Dry Gelatin	Usage
Hard	0.4/1	Oral, oil-based, or shell-softening products and those destined primarily for hot, humid areas.
Medium	0.6/1	Oral, tube, vaginal oil-based, water-miscible-based, or shell-hardening products and those destined primarily for temperate areas.
Soft	0.8/1	Tube, vaginal, water-miscible-based or shell-hardening products and those destined primarily for cold, dry areas.

In general, **the additional components of the gelatin mass are limited in their use** by:

1) The amounts required to produce the desired effect,
2) Their effect on capsule manufacture, and
3) Economic factors.

Examples of ingredients falling into the first two categories are shown in **table 5.2**:

Table 5.2: Additional Components of the Gelatin Mass

Ingredient	Concentration	Purpose
Category I		
Methylparaben, 4 parts; Propylparaben, 1 part	0.2%	Preservative
FD&C and D&C water-soluble dyes, certified lakes, pigments, and vegetable colours, alone or in combination	q.s	Colourant
Titanium dioxide	0.2-1.2%	Opacifier
Ethyl vanillin	0.1%	Flavouring for odour and taste
Essential oils	Up to 2%	Flavouring for odour and taste
Category II		
Sugar (Sucrose)	Up to 5%	To produce chewable shell and taste
Fumaric Acid	Up to 1%	Aids solubility; reduces aldehydic tanning of gelatin

Addition of medicaments to the gelatin mass is usually not recommended for economic reasons. Since only 50% of the gelatin mass is incorporated into the capsules, a 50% loss of the added medicament is observed. However, certain highly active, relatively inexpensive compounds such as benzocaine (3mg/capsule shell) in chewable cough capsules may be used successfully. The capsule shell colour should never be lighter in hue than the capsulated material.

5.1.3. Nature of Capsule Content

Soft gelatin capsules can be used to dispense a variety of liquids and solids. Requirements and specifications of these materials vary, depending on the equipment of the manufacturer. But there are basic precepts that may be used as a guide for the formulation and production of commercially and therapeutically acceptable capsules, regardless of the capsulation method. The formulation of capsule content for each product is individually developed to fulfil the specifications and end-use requirements of the product.

Except for the Accogel process, which is primarily concerned with the capsulation of dry powders, the content of a soft gelatin capsule is a liquid, or a combination of miscible liquids, a solution of a solid(s) in a liquid(s), or a suspension of a solid(s) in a liquid(s). All such materials for capsulation are formulated to produce the smallest possible capsule consistent with maximum ingredient and physical stability, therapeutic effectiveness, and production efficiency.

Once the smallest capsule size is determined, personnel in the sales or marketing departments usually choose the colour, shape, and ultimate size of the retail product, unless there is a technical or production reason for the development chemist to specify a particular size, shape, and colour. The maximum capsule size and shape for convenient oral use in humans is the 20 minim oblong, the 16 minim oval, or the 9 minim round.

Liquids are an essential part of the capsule content. Only those liquids that are both water-miscible and volatile cannot be included as major constituents of the capsule content since they can migrate into the hydrophilic gelatin shell and volatilise from its surface. Water, ethyl alcohol, and emulsions fall into this category.

Similarly, gelatin plasticisers such as glycerine and propylene glycol cannot be the major constituents of capsule content, owing to their softening effect on the gelatin shell, which thereby makes the capsule more susceptible to the effects of heat and humidity.

As minor constituents (up to about 5% of the capsule content) water and alcohol can be used as co-solvents to aid in the preparation of solutions for capsulation. Also, up to 10% glycerine and/or propylene glycol can be used as co-solvents with polyethylene glycol or other liquids having a shell-hardening effect when capsulated alone.

5.1.4. Size of Capsules

Soft gelatin capsules are available in oblong, spherical, elliptical, and other shapes. Spherical or oval capsules are also known as pearls or globules. They are also available in different sizes ranging from 0.1 to 30ml volume. Different shapes of soft gelatin capsules are shown in **figure 5.1**.

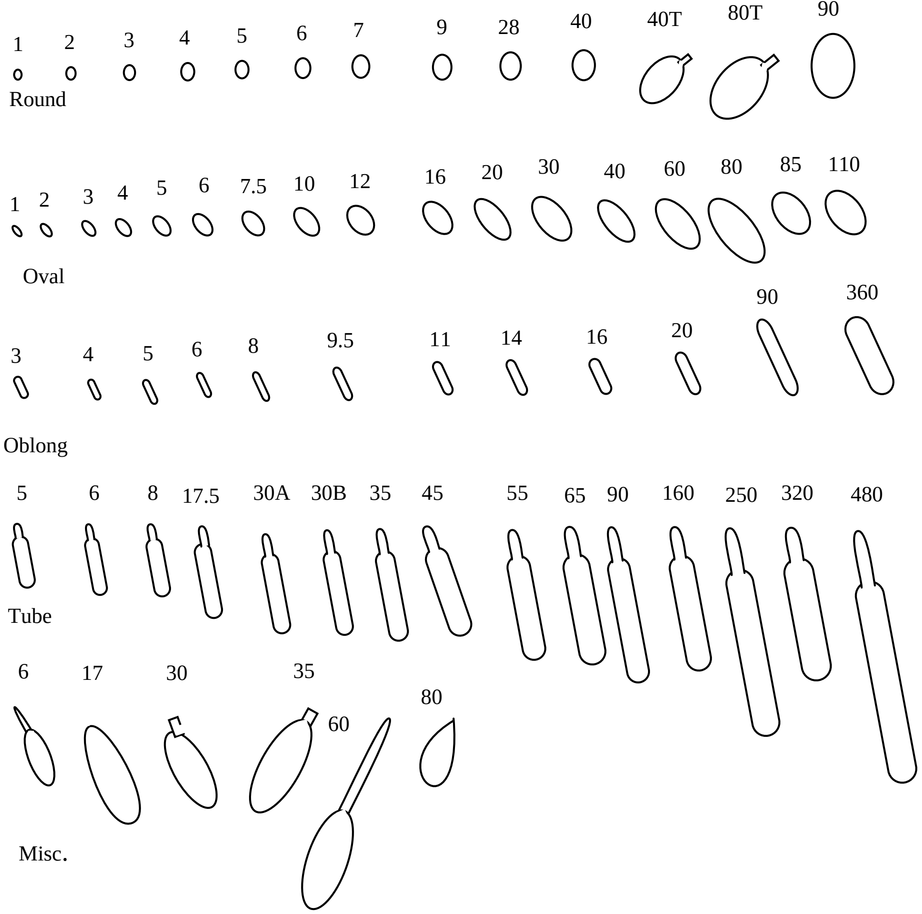


Figure 5.1: Sizes and Shapes of Soft Gelatin Capsules. Numbers represent the nominal capacity in minims (16.23 minims = 1 cc)

Different **shapes** and **capacities of soft gelatin capsules** are:

1) **Spherical:** 0.05-5ml
2) **Ovoid:** 0.05-7ml
3) **Cylindrical:** 0.15-25ml
4) **Tubes:** 0.5-0ml
5) **Pear Shaped:** 0.3-5ml

5.1.5. Production

Manufacturing process of soft gelatin capsule is divided into the following steps:

1) **Gelatin Preparation:** Raw granular gelatin is mixed with glycerine and water. Glycerine acts as a plasticiser in the gelatin compound . Other plasticisers can also be used either alone or in combination with glycerine, such as sorbitol. Colouring agent can also be added at this stage. The proportions of each ingredient involved in the mixture should be considered carefully because the shell material needs to be adapted to formulation and/or environmental requirements.

   After the ingredients are combined, the mixture is placed into a reactor, called as **gelatin melter (figure 5.2)**. This reactor is surrounded by a thermal jacket and heats the mixture while a very high torque turbine mixer stirs it under vacuum. At this stage, approximately 20% of gelatin mixture consists of water.

   This process takes around 3 hours until the gelatin turns into a molten liquid mass. As soon as the liquid gelatin mass is ready for encapsulation process, it is transferred to ground **heated tanks (figure 5.3)** which are wheeled into a clean room where the main encapsulation machine is located. The only way to keep the gelatin mixture in liquid form is to keep it warm; otherwise it will solidify into a gel.

Figure 5.2: Gelatin Melting Tank

Figure 5.3: Heated Tank

2) **Material Filling:** A homogeneous fill material plays a vital role to ensure the uniformity of each soft gel dose. Various equipment should be available such as processing tanks, high-shear mixer, homogeniser, and variety of mills. There are **two types of fill materials** , i.e., **oil mixtures** or **pastes**. Oil mixtures are very easy to formulate. The oils are mixed, deposited into a ground material tank, and moved into the hopper of the encapsulation machine. Pastes are oils or polyethylene glycols added with powders.

   Filling of Soft Gelatin Capsules

   i) **Plate Process:** A warmed sheet of plasticised gelatin is placed over a plate having a number of depressions or moulds; the sheet is drawn into these depressions by applying vacuum. A measured quantity of liquid medicament is poured over it, and then another sheet of gelatin is placed on it. Over this, another plate of the mould is placed and pressure is applied to the combined plates. The capsules are simultaneously shaped, filled, sealed, and cut into individual units.

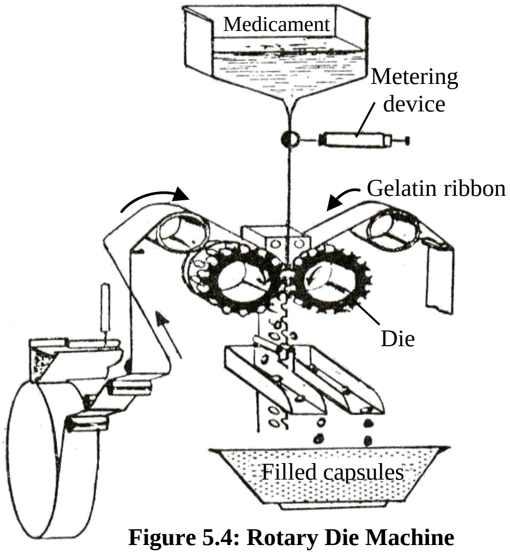


Figure 5.4: Rotary Die Machine

ii) **Rotary Die:** In this process, filled capsules are produced continuously and automatically. Two continuous sheets of gelatin are supplied to the two die rolls of the machine having a number of matching dies and rotate at the same speed in opposite direction. As the gelatin sheets come between the rollers, the material to be filled is injected through a metering device. The pressure exerted by the material forces the gelatin sheet to enter the cavities of the die rolls and form two halves of the capsule and fill them. These rotary die machines can produce 25000-30000 capsules per hour.

3) **Encapsulation:** It is the manufacturing process that brings the gelatin shell and the fill material together to form soft gel capsules. This process is carried out in a closed environment called **clean room** where the relative humidity is around 20%. The gelatin shell and fill material are brought together simultaneously in the **encapsulation machine** (**figure 5.5**).

The **process of encapsulation** involves the following **steps**:

i) A pump delivers the warm gelatin over two chilled drums located at the opposite sides of machine, through a spreader box that sits over each drum.

ii) The revolving stainless steel drum is about 24 inches in diameter and exposed to 400 CFM of 57-59°F air at 20% RH.

iii) The warm liquid gelatin flows over the drums and transforms the liquid gelatin into two solid ribbons of gel.

iv) The left and right ribbons pass over the rollers which feed them through two die rolls.

v) These die rolls determine the shape and size of soft gels and cut the soft gel shell from the ribbons as they turn around.

vi) Simultaneously, a sensitive and high accuracy, positive displacement pump delivers the fill materials into a heated wedge which sits between rotary dies.

vii) This wedge injects the fill material into the die cavities between ribbons just right before the die rolls, cut the ribbons and seal the two halves together.

viii) The cool, dry air congeals the gelatin as the drum rotates so that a tacky, elastic band rolls off the other end.

ix) This thin band is then automatically formed into capsules; filled with medicine, vitamins or other products; sealed and dropped into a tray.

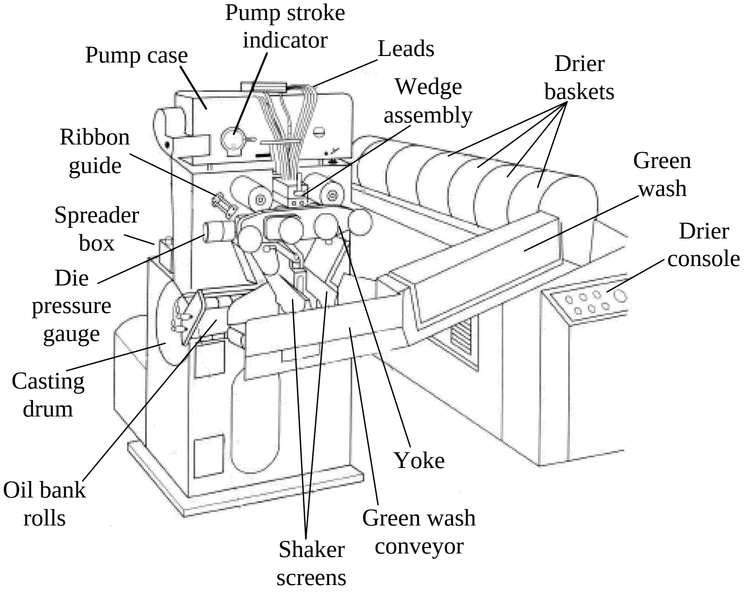


Figure 5.5: Soft Gelatin Encapsulation Machine

4) **Drying:** The purpose of this step is to decrease the moisture content and create hard and durable finished soft gel capsules. After the soft gels are formed through the die rolls, they contain around 20% water. This amount of water content is needed to keep the gel flexible enough to form capsules. Drying process requires an environment with low relative humidity in the air but not hot air.

The **drying process is divided into two stages**:

i) **First Stage:** This is performed by a **tumble dryer** (**figure 5.6**) which tumbles the soft gels around 30-40 minutes and removes approximately 25% of the water content.

Figure 5.6: Tumble Dryers – Leading to Drying Tunnels

ii) **Second Stage:** Soft gel capsules are spread on **stackable trays** (**figure 5. 7**) and transferred to the drying room or tunnel where high air flow exists. They stay around 24-48 hours in these rooms or until the soft gels become hard enough. This process is called **natural manual drying**. By using a fully automatic soft gel drying machine, this long drying process time can be reduced to a few hours.

Figure 5.7: Drying Trays and Soft gel Trays Cart

5) **Inspection:** Due to air pockets in the gelatin and fill material, the soft gel capsules may vary in size and need to be inspected visually. Any misshaped, damaged and/or not fully filled capsules are removed manually by using an inspection table. Manual inspection process can be preferred if the batch size is small; but if soft gel capsules are in large quantities, manual inspection will be a time consuming process which may also lead to accuracy problems. In order to reduce process time and increase the accuracy, fully automatic soft gel sorting machine equipped with electronic sensors can be used which sorts and removes the damaged, misshaped, broken, etc. gelatin capsules. An acceptable reject rate is 2-3%.

6) **Polishing:** The final step before packaging is to clean and polish the soft gel capsules to remove any mineral oil or glycerine that the capsules may have on their exterior skin. Tumbling is the most commonly preferred production method for cleaning the soft gel capsules instead of washing with solvent.

7) **Packaging:** There is no difference between packaging of soft gels and traditional tablets or hard capsules. Any finished soft gel product should be stored in an environment with temperature around 20-24°C and 35% relative humidity.

5.1.6. Importance of Base Adsorption (BA)

Base adsorption is expressed as the **number of grams of liquid base required to produce a capsulatable mixture when mixed with one gram of solid(s)**. The base adsorption of a solid is influenced by the solid particle's size and shape, its physical state (fibrous, amorphous, or crystalline), its density, its moisture content, and its oleophilic or hydrophilic nature.

In the determination of base adsorption, the solid(s) should be completely wetted by the liquid base. For glycol and non-ionic type bases, the addition of a wetting agent is seldom required, but for vegetable oil bases, complete wetting of the solid(s) is not achieved without an additive. Soy lecithin, at a concentration of 2-3% by weight of the oil, serves excellently for this purpose, and being a natural product, is universally accepted for drug use. Increasing the concentration above 3% appears to have no added advantage.

A practical procedure for **determining base adsorption** and for judging the adequate fluidity of a mixture involves the following **steps**:

1) A definite amount of the solid (40gm is convenient) is weighed and added into a 150ml tarred beaker.

2) In a separate 150ml tarred beaker, about 100gm of the solid base is added.
3) Small increments of the liquid base are added to the solid, and using a spatula, the base is stirred after each addition until the solid is thoroughly wetted and uniformly coated with the base.
4) This produces a mixture with soft ointment-like consistency.
5) The liquid is continued to added and stirred until the mixture flows steadily from the spatula blade when held at a 45-degree angle above the mixture.
6) At the conclusion of the foregoing test, the base adsorption is obtained by the following formula:

$$\frac{\text{Weight of Base}}{\text{Weight of Solid}} = \text{Base Adsorption}$$

5.1.7. Importance of Minim per Gram Factor (M/g)

The base adsorption is used to determine the minim per gram factor (M/g) of the solid(s). The minim per gram factor is the **volume in minims** that is **occupied by one gram (S) of the solid plus the weight of liquid base (BA) required for making a capsulatable mixture**. The minim per gram factor is calculated by dividing the weight of base plus the gram of solid (BA + S) by the weight of mixture (W) per cubic centimetre or 16.23 minims (V):

$$\frac{(BA + S) \times V}{W} = M/g$$

Thus, lower the base adsorption of the solid(s) and higher the density of the mixture, smaller the capsule will be. It also indicates the importance of establishing specifications for the control of those physical properties of a solid that can affect its base adsorption. The BA and M/g data need not be obtained on any material that is to be capsulated at concentrations of 50mg or less, since, the smallest capsules can accommodate such quantities. If such a material is to be used in combination, the data becomes necessary to allow for its inclusion in the formulation. The convenience of using M/g factors is particularly evident in the vitamin field, where there may be many ingredients and numerous combinations.

5.1.8. In-Process and Final Product Quality Control Tests

During the encapsulation process, the four most important **IPQC tests** are:
1) The gel ribbon thickness,
2) Soft gel seal thickness test conducted at the time of encapsulation,
3) Fill matrix weight and capsule shell weight test, and
4) Soft gel shell moisture level and soft gel hardness test conducted at the end of the drying stage.

Appropriate control levels for these parameters are established during process development for each soft gel product and are applied in routine production-scale manufacture.

Finished soft gels are subjected to a number of tests in accordance with compendia requirements for unit dose capsule products. These **QC tests** include:
1) Capsule appearance,
2) Active ingredient assay and related substances assay,
3) Fill weight (weight variation),
4) Content uniformity,
5) Microbiological testing, etc.

Some of the tests are discussed below:

1) **Permeability and Sealing:** This test ensures the physical reliability (absence of leakage) by visual examination of soft gelatin capsules.

2) **Potency and Impurity Content:** This test is performed to check the potency of drug as a percentage of drug content specified on the label. Many drug products are also checked for adulterated substances or impurities. These tests should meet certain predefined specifications required to pass a batch.

3) **Average Weight and Weight Variation:** In this test, 10 tablets are individually weighed. Each capsule is cut open and emptied by removing the contents through washing with a suitable solvent (which only dissolves the fill and not the shell). The solvent is allowed to evaporate at room temperature and then the empty shells are weighed again.

   The net content weight is calculated by subtracting the weight of empty capsules from that of filled capsules. The API quantity in each capsule is analysed by measurement based on the per cent drug content in the formulation.

4) **Uniformity of Content:** This test can be performed to determine the weight variation of filled soft gelatin capsules, if the drug loading is above 50% w/w. However, if the drug loading is below the standard threshold, every capsule needs to be analysed individually through potency method to determine the API content. The specifications for the range of weight variation of the APIs should meet with the predetermined standards to ensure content uniformity.

5) **Disintegration:** This test is performed to determine the dissolution and absorption of the drug from the GIT. Depending upon the type of capsule to be tested, the disintegration media may vary.

6) **Dissolution:** The dissolved state of the drug substance at the drug absorption site (the GI fluids) determines the absorption and physiological availability of the drug. Dissolution test evaluates the rate and extent of drug dissolution from the capsule dosage form. This test is an indispensible part of quality control process and it ensures:
   i) A number of drug batches having same drug release features, and
   ii) A batch with dissolution properties similar to previously prepared clinically effective capsules batch.

7) **Moisture Content:** This test is performed to assure appropriateness for packaging capsules by analysing several moisture-penetration features of a single-unit and unit-dose containers. In this test, a unit dosage is packed together with a colour-revealing desiccant pellet and this package is exposed to known relative humidity for a specific time period.

   The pellet is examined for any colour change (indicating moisture absorption). Finally, the pre- and post-weight of the packaged unit are compared to ensure test results. This test proves very helpful in determining the degree and rate of moisture penetration (if any).

8) **Microbial Content:** Microbiological tests are performed to check any bacterial and mould growth within the product. In these tests, capsule content is incubated in a sterile growth medium and observed after a definite time period for the presence of any bacterial colony. Microbial contamination can be successfully determined by considering the factors, like choice of growth medium, duration of test, and maintenance of aseptic conditions during test.

5.1.9. Packaging and Storage of Soft Gelatin Capsules

Dispensing of capsules should be carried out in **tightly closed containers** made up of glass or plastic. The containers should be **protected from dust** and **extreme conditions of humidity** and **temperature**. Controlled conditions of temperature and humidity should be maintained for storing capsule shells. They should have **10-15% of moisture content**. The shells become soft and sticky in high humidity conditions. The capsule shells intended for consumption by human are marketed in 8 sizes; among which the largest size is 000 and the smallest size is 5. For efficient handling and storing of capsules, extremes of temperature should be avoided and a **relative humidity of 40-60%** should be maintained.

The amount of drug a capsule can incorporate depends on its density and compressibility. The shell manufacturers provide a guidance regarding the quantities of drugs to be filled in capsules of different sizes.

The **glass or plastic containers** used for preserving capsules are preferred over cardboard boxes; this is because these containers are more convenient during handling and transportation of capsules, and they also provide **protection against moisture and dust**. The rattling (making sharp sounds due to agitation) of capsules can be prevented by placing a **cotton tuft over and under the capsules in the vials**.

A packet of **desiccant** (**e.g.,** silica gel or anhydrous calcium chloride) should be placed in the vials containing very hygroscopic capsules. Desiccant prevents excessive absorption of moisture by the capsules. At the present time, capsules are **strip packaged** which provide sanitary handling of medicines, and also eases their counting and identification.

Capsules should be stored in a **cool place**, at temperature not beyond 30 °C. The capsules contain 10-15% water; however this amount varies with the storage conditions. Under low humidity conditions, the capsules become brittle; while under high humidity conditions, they become soft and shapeless.

5.1.10. Stability Testing of Soft Gelatin Capsules

As per the effect of temperature and humidity on soft gelatin capsules, they are limited to a control capsule having mineral oil, a gelatin shell (with dry glycerine to dry gelatin ratio of approximately 0.5 to 1 and a water to dry gelatin ratio of 1 to 1), and dried to equilibrium having 20-30%RH at 21-24°C temperature.

Soft gelatin capsules have their physical stability affected by absorbing or losing water from capsule shell. The control capsule should have adequate physical stability at temperatures from above freezing to as high as 60°C.

With rise in humidity within an adequate temperature range, the unprotected control capsule shell attains moisture in proportion to its glycerine and gelatin. At equilibrium, the total moisture content of the capsule shell can be determined by relative humidity within a reasonable temperature range.

High humidities (>60% RH at 21-24°C temperature) affect the capsule shells more adversely as with the absorption of moisture the capsule shells become softer, tackier, and bloated. Leakage in capsule is observed when the moisture level makes the deleterious ingredient inside the capsule to attack gelatin. At optimum storage conditions, the capsules appear dull and stick together.

At elevated temperature (>24 °C) and humidity (>45% RH), rapid and marked effects like melting and fusion of unprotected capsules occur. Capsules with water-soluble or miscible liquid bases are affected more as compared to oil-based capsules, considering the residual moisture in the capsule content and the dynamic relationship among capsule shell and capsule fill during drying.

Each batch of new capsule undergoes accelerated physical stability tests as per the product development program. The IPQC tests are adequate to deduce the effect of capsule content over the gelatin shell. These tests are relevant to understand the integrity of the gelatin shell but should not be considered as stability tests for the active ingredients in the capsule. Such test results aid in the reformulation of capsule content or its shell, or for proper retail package selection. The **test conditions** are as follows:

1) At room temperature with 80% RH in an open container,
2) At 40°C in an open container, and
3) At 40°C in a closed container (glass bottle tightly closed).

At these stations, periodic inspection of capsules for two weeks is required. The gross and subtle effects on the capsule shell upon storage are recorded. There should be no effect on control capsule except at the 80% RH, where the capsule reacts as stated in effects of high humidity.

In new products, the gross effects like disintegration, leakers, unusual brittleness or softening, apparent colour fading, or discoloration are normally observed. The subtle changes involve evaporation of volatile ingredient as observed by slight capsule indentation, slight darkening or widening of the capsule seams, or minute alteration in colour hue. Capsules produced depict a "soft spot" at the site through which they lie next to the tray or touch another capsule. This spot occurs due to slower drying and has no consequence for the control capsule, as it will firm up and will not present flaws in the capsule shell.

However, if this site did not become firm due to the action by the capsule content, the physical stability problems for the shelf-life of the product can occur. Correction of such defects is crucial for production, and is achieved by identifying their cause. Majority of defects are rectified through suitable changes in gelatin or fill material. On the other hand, some defects are corrected utilising different colourants, machine speeds, and machine dies. Chemists performing physical stability tests in separate laboratories should consider the following two points:

1) Before testing, the capsules should be equilibrated to known atmospheric conditions (usually 20-30%RH at 21-24°C), and
2) The previously described heat test results should be evaluated after the capsules return to equilibrium with the room temperature.

5.1.11. Applications

The soft gelatin capsules are widely employed in pharmaceutical field. Some of them are stated below:

1) **Ophthalmic Soft Gelatin Capsules:** The ophthalmic ointments should be sterile and free from irritant effect. Therefore, they should be packed such that the product remains sterile until completely used up. Packing in single dose containers keeps the product free from contamination. Presently, soft gelatin capsules are commonly used for filling ophthalmic ointments. These capsules provide single application to the eye. They are punctured with a sterile needle before application, the drug inside is applied to the eyes, and the shells are discarded.

2) **Chewable Soft Gelatin Capsules:** These dosage forms offer good chewing experience than other chewable dosage forms. They are suitable for paediatric populations, where intake of whole tablets or capsules is problematic, and chewable tablets are not acceptable.

3) **Controlled Release Soft Gelatin Capsules:** A controlled release technology provides large variety of release patterns. The controlled release soft-gel can be used for a wide range of active molecules. This technology uses a lipid matrix in a standard soft-gel shell. As per the physicochemical properties of the API, the matrix could be an emulsion or a suspension. Finally, an oral dosage form is obtained providing controlled release of the active molecules, along with all the benefits of soft-gel dosage form.

4) **Enteric Coated Soft Gelatin Capsules:** The new enteric soft-gel requires no coating. The enteric features of this dosage form are present in the shell. The output is a clear enteric dosage form having the same appeal and patient benefits as the standard soft-gel offers. Conventionally, enteric soft-gels need to be coated with enteric polymers through the aid of traditional coating technology. Coating puts certain disadvantages like improper sticking of the enteric polymer over the soft gelatin shell due to the inherently flexible nature of the shell.

5) **Gelatin-Free Soft Gelatin Capsules:** These capsules are prepared from vegetable ingredients. They show advantages of standard soft-gels, but have no gelatin. They are a good option for vegetarians or other populations that prefer non-animal products.

6) **Suckable Soft Gelatin Capsules:** These capsules have a gelatin shell with flavoured medicament and a liquid matrix or simply air within the capsule. The drug may be added in both the shell and fill matrix.

7) **Twist-Off Soft Gelatin Capsules:** These capsules are formed with a tag to be twisted or snipped off, thereby releasing the fill material. Such dosage forms are suitable for unit dosing of topical medication, inhalations, or for oral dosing in paediatrics.

5.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) Soft capsules or liquid gel caps are formed from liquid gelatin that is later hardened in a humid environment.

2) Soft capsules have thicker shells than hard capsules, and contain antimicrobial preservatives.

3) The capsule shell is basically composed of gelatin, a plasticiser, and water; it may contain additional ingredients such as preservatives, colourants, and opacifying agents, flavours, sugars, acids, and medicaments to achieve the desired effects.

4) The bloom or gel strength of gelatin is a measure of the **cohesive strength of the cross-linking between gelatin molecules** and is proportional to the molecular weight of the gelatin. Bloom is determined by measuring the weight in grams.

5) The **higher the bloom strength of the gelatin** used, the **more physically stable is the resulting capsule shell**.

6) The ratio by weight of dry plasticiser to dry gelatin determines the **hardness of gelatin shell**, assuming that there is no effect from the capsulated material.

7) Spherical or oval capsules are also known as pearls or globules.
8) Dispensing of capsules should be carried out in **tightly closed containers** made up of glass or plastic.
9) The shells become soft and sticky in high humidity conditions.
10) Capsules should be stored in a **cool place**, at temperature not beyond 30°C.
11) The ophthalmic ointments should be sterile and free from irritant effect.
12) Base adsorption is expressed as the **number of grams of liquid base required to produce a capsulatable mixture when mixed with one gram of solid(s)**.

5.3. EXERCISE

5.3.1. True or False

1) Soft capsules are also known as liquid gel caps.
2) Capsules should be stored in a cool place, at temperature not beyond 40°C.
3) The bloom or gel strength of gelatin is a measure of the cohesive strength of the cross-linking between gelatin molecules.
4) Soft gel capsules are one continuous piece of gelatin.
5) Twist-off soft gelatin capsules have a gelatin shell with flavoured medicament.

5.3.2. Fill in the Blanks

6) __________ are also called as liquid gel caps.
7) ____________ test is performed to determine the dissolution and absorption of the drug from the GIT.
8) The shells become soft and sticky in high ___________ conditions.
9) Spherical or oval capsules are also known as _______ or globules.
10) The ratio by weight of dry plasticiser to dry gelatin determines the _________ of gelatin shell.

Answers

1) True
2) False
3) True
4) True
5) Fals
6) Soft gelatin capsules
7) Disintegration
8) Humidity
9) Pearls
10) Hardness

5.3.3. Very Short Answer Type Questions

1) Write a short note on soft gelatin capsules.
2) Discuss bloom or gel strength.
3) Write a short note on gelatin preparation.
4) Discuss the size of capsules.
5) Write about the viscosity of gelatin.

5.3.4. Short Answer Type Questions

1) Write a short note on encapsulation of soft gelatin capsule.
2) Discuss drying procedure of soft gelatin capsule.
3) Write the applications of soft gelatin capsules.
4) Discuss the importance of minim per gram factor.

5.3.5. Long Answer Type Questions

1) Write a detailed note on stability testing for soft gelatin capsules.
2) Give an exhaustive account on production of soft gelatin capsules.
3) Write a note on in-process and final product quality control tests for soft gelatin capsules.

CHAPTER 6

Pellets

6.1. PELLETS

6.1.1. Introduction

Pharmaceutical pellets are spherical or semi-spherical, free-flowing solid units with a narrow size distribution, varying between 500-1500µm in diameter. With the increase in complexity of drug-delivery systems, the role of pellets in design and development of dosage forms has increased. Drug formulation in multiple-unit dosage forms (like coated pellets filled in capsules or compressed into tablets) offers flexibility to target release properties. The safety and efficacy of such formulation is also relatively higher.

During the design and development of oral dosage, pellets provide a high degree of flexibility. They can be divided into desired dose strengths without changes in formulation or process, and can also be blended to deliver incompatible bioactive agents or particles with different release profiles at the same or different sites within the gastrointestinal tract.

An **ideal pellet** should have the following **properties**:

1) It should be spherical in shape.
2) It should have a smooth surface texture.
3) Its particle size should range between 500-1500µm.
4) It should hold maximum quantity of active ingredient to maintain its size.

Pellets also have many therapeutic advantages over traditional single units, such as tablets and powder-filled capsules. On oral administration, the pellets disperse freely in the gastrointestinal tract, maximise the drug absorption, minimise local irritation of the mucosa by some of the irritant drugs (because a small quantity of drug is incorporated in a single pellet), and reduce inter and intra-patient variability.

6.1.2. Formulation Requirements

Formulation aids or excipients are added to pharmaceutical dosage forms for satisfactory delivery of the drug to the target site, to impart favourable features to the dosage form, and to facilitate product manufacture. Since pellets are meant for oral administration, the excipients used are the same as those used in the formulation of tablets or capsules. Excipients, disintegrants, surfactants, pH adjusters, separating agents, spheronisation enhancers, glidants, release modifiers, etc. are some of the excipients (**table 6.1**) used in the formulation of pellets.

Table 6.1: Commonly Used Excipients for Formulation of Pellets

Excipients	Examples
Binders	Sucrose, Starch, HPMC, HPC, Gelatin, MC, and PVP.
Lubricants	Glycerine, PEG, Magnesium stearate, and Calcium stearate.
Separating agents	Kaolin, Talc, and Silicon dioxide.
Disintegrants	Alginate and Croscarmellose sodium.

pH adjusters	Citrate, Phosphate, and Meglumine.
Surfactants	SLS and Polysorbate.
Spheronisation enhancers	MCC and Sodium CMC.
Glidants	Talc, Starch, and Magnesium stearate.
Release modifiers	Ethyl cellulose, Shellac, and Carnauba wax.

6.1.3. Pelletization Processes

Pelletisation is an **agglomeration process** in which the fine powders or particles of bulk drugs and excipients are converted into small, free-flowing, and roughly spherical units called **pellets**. Pelletisation is often referred to as a **size-enlargement process** that involves the manufacture of agglomerates or pellets having a relatively narrow size range (mean size from 0.5-2.0mm). Pellets have free-flowing properties and a low porosity (about 10%).

The different types of pelletisation techniques are:

1) Direct pelletisation,
2) Pelletisation by drug layering,
3) Pelletisation by powder layering,
4) Pelletisation by suspension or solution layering,
5) Pelletisation by extrusion and spheronization,
6) Spherical agglomeration/balling,
7) Cryopelletisation,
8) Hot-melt extrusion technology (HME),
9) Globulation or droplet formation,
10) Compression,
11) Freeze pelletisation,
12) Fluid bed coating, and
13) Tangential spray coating (rotor pellet coating).

6.1.3.1. Direct Pelletization

In direct pelletisation technique, pellets are manufactured directly from powder with a binder or solvent. This process is fast and requires less auxiliary materials. By this technique, compact and round pellets of diameter between 0.2-1.2mm are obtained. Such pellets are ideal for automatic dosing and uniform coating. Pellets have a density higher than the spray granulates and agglomerates.

Process Principles

Powder is mixed and moistened with a solvent or binder. The obtained powder bed is subjected to centrifugation. The resultant impact and acceleration forces lead to the formation of agglomerates, which become rounder into uniform and dense pellets. The rotation speed directly influences the density and size of pellets. The moist pellets are dried in the fluid bed.

Direct pelletisation can also be carried out by spray granulation. With the addition of suitable excipients, pellets are either compressed into tablets or filled into capsules. The round shape of pellets makes them ideal for uniform coating, and they are also good for automatic dosing.

Figure 6.1 represents the various steps in the process of direct pelletisation:

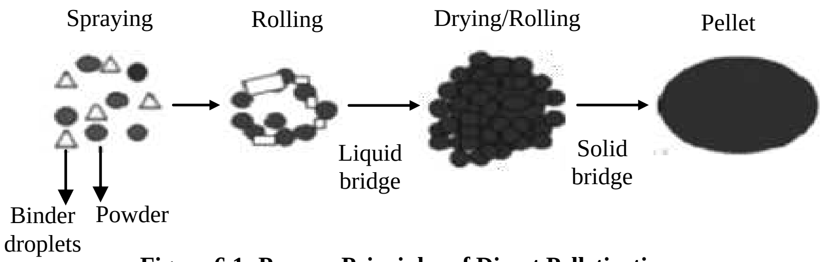


Figure 6.1: Process Principles of Direct Pelletization

6.1.3.2. Pelletization by Drug Layering

In the process of drug layering, successive layers of drug entities from solution, suspension, or dry powder are deposited on nuclei (crystals or granules of the same material or inert starter seeds). In solution or suspension layering, drug particles are dissolved or suspended in the binding liquid; while in powder layering, first a binder solution is sprayed on previously prepared inert seeds, and then the powder is added.

6.1.3.3. Pelletization by Powder Layering

In the process of powder layering (**figure 6.2**), dry powders of drugs and excipients are deposited with the help of binding liquids on pre-formed nuclei or cores. Since powder layering involves simultaneous application of binding agents and dry powders, it requires specialised equipment like spheroniser. The principal requirement of this process is that the product container should have solid walls with no perforations so that powder is not lost from beneath the product chute before the powder is picked-off by the wet mass of pellets being layered.

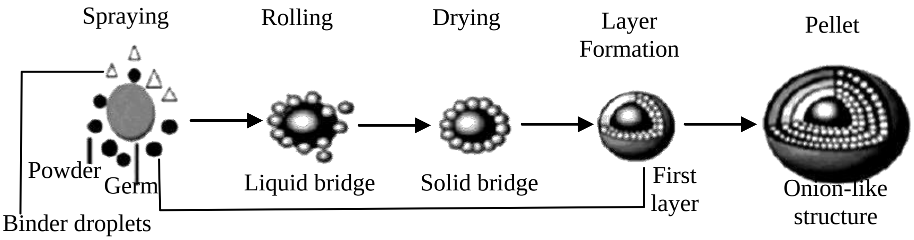


Figure 6.2: Principle of the Powder Layering Process

6.1.3.4. Pelletization by Suspension or Solution Layering

In the process of solution or suspension layering (**figure 6.3**), successive layers of solution and/or suspensions of drug substances and binder are deposited over the starter non-peril seeds (inert material or crystals or granules of the same drug). Since the general coating process is involved in solution or suspension layering, conventional coating pans, fluidised beds, centrifugal granulators, and Wurster coaters are used for manufacturing pellets. The efficiency of this process and the quality of obtained pellets are partially related to the type of equipment used.

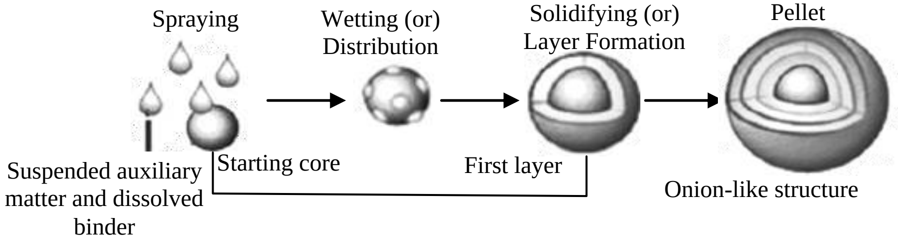


Figure 6.3: Principles of the Suspension and Solution Layering Process

6.1.3.5. Pelletization by Extrusion and Spheronization

In the process of extrusion and spheronisation (**figure 6.4**), first extrudes are made from the powder material using the extruder and then converted into beads (as fine as 0.6mm) using the spheroniser. The powder material could be a drug powder, Ayurvedic powder, food ingredient powder, detergent powder, nuclear powder, etc. The capsule filling method has to be gentle enough on the pellets to retain the integrity of coating; while in case of powder filling, the filling of pellets into capsules can be dependent or independent.

In the **dependent method**, a modified augur type machine is used, and the pellets are poured in the capsule shells under gravity. The formulation aspect of this approach is to ensure that the required dosage of active substance is present in the volume of pellets taken to fill the capsule body. In the **independent method**, a volumetric fill by a modified dosator method is used.

Since the piston in the dosator is narrower than that used for powder filling, the air flows between the piston and the dosator wall. The dosator is lowered into the pellet bed, but no compression is applied. A vacuum source is applied from above the piston to retain the pellets as the dosator is moved above the capsule body. The vacuum is removed once the dosator is over the capsule body, and the pellets are ejected with the help of an air jet.

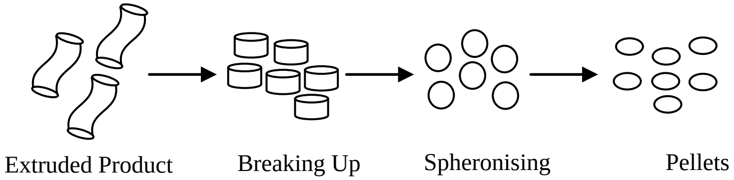


Figure 6.4: Principle of the Extruded Product Spheronising Process Filling Capsules with Pellets

6.1.3.6. Spherical Agglomeration/Balling

In spherical agglomeration process, powders are added with a suitable quantity of liquid or subjected to high temperatures to convert into spherical particles by a continuous rolling or tumbling action. Spherical agglomeration can be divided into **liquid-induced** and **melt-induced** agglomeration. Since many years spherical agglomeration is carried out in horizontal drum pelletiser, inclined dish pelletiser, and tumbling blenders. However in the recent technologies, rotary fluid bed granulators and high shear mixers are used.

6.1.3.7. Cryopelletization

In the process of cryo pelletisation, liquid nitrogen is used as a fixing medium to convert the droplets of liquid formulations into solid spherical particles or pellets. The technology initially developed for lyophilisation of viscous bacterial suspension can be used to produce drug-loaded pellets in liquid nitrogen at 160°C temperature. The procedure allows instantaneous and uniform freezing of the processed material due to the rapid heat transfer between the droplets, and thus the large surface area facilitates the drying process. The amount of liquid nitrogen required for manufacturing a given quantity depends on the solid content and temperature of the solution or suspension being processed. It is usually between 3-5kg per kilogram of finished pellets.

6.1.3.8. Hot-Melt Extrusion Technology (HME)

In the process of HME, the raw materials are pumped through a die (with a rotating screw under elevated temperature) into a uniformly-shaped product. Rotating screw facilitates mixing and agitation de-aggregates the suspended particles in the molten polymer, thus forming a more uniform dispersion.

6.1.3.9. Globulation or Droplet Formation

In the process of globulation, two related processes, i.e., spray drying and spray congealing are involved. In spray drying, the drugs in the suspension or solution without excipients are sprayed into a hot stream to produce dry and more spherical particles. This process is used for improving the dissolution rates, and hence the bioavailability of poorly soluble drugs.

6.1.3.10. Compression

In the process of compression (a type of compaction technique for preparing pellets), mixtures or blends of active ingredients and excipients are compacted under pressure to obtain pellets of definite sizes and shapes. The formulation and process variables controlling the quality of the obtained pellets are similar to those used in tablet manufacturing.

6.1.3.11. Freeze Pelletization

In the process of freeze pelletisation, a molten-solid carrier/matrix is introduced in the form of droplets into an inert column of liquid in which the molten solid is immiscible. The molten solid droplets move either upward or downward in the liquid column (depending on the droplet's density with respect to the liquid in the column) and solidify as spherical pellets.

If the density of the molten-solid carrier/matrix is less than that of the liquid in the column, the droplets are introduced from top of the column and the pellets solidify in the bottom. On the other hand, if the density of molten solid carrier/matrix is more than that of the liquid in the column, the droplets are introduced from the bottom and the pellets solidify at the top.

6.1.3.12. Fluid Bed Coating

Fluid bed coating for preparing pellets is of the following **three types**:

1) **Top Spray Coating:** With top spray coating in the fluid bed (batch and continuous), particles are fluidised in the flow of heated air introduced into the product container through the base plate (**figure 6.5**). The fluid bed is sprayed with the coating liquid through a nozzle from above against the air flow (counter-current). The particles dry as they continue to move upwards in the air flow. The coating liquid distributes uniformly owing to the small size of the droplets and low viscosity of the spray medium.

   Coating in the continuous fluid bed is suitable for protective or colour coatings where the product throughput rates are high. In this method, the product is continuously fed into one side of the machine and by means of air flow is transported forward via the sieve bottom. The dry coated particles are extracted continuously.

2) **Bottom Spray Coating (Wurster Coating):** This process is used when a controlled release of active ingredients is required. In the Wurster coating process (**figure 6.5**), the surface is sealed completely by less use of coating substance. The spray nozzle is fitted in the base plate resulting in a spray pattern concurrent with the air feed. By using a Wurster cylinder and a base plate with different perforations, the particles to be coated are accelerated in the Wurster tube and concurrently fed through the spray cone. As the particles move upwards, they dry and fall outside the Wurster tube back towards the base plate. They are guided from the outside back to the inside of the tube, where they are again accelerated by the spray, thus producing a highly uniform film even on different sized particles.

3) **Bottom Spray Coating (Continuous Fluid Bed):** This process is suitable for protective or colour coatings where the products throughput rates are high. The product is continuously fed into one side of the machine and by means of air flow is transported forward via the sieve bottom. Depending on the application, the system is sub-divided into pre-heating zones, spray zones, and drying zones where coating liquid is sprayed from below in the form of a bottom spray. The dry and coated particles are continuously extracted.

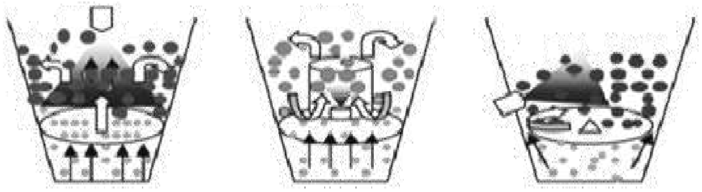

Top Spray Bottom Spray Tangential Spray

Figure 6.5: Tangential Spray Coating

6.1.3.13. Tangential Spray Coating (Rotor Pellet Coating)

In the process of tangential spray coating (**figure 6.5**), the product is set into a spiral motion by means of a rotating base plate which has air fed into the powder bed at its edge. The spray nozzle is arranged tangentially to the rotor disc and is sprayed simultaneously into the powder bed. This method is ideal for coatings with high solid content, and for applying thick film layers.

6.1.4. Equipments for Manufacture of Pellets

A pelleting system is made up of different machines designed to efficiently complete the task of pelletisation. An arrangement of a pelleting system showing all the equipments is represented in **figure 6.6**.

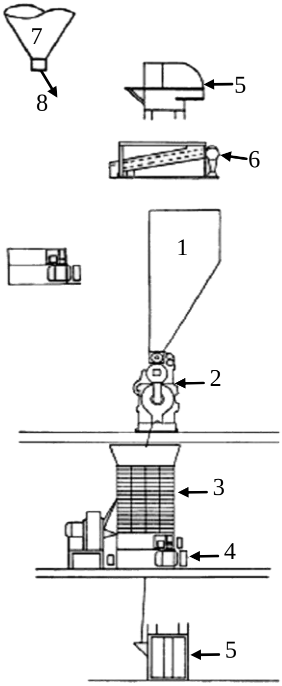


Figure 6.6: A Pelleting System with All the Equipments

The process of pelleting starts in the bin (**figure 6.6, item 1**) storing the mixture of mash, which flows into the pellet mill (**figure 6.6, item 2**) under gravity. The hot, extruded mash (now called pellets) from the pellet mill now flows into a cooler (**figure 6.6, item 3**) under gravity. Here it is cooled and dried by a flow of air for 3-6 minutes. This air is drawn through the mass of pellets and passed into a dust collecting device, such as a cyclone collector (**figure 6.6, item 7**). The dust from the outlet of the collector (**figure 6.6, item 8**) is returned to the pellet mill (**figure 6.6, item 2**) to be compacted again into a pellet.

The pellets from the cooler (**figure 6.6, item 3**) are passed through a pair of crumble rolls (**figure 6.6, item 4**) to be crushed to a smaller size so that a relatively fine product is obtained. If the full pellet size is to be obtained, the pellets from the cooler are flowed around the crumble rolls. The product from the crumble rolls flows into a bucket elevator (**figure 6.6, item 5**) to be raised to a higher point, where the shaker (**figure 6.6, item 6**) separates the product into various sizes by passing the material through a number of screens, each of a different opening size. This step allows the separation of the desired product from the larger or smaller particles and then delivering the finished product to the bin. The remnants are returned to the pellet mill for re-pelleting or, in case of crumbles, they are returned to the cooler, and then through the crumble rolls for re-crumbling. The fines or smaller materials are routed back to the pellet premix bin and reprocessed through the pelleting system.

6.1.4.1. Supply Bins

The supply bins located ahead of the pellet mill, should store a sufficient quantity of feed to provide a continuous operation of the pelleting unit and also a continuous operation of the mixer which provides mash to the pelleting unit. The supply bin should have at least two bins, each of a capacity thrice the capacity of the batch mixer used to supply feed to the pelleting unit. This type of supply bin results in an efficient mixing as well as pelleting.

These supply bins should be constructed of sheet metal. Rectangular or square construction is suited best; however, round bins can also be used. Numerous vertical sides should be incorporated into the design. In many pelleting systems, a small feed supply bin (of capacity less than 1000 lb.) is fed by start-and-stop conveyors from the main supply bins, and is equipped with bin level controls.

6.1.4.2. Pellet Mills

The thoroughly mixed ingredients (now called mash or meal) flow into a flow rate regulator called a feeder (**figure 6.7, item 1**) under gravity. Feeder is a screw-type with some variation in flight arrangement, such as single flight, double flight, full pitch, or one-half pitch to perform even under varying conditions. It is equipped with speed controlling devices, such as a variable speed electric drive. It provides a constant, controlled and uniform flow of feed to the mixing and pelleting operation, and variation in this flow leads to poor conditioning and a variable product.

The feeder delivers a constant and prescribed amount of the mash to a conditioning chamber (**figure 6.7, item 2**) to be thoroughly mixed with steam (heat and water) and other desirable liquids, such as molasses. A mixer is provided for conditioning the feed appropriately by adding controlled amounts of steam, which supplies moisture for lubrication, liberates natural oils, and results in partial gelatinisation of starches. This mixer if properly equipped can also be used for adding 6-8% molasses.

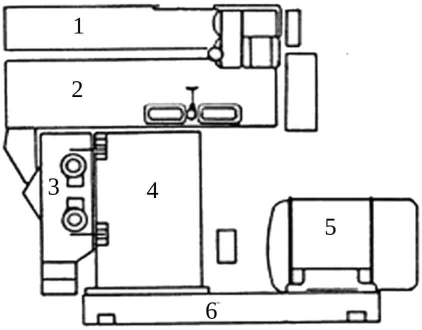


Figure 6.7: Component Parts of a Conventional Pellet Mill; 1) Feeder; 2) Conditioning Chamber; 3) Pelleting Device; 4) Speed Reduction Device; 5) Motor; 6) Base

The conditioned mash now flows under gravity into the pellet mill die chamber (**figure 6.7, item 3**) where the softened mash is pressed by the rollers (**figure 6.8, item 4**) through the holes in a circular die (**figure 6.8, item 5**). Stationary knives (**figure 6.8, item 3**) equipped outside the die cut off the shaped, dense pellet in desired length.

In the modern pellet mills, a ring type die and rollers are mounted in a vertical plane with the die turning about the two fixed rollers. In some mills, the dies and rollers are mounted in a horizontal plane with the rollers turning within the stationary die.

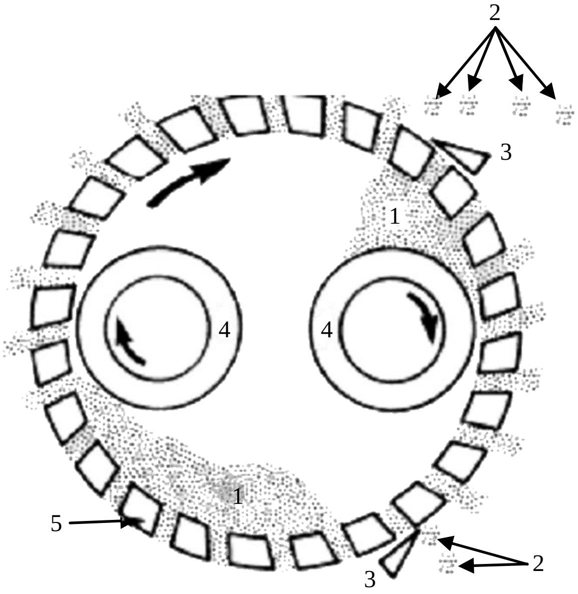


Figure 6.8: Typical Die and Roller Assembly used for Producing Pellets [1) Meal or Mash; 2) Pellets; 3) Blades; 4) Rollers; 5) Die]

In the pelleting unit, the conditioned mash is forced by roller pressure through the die holes. Die thickness should be accurately balanced with the formulation and conditioning as it is responsible for the production of high quality pellets.

The pellet mills are also equipped with speed reduction devices (**figure 6.7, item 4**) (such as direct coupled gear trains, V-belts, cog belts and combinations of belts and gear trains), since the speed of dies is always less than the conventional motor speeds. Pellet mills are mostly installed with an electric motor (**figure 6.7, item 5**) as the prime mover; however, internal combustion engines may also be used.

When internal combustion engines are used, the horsepower rating should be at least twice of that of the electric motor used. The pellet mill and motor are mounted on the same base (**figure 6.7, item 6**) to maintain alignment of the pellet mill and motor and to provide a rapid, simple and efficient method of installing the equipment. An ammeter should be equipped as part of the electrical system for adjusting the feed rate to secure the maximum capacity of the mill without overloading the motor.

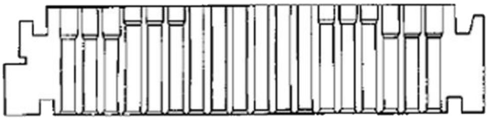
6.1.4.3. Pelleting Dies

Die thickness and hole size varies with the type of product to be pelleted. Relieved dies have an enlarged diameter on the discharge side of the hole. Relief length is the distance of the die hole with a greater diameter than the other holes.

Standard Die

Standard Relieved Die

Standard Variable Relief Die



Staggered Relief Die

Figure 6.9: Types of Dies

The following **types of dies** (**figure 6.9**) are generally used in the pelleting system:

1) **Standard Die:** In this type, all the holes have the same effective thickness.
2) **Standard Relieved Die:** In this type also, the holes have the same effective thickness, but the discharge side of the hole is enlarged to a depth of 1/4” (relieved). This die is used for adding strength to the die without increasing the thickness of the hole depth.
3) **Standard Variable Relief Die:** In this type, all the holes are same except the two or three outside rows of the die, which are relieved by 1/4”. Some products while being pelleted squeeze out to the side of the die, thus plugging the two or three outside rows. This loses 25% of the die effectiveness.
4) **Staggered Relief Die:** This type serves as the standard variable relief die, except that the two or three outside rows are relieved by 1/2” and the next two or three rows are relieved by 1/4”.

6.1.4.4. Coolers

The pellets from the pellet mill flow under gravity into a device for cooling and drying. When the pellets leave the pellet mill, they are at very high temperatures (190°F) and also have high moisture content (17-18%). Proper storage and handling of the pellets demand their moisture content to be reduced to 10-12% and their temperature to be maintained at 15°F above atmospheric temperature.

This can be accomplished by passing an air stream through a bed of pellets, which evaporates the excess moisture and cools down the pellets (by evaporating the water from the pellets and also by contact with them). The capacity of air to hold water increases two folds with every 20° rise in temperature. Thus, warmer the air, the more moisture it should remove from the pellets.

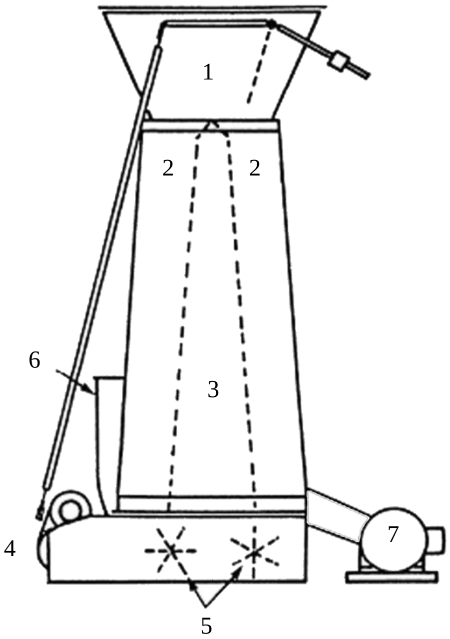


Figure 6.10: Component Parts of a Vertical Pellet Cooler 1) Hopper and Level Sensing Device to Maintain a Supply of Pellets Ahead of Cooling Columns; 2) Cooling Columns; 3) Air Chamber; 4) Discharge Drive Gate Motor and Controls; 5) Discharge Gates; 6) Centrifugal Fan; 7) Fan Drive Motor

Most coolers are either vertical or horizontal. The construction and working of a **vertical cooler** is simple. It has two columns of pellets located side by side and held by wire mesh on both sides. A fan is used to pass air through these columns. The pellets from the pellet mill flow under gravity into the columns (**figure 6.10, item 2**) through the funnel-shaped hopper (**figure 6.10, item 1**) above them, up to the level sensing device near the top of the hopper. Pellets resting in the hopper act as an air seal and forces the cooling air to pass through the column of pellets to reach the fan (**figure 6.10, item 6**).

The pellets on reaching the level sensing device in the hopper starts the discharge gate drive motor (**figure 6.10, item 4**) that turns the discharge gates (**figure 6.10, item 5**) at the bottom of each column. As a result, the level of pellets in the cooler is lowered to accommodate the continuous flow of hot pellets from the pellet mill. While the flow of pellets through the columns is being automatically related to the production rate of the pellet mill, the fan (**figure 6.10, item 6**) draws air through the columns of pellets into the air plenum chamber (**figure 6.10, item 3**), and discharge this feed dust laden air to a cyclone dust collector.

The working of **horizontal cooler** is similar to that of the vertical cooler; however, its construction (shape) is significantly different. The horizontal cooler instead of two columns of pellets moving down, has a bed of pellets resting on a perforated steel or solid pan moving belt that is slowly passed through the cooling air stream. The major **advantage** of the horizontal cooler over the vertical cooler is that the former with its moving bed mechanically moves and discharges the pellets, thus providing the positive flow action required while processing the pellets which otherwise may congeal. In a vertical cooler on the other hand, the pellets which are sticky due to high molasses content may stick together during drying and cooling, thus preventing their normal flow through the unit.

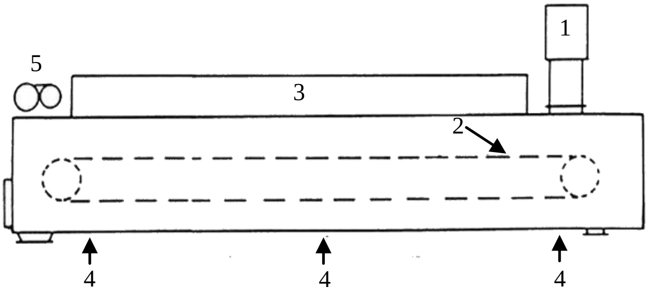


Figure 6.11: Component Parts of a Horizontal Pellet Cooler. 1) Feeder Device; 2) Product Carrying Belt; 3) Air Chamber; 4) Air Inlets; 5) Cooling Belt Drive

In a **horizontal cooler**, the pellets flow under gravity into a spreading device that spreads them to a uniform bed depth across the belt (**figure 6.11, item 2**). This device can be an oscillating feeder (**figure 6.11, item 1**) or a surge hopper with a discharge gate having a fixed opening so that the belt gets filled with pellets to a specific depth. A level control on the inlet hopper senses the accumulation of pellets, and starts and stops the cooling belt drive (**figure 6.11, item 5**).

This type of control is similar to the operating control in the vertical coolers. When the product is conveyed by the perforated belt, a suction fan draws cooling air through the air inlets (**figure 6.11, item 4**). These inlets are holes cut into an airtight housing to direct the air to a point under the bed of pellets. The air travels up through the bed into the air plenum chamber (**figure 6.11, item 3**), and then to the fan and/or the dust recovery system.

6.1.4.5. Crumble Rolls

A crumbling process should be used for producing pelleted feed particles smaller than 10/64". In this process, small pellets are broken between two powered corrugated rolls, placed below the cooler; thus an additional rate controller is not required.

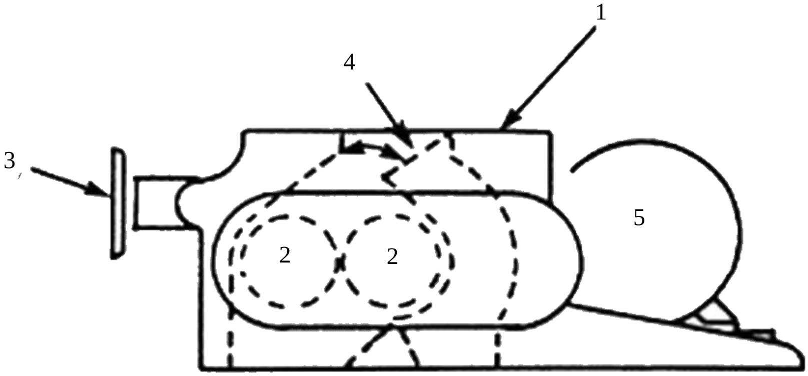


Figure 6.12: Typical Crumbling Roll. 1) Framework and Housing; 2) Corrugated Rolls; 3) Roll Adjustment; 4) By-pass Valve; 5) Motor

A crumbling roll has heavy steel frame and housing (**figure 6.12, item 1**). The corrugated rolls (**figure 6.12, item 2**) are 8 -12 inches in diameter and 72 inches long. Each corrugation is spaced at 6 -12 inches (**figure 6.12, item 3**). This controls the sizing or degree of crumbling of the product. A by -pass valve (**figure 6.12, item 4**) directs the pellets around the outside of the rolls when the product is not required to be crumbled.

6.1.4.6. Shaker

The product (either whole or crumblised) from the crumbling device is passed to a shaker (screening device) that extracts the undesirable undersized portions of the product from the correctly sized material. The undersized product is returned to the pellet mill for re-pelletisation and is termed recycle or fines. When a product is being crumblised, some pellets may not properly break to a specific size and remain oversized. These particles are removed by screening and returned to the original crumbler roll for reprocessing and are again screened. Around 25-30% of fine materials are returned through the crumbling process for reworking.

The screening devices used today are mainly oscillating, vibrating, or gyrating wire or metal screens with appropriate opening sizes. An oscillating pellet screen (or scalper) has a steel or wood frame (**figure 6.13, item 1**) from which the screens (**figure 6.13, items 4 and 5**) are supported or suspended. The screen frames are oscillated by an eccentrically-weighted drive unit (**figure 6.13, item 2**) powered by an electric motor (**figure 6.13, item 3**).

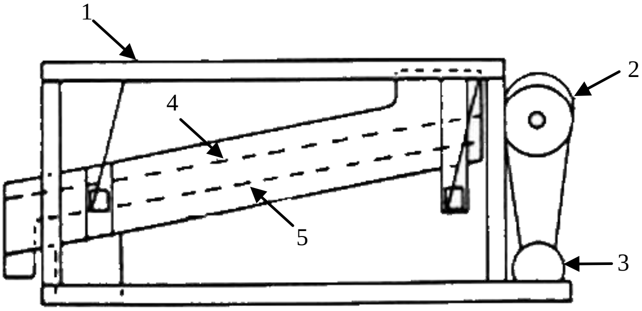


Figure 6.13: Component Parts of an Oscillating Pellet Scalper 1) Frame; 2) Drive; 3) Motor; 4) Top Screen for Finished Pellets and for Rejection of Larger-Than-Desired Crumble Particles; 5) Bottom Screen for Finished Crumbles

6.1.4.7. Pellet Elevating Systems

The correct sized product in its finished form is obtained from the shaker and is ready for packaging or shipment. In many mills, the pellet shaker is located on the upper floors of the unit so that the screened product, the oversize crumbles, and the fines flow under gravity to their correct destination. This requires that the unscreened pellets are conveyed vertically (elevated) from the cooler to the shaker.

In other mills, the shaker is located below the cooler and the sized finished product is conveyed to the packaging or bulk shipping point. In both the cases, an elevating system (vertical conveyor) is required. This can be done either mechanically by using a bucket elevator (also called a leg) or pneumatically by using an air conveying system. Air systems are used for conveying the hot pellets because they are not as subject to the build-up of hot, wet material as is a bucket elevator. Bucket elevators are used as they are less expensive, and their installation, maintenance and working is easy.

6.1.5. Evaluation of Pellets

Pellets can be evaluated based on the following parameters:

1) **Size Distribution:** The size of pellets can be determined by sieve shaking method, microscopy, Scanning Electron Microscopy (SEM), using vernier calliper, etc. Out of these, the **sieve shaking method** is most extensively used for measuring particle size distribution. Microscopy is a direct method for determining particle size distribution. The diameter of pellets can be measured by **optical microscopy** and **SEM**.

2) **Pellet Shape:** The shape of pellets can be determined by microscopic and non-microscopic techniques. Pellets shape is related to geometric shape and shape regularity (rugosity), thus it affects the surface area, flow of particles, packing and compaction properties of the pellet. Determining whether the particle shape is spherical or asymmetric is also possible.

   Since a sphere has minimum surface area per unit volume, these properties can be compared for spheres and asymmetric pellets. The shape factor of a pellet can be expressed as the ratio of surface to volume. If the pellet has a minimum value for shape factor, i.e., 6, it is considered to be spherical; and if the ratio is more than this factor, the pellet is asymmetric.

3) **Surface Morphology:** The surface morphology and cross-section of pellets can be determined by SEM. Before the pellets are examined under a SEM, their coatings were sputtered with aluminium under argon atmosphere. Micromeritic properties of pellets include **angle of repose** (θ), which is the measure of frictional force between the pellets and also measures the angle between the horizontal plane and the surface of the pile of pellets.

   Angle of repose is measured to determine the flow property of matrix pellets. **Tap and bulk density** of the pellets are determined using tap density tester, and **granule density** is determined by petroleum ether displacement method. **Friability** of pellets is determined using Roche friability tester in which a known mass of pellets are placed and rotated at 25 rpm for 4 minutes.

4) **Mechanical Strength**
   i) **Tensile Strength:** It can be determined using tensile apparatus. Pellets are strained with 5kg load cell until failure occurs. Tensile strength is determined by measuring the value of failure load and the radius of pellets.

   ii) **Crushing Strength and Elastic Modulus:** Crushing strength is the measure of load required to break the pellets, while elastic modulus is the measure of load required to begin plastic deformation. Crushing strength and elastic modulus of 15 pellets (850-1000mm size fraction) can be measured using material testing machine.

5) **Specific Surface Area:** It is the surface per unit volume, and it directly affects the size and shape of pellets. The knowledge of surface area is significantly important if the film coating of the pellets is to be done. It is also important for uncoated pellets as the surface area of pellets directly influences the drug release profile.

   Specific surface area of pellets is determined by the following **methods**:
   i) **Mathematical Calculations:** Surface area is calculated by πr^2, since smooth and dense spherical pellets has minimum surface area per unit volume, it can be characterised by its diameter.

   ii) **Air Permeability Method:** Surface area of pellet is the measure of hindrance that occurs to the fluid flow such as air through a plug of compact pellets. Greater the surface area per gram of pellet, greater is the resistance to flow.

   iii) **Gas Adsorption Technique:** In this technique, the volume of nitrogen adsorbed by the pellets contained in an evacuated glass bulb at different pressure can be determined from the linear plot of the BET (Brunauer, Emmett and Teller) equation.

6) **Disintegration Time:** It is an important characteristic for immediate release pellets, and is determined using the disintegration apparatus. Disintegration of pellets can be performed in a reciprocating cylinder (USP Apparatus 3) or in a tablet disintegration tester having transparent tubes attached with a sieve (710 mm) at the top and bottom.

7) ***In vitro* Dissolution Studies:** This evaluation parameter determines the release behaviour of a dosage form. The relationship between *in vitro* release and *in vivo* absorption can be determined by performing this test for different formulations in different dissolution media.

   The release behaviour of a dosage form is influenced by its composition (i.e., the type of polymer and binder used), characteristic of the pellets (like hardness and surface area), size of pellets, type of granulating liquid, the drug properties (like aqueous solubility and physical properties of the drug), and the additives (like surfactants, polymers, etc.). *In vitro* dissolution studies are carried out using USP Apparatus I or II.

6.1.6. Advantages of Pelletization

The advantages of pelletisation technique are given below:

1) Pelletisation reduces variations in gastric emptying rates and overall transit times, thus reduces intra- and inter-subject variability of plasma profiles.
2) It also produces spheroids with high loading capacity of active ingredient without producing large particles. Pellets when formulated as modified release dosage forms are less susceptible to dose dumping than compared to reservoir type single unit formulations.
3) Incompatible drugs processed separately and mixed later, or pellets with different release mechanisms can be mixed to obtain a new modified release profile.
4) They can be given to patients having difficulty in swallowing and dysphagia.
5) They exhibit better roundness and have excellent flow and packing properties.
6) They are composed of different drugs blended and formulated in single unit dosage form, thus facilitates the delivery of two or more chemically compatible or incompatible drugs at the same or different sites in GIT.
7) They reduce peak plasma fluctuations and the potential side effects without affecting the drug bioavailability.
8) They freely disperse in the GIT, thus providing greater surface area for the absorption of active drug.
9) Small pellets (less than 2-3mm) rapidly pass the pylorus irrespective of the filling level of the stomach or the size and density of chyme.
10) The particles also spread in the intestine, thus cause limited GI irritations.

6.1.7. Disadvantages of Pelletization

The disadvantages of pelletisation technique are given below:

1) **Higher Processing Costs:** Use of a binder and the drying step results in higher processing costs when compared to compaction granulation.

2) **Requirement of a Skilled Operator:** For producing pellets with desired quality and characteristics and to keep the pelletisation process running smoothly, well-trained and skilled operators are required.

6.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) Pharmaceutical pellets are spherical or semi-spherical, free-flowing solid units with a narrow size distribution, varying between 500-1500μm in diameter.
2) Pelletisation is an **agglomeration process** in which the fine powders or particles of bulk drugs and excipients are converted into small, free-flowing, and roughly spherical units called **pellets**.
3) Pelletisation is often referred to as a **size-enlargement process** that involves the manufacture of agglomerates or pellets having a relatively narrow size range (mean size from 0.5-2.0mm).
4) In direct pelletisation technique, pellets are manufactured directly from powder with a binder or solvent.
5) In the process of drug layering, successive layers of drug entities from solution, suspension, or dry powder are deposited on nuclei (crystals or granules of the same material or inert starter seeds).
6) In the process of powder layering, dry powders of drugs and excipients are deposited with the help of binding liquids on pre-formed nuclei or cores.
7) In the process of solution or suspension layering, successive layers of solution and/or suspensions of drug substances and binder are deposited over the starter non-peril seeds (inert material or crystals or granules of the same drug).
8) In the process of extrusion and spheronization, first extrudes are made from the powder material using the extruder and then converted into beads (as fine as 0.6mm) using the spheroniser.
9) In spherical agglomeration process, powders are added with a suitable quantity of liquid or subjected to high temperatures to convert into spherical particles by a continuous rolling or tumbling action.
10) Spherical agglomeration can be divided into **liquid-induced** and **melt-induced** agglomeration.
11) In the process of cryo pelletisation, liquid nitrogen is used as a fixing medium to convert the droplets of liquid formulations into solid spherical particles or pellets.
12) In the process of Hot-melt extrusion, the raw materials are pumped through a die (with a rotating screw under elevated temperature) into a uniformly-shaped product.
13) In the process of globulation, two related processes, i.e., spray drying and spray congealing are involved. In spray drying, the drugs in the suspension or solution without excipients are sprayed into a hot stream to produce dry and more spherical particles.
14) In the process of compression (a type of compaction technique for preparing pellets), mixtures or blends of active ingredients and excipients are compacted under pressure to obtain pellets of definite sizes and shapes.
15) In the process of freeze pelletisation, a molten-solid carrier/matrix is introduced in the form of droplets into an inert column of liquid in which the molten solid is immiscible.
16) In the process of tangential spray coating, the product is set into a spiral motion by means of a rotating base plate which has air fed into the powder bed at its edge.
17) The diameter of pellets can be measured by **optical microscopy** and **SEM**.
18) **Tensile Strength** can be determined using tensile apparatus.
19) Pellets reduce peak plasma fluctuations and the potential side effects without affecting the drug bioavailability.

6.3. EXERCISE

6.3.1. True or False

1) Tensile Strength is determined using tensile apparatus.
2) In the process of cryo pelletisation, liquid nitrogen is used as a fixing medium to convert the droplets of liquid formulations into solid spherical particles or pellets.
3) The safety and efficacy of formulations containing pellets is relatively lower.
4) Greater the surface area per gram of pellet, lesser is the resistance to flow.
5) The pellets from the pellet mill flow under gravity into a device for cooling and drying.

6.3.2. Fill in the Blanks

6) ___________ can be determined using tensile apparatus.
7) Spherical agglomeration can be divided into liquid-induced and ____________ agglomeration.
8) __________ is the measure of load required to break the pellets.
9) __________ is the measure of load required to begin plastic deformation.
10) A pelleting system is made up of different machines designed to efficiently complete the task of _________.

Answers

1) True
2) True
3) False
4) False
5) True
6) Tensile Strength
7) Melt-induced
8) Crushing strength
9) Elastic modulus
10) Pelletisation

6.3.3. Very Short Answer Type Questions

1) Write a short note on pellets.
2) Give the formulation requirements for pellets.
3) Discuss direct pelletisation.
4) Discuss cryopelletisation.
5) Write a short note on supply mills.

6.3.4. Short Answer Type Questions

1) Give the advantages and disadvantages of pelletisation.
2) Write a short note on coolers used for pelletisation process.
3) Discuss any three pelletisation processes.
4) Write a short note on supply mills and pelleting dies.

6.3.5. Long Answer Type Questions

1) Give the evaluation procedures of pellets.
2) Discuss the equipments used for manufacturing pellets.
3) Give a detailed account on pelletisation processes.

CHAPTER 7

Parenteral Products

7.1. PARENTERAL PRODUCTS

7.1.1. Introduction and Definition

The term **parenteral** has been derived from the Greek word ***para enteron*** which means **outside the intestine**. Parenteral dosage forms are unique from other dosage forms as they are administered by injecting directly into the body tissues through skin and mucous membranes, which form the primary protective systems of the body. Thus, parenteral preparations (par + enteral) as the name suggests are **administered from other than enteral routes** (i.e., oesophagus, stomach, intestinesare bypassed by the parenteral drugs).

The parenteral products should be pure and should not be contaminated with agents of physical, chemical, and biological origin. To meet these requirements, the pharmaceutical industries manufacturing parenteral dosage forms should practice the current Good Manufacturing Practices (cGMPs). The pharmacists and other health care professionals while dispensing parenteral dosage forms to patients should also practice Good Aseptic Practices (GAPs).

7.1.2. Types

Given below are the different types of available parenteral formulations:

1) **Transfusion Fluids:** These are parenteral solutions administered by intravenous route. Some **examples** are sodium chloride, Ringer's solution, and dextrose.
2) **Solutions or Emulsions of Medicaments for Injections:** These are used as injections and available in single dose or multiple dose containers. Some **examples** are diclofenac sodium and dexamethasone.
3) **Powder for Injections:** These are sterile solid preparations distributed in their final volume when the vial or container is shaken to form a clear particle-free solution.
4) **Lyophilised Powders for Injections:** These dosage forms during administration are converted into solutions or suspensions after reconstitution. An **example** is ceftriaxone injection.
5) **Colloidal Solutions:** These are homogeneous solutions in which the particles are dispersed in the liquid phase. These are normal solutions of sodium chloride (0.9% w/v concentration, i.e., close to the concentration in blood). An **example** is iron dextran.
6) **Concentrated Solutions for Injections:** These solutions are diluted with water for injection before administering through injection or intravenous infusion.
7) **Injectable Emulsions:** These are liquid preparations in which the drug substances are dissolved or dispersed in a suitable emulsion medium. Injectable lipid emulsions provide essential fatty acids and vitamins, thus have been used since ages as a source of energy for hospitalised patients. Nowadays they are administered intravenously for delivering lipid-soluble therapeutic agents due to the biocompatible nature of the lipid-based delivery systems. An **example** is propofol US.

8) **Injectable Suspensions:** These are liquid preparations in which the solids are suspended in a liquid medium. They are used as sustained or controlled release parenteral dosage forms for prolonging the drug action. On subcutaneous or intramuscular administration, they provide prolonged action compared to the aqueous solutions. An **example** is methylprednisolone acetate.

9) **Oily Injections:** These are used to prepare parenteral controlled release dosage forms. The drug release in oily injections is controlled by the drug partitioning into the aqueous medium from the oil medium. An **example** is dimercaprol injection.

10) **Implants:** These are sterile solids implanted in the tissues to release the active ingredient for prolong periods. They are stored in individual sterile containers.

11) **Sterile Solids:** These preparations are dry sterile solids dissolved in a solvent and then administered in the body. They are available in dry solid forms as the drugs lose their stability in solution forms. An **example** is benzylpenicillin G sodium injection.

Parenteral preparations are further categorised into the following types as per their dosing:

1) **Single-Dose Preparations:** These preparations can be used once. They contain sufficient quantity of the injection which permits easy drawing and administration of the volume specified on the label.

2) **Multi-Dose Preparations:** These preparations contain an antimicrobial preservative in appropriate concentrations; however, the formulations already exhibiting antimicrobial properties are not added with preservatives. They are meant for multiple dosing, thus the chances of contamination increases after partial withdrawal. Therefore, the containers should be equipped adequately to ensure protection of the contents that should not exceed 30ml (as the contamination risk is high with multiple penetrations of closures).

7.1.3. Advantages

Given below are the advantages of parenteral formulations:

1) On intravenous administration, an immediate physiological response is achieved, which is important in acute medical conditions, **e.g.,** cardiac arrest, anaphylactic shock, asthma, hyperglycaemia, hypoglycaemia, etc.
2) They are essential for drugs with poor bioavailability or that degrade rapidly within the gastrointestinal tract (**e.g.,** insulin and other peptides).
3) They can be administered to unconscious or uncooperative patients or to the patients with nausea and vomiting.
4) They are administered by trained medical staff, thus the dosage and frequency of administration are both controlled.
5) They may give rise to local effects, **e.g.,** local anaesthesia.
6) They are also used to correct the electrolyte imbalances (using infusion solutions).
7) They may be readily formulated to offer a wide range of drug release profiles, including:
    i) Rapidly acting formulations (intravenously administered drug solutions), and
    ii) Long-acting formulations (intramuscularly or subcutaneously administered drug suspensions or solutions in which the drug is precipitated out of solution at the injection site). Intermediate/long-acting insulin formulations and steroid injections are the **examples** of such formulations.
8) Specially formulated solutions are infused to provide total parenteral nutrition to the patients who cannot consume food.

7.1.4. Limitations

Given below are the limitations of parenteral formulations:

1) Their manufacturing process requires aseptic techniques, thus is complicated than other formulations.
2) Highly trained staff and special equipments are required for manufacturing parenteral formulations to achieve the finished product specifications.
3) The staff should be skilled to ensure adequate administration of the dosage form via proper route. **For example**, if a parenteral suspension (to be administered intramuscularly or subcutaneously) is administered intravenously, a pulmonary micro-capillary blockage occurs in the blood flow at that site.
4) Parenteral formulations give rise to pain at the time of administration.
5) They result in rapid and intense allergic reactions if the patient is allergic to the formulation being administered.
6) The effects of drugs administered parenterally cannot be reversed even immediately after administration.

7.1.5. Pre-Formulation Factors and Essential Requirements

Pre-formulation involves studying the physical and chemical properties of drug prior to formulation. It is related to analytical and pharmaceutical investigations supporting the efforts of formulation development for all dosage forms. Pre-formulation studies are performed under stressed conditions of temperature, humidity, light, and oxygen so that the reactions are accelerated and potential reactions can be detected. A few **physicochemical properties** that affect a drug substance are discussed below:

1) **Colour:** It is a property of inherent chemical structure of drug and indicates the intensity or level of unsaturation. The intensity of colour depends on the extent of conjugated unsaturation, and also on the presence of chromophores (**e.g.,** $-CO$, $-NO_2$, and $-NH_2$). Some saturated compounds have minute traces of highly unsaturated, intensely coloured impurities and/or degradation products, and thus exhibit colour. These compounds under highly stressed conditions of heat, light, and oxygen produce colour. A significant colour change in a parenteral product beomes a limiting factor to its shelf-life even before a significant change in chemical stability is noted.

2) **Odour:** This property of a new drug substance is examined by smelling the headspace of the drug container previously closed to allow concentration of volatiles. The presence and description of any odour is recorded.

3) **Molecular Structure and Weight:** These are the basic characteristics of the drug from which the potential properties and reactivities of functional groups can be determined.

4) **Particle Size and Shape:** These characteristics are determined by microscopic evaluation using a **scanning electron microscope** or an optical microscope with polarising attachments. The morphological characteristics of the drug substances should be recorded by a sketch or by a photomicrograph (as a permanent record) so that they can be compared with the future batches. A **polarising microscope** is used to determine whether the drug is crystalline or amorphous, as polarised lights are refracted by crystalline materials (and are thus visible when polarisation attachments in the ocular and objectives are crossed at an angle of 90°) while the amorphous or glassy substances become invisible.

5) **Thermal Analytical Profile:** The drug samples are heated between ambient temperature and its melting point, thus are exposed to changes in temperature during synthesis and isolation which may be exhibited as a thermal profile. The samples neither absorb nor emit heat prior to its melting point, if no thermal history exists for the compound.

The technique used for studying this phenomenon is called **Differential Thermal Analysis** (DTA) that can detect the endothermic transitions like melting (or fusion), boiling, sublimation, and desolvation. **Differential Scanning Calorimetry** (DSC) is a similar process. **Thermo Gravimetric Analysis** (TGA) is another thermal analytical method used for detecting the existence and stability of solvated drug molecules.

6) **Melting Point:** It is the temperature at which the solid and liquid phases are in equilibrium. Its determination is a primary indication of purity as even the presence of small amounts of impurity can be detected by lowering and increasing the melting point range.

7) **Hygroscopicity:** It is the phenomenon of moisture absorption by compounds under specific conditions of moisture and humidity. A high degree of hygroscopicity can adversely affect the physical and chemical properties of a drug substance, making it pharmaceutically unfit. These studies are conducted by placing tarred containers containing correctly weighed drug samples at different conditions of humidity for up to 14 days. Any gain or loss in weight is detected at pre-determined intervals till equilibrium is reached. The drug is recommended to be stored under dry and low humidity conditions if it is determined to be very hygroscopic or unstable in the presence of moisture.

8) **Solubility:** This property is essential for developing solutions to be injected either intravenously or intramuscularly. Solubility is a function of chemical structure; salts of acids or bases are the drugs that can achieve the desired degree of water solubility. The analytical method used for measuring solubility can vary according to the drug moiety. If unsaturated conjugation is present in the drug structure, it absorbs visible or UV light, and can be analysed by **spectrophotometry**.

   However, the compounds that do not absorb UV or visible light can be analysed by transferring filtered aliquot solutions to previously tarred weighing pans, evaporating the solvent, and drying to a constant weight under low temperature conditions.

9) **Optical Activity:** It is the phenomenon in which the plane polarised light is rotated by a compound. If the beam of light is rotated to the right or in clockwise direction by an angle, the substance is **dextrorotatory** and if the compound rotates the beam of light to the left or in anti-clockwise direction, the substance is **levorotatory**.

10) **Ionisation Constant:** This property is used to determine the pH-dependent solubility of a compound. **Potentiometric pH titration** or **pH-solubility analysis** is used for determining the pka value. Ionisation constant of a compound also helps in determining the ionisation degree of an acid or base.

11) **Partition Coefficient (P):** It is the measure of a compound's lipophilicity. It can be determined by measuring the equilibrium concentration of a drug in aqueous and oily phases in contact with each other at a constant temperature. Partition coefficient can be expressed as:

$$P = [C_{oil}]/[C_{water}]$$

Pharmaceutical Factors Affecting Parenteral Administration

1) **Solubility of Drug and Volume of Injection:** Before a drug is administered via intravenous injection, it should be completely solubilised in water. Volume of the injection can be determined by the extent of drug solubility in its intended vehicle and the dose required for the desired therapeutic effect. Other parenteral routes (i.e., excluding intravenous route) have limitations on the subject of the maximum volume of medication administered.

2) **Vehicle Nature:** The drugs in aqueous vehicles can be administered by any parenteral route, while those in non-aqueous vehicles (which may or may not be water miscible) are administered intramuscularly. Intravenous routes are used for the drugs in mixed solvent system, but drug precipitation at the infusion site should be prevented.

3) **Type of Dosage Form:** Parenteral dosage forms include solutions, suspensions, and sterile solids for reconstitution. Suspensions are administered via intramuscular or subcutaneous route. The drugs to be administered intravenously or by any other parenteral route in which the drug directly enters the biological fluid or sensitive organ tissues (like brain or eye) should not contain any particles. Before administering the sterile solids via intravenous route, they are dissolved in reconstituting diluents.

4) **Formulation Ingredients:** The parenteral formulations are made up of the therapeutically significant active pharmaceutical ingredients and various active and inactive excipients. Antimicrobial agents are added to multi-dose parenterals for preserving the sterility. Surface active agents (**e.g.,** polysorbate 80) are added for maintaining drug solubility in the solution vehicle.

   Sustained or prolonged release of drug delivery employs various formulations and additives (high molecular weight polymers or oily solvents) that help in achieving the desired duration of drug action. Formulations containing these macromolecules are administered subcutaneously or intramuscularly to allow the delayed release of the active ingredient in the deeper body tissues.

5) **pH and Osmolarity of Injectable Solutions:** Injections should be formulated at a pH and osmolarity similar to that of the biological fluids; however, this is not possible for those parenteral dosage forms that are unstable at neutral pH; thus they should be formulated at pH at which they are stable. Some parenteral formulations are hyper osmotic with biological fluids. They contain a high dose of active ingredient(s) to achieve the desired biological activity.

   Such hypertonic parenteral dosage forms should not be administered as injections via subcutaneous or intramuscular routes. Vitreous humour can tolerate a very few narrow ranges of osmotic values from an injected medication. Therefore, they should be formulated with solute contents equal to those of biological fluids even if stability and solubility problems prevent the dosage forms from being formulated at physiological pH.

7.1.6. Formulation of Injections

Parenteral preparations are formulated using the following ingredients:

1) Solutes,
2) Vehicles, and
3) Additives.

7.1.6.1. Solutes

Active pharmaceutical ingredients and excipients should be selected such that their quality is best suited for parenteral administration. Low microbial level enhances the effectiveness of either the aseptic or terminal sterilisation process used for the preparation. The non-pyrogenic ingredients in the similar manner enhance the non-pyrogenicity of the finished injectable product. It is a common GMP procedure to establish microbial and endotoxin limits on active pharmaceutical ingredients and other excipients.

Chemical impurities present in the active pharmaceutical ingredients used for parenteral preparations cannot be removed during the processing; thus they should be non-existent. Even trace amounts of these impurities may produce harmful effects to the patient or cause stability problems in the product. Therefore, the best grade of chemicals should be used and their analytical profile should be determined by the manufacturers to ensure that each chemical lot used in the formulation fulfils the required standards. Reputable chemical manufacturers follow the strict requirements for quality parenteral products and apply the GMPs to their chemical manufacturing. **Examples** of critical bulk manufacturing precautions are:

1) Preventing cross-contamination and transfer of impurities by using a suitable equipment or properly validated cleaning method,
2) Washing the equipment with water for injection,
3) Using closed systems for bulk manufacturing steps not followed by purification, and
4) Maintaining the standard endotoxin and bio-burden testing limits for the substance.

7.1.6.2. Vehicles

Both aqueous and non-aqueous vehicles can be used in the formulation as per the requirement:

1) **Aqueous Vehicles:** These are of the following types:
    i) **Water for Injection U.S.P.**
        a) It is the most commonly used solvent in the large-scale manufacturing of injections.
        b) Its purification is carried by distillation or reverse osmosis, and this water fulfils the standards same as of purified water for the presence of total solids, which is not more than 1mg/100ml of water for injection U.S.P., and may not contain added substances.
        c) This water if not sterile, should be free from pyrogens.
        d) It can be used for manufacturing injectable products terminally sterilised after preparation.
        e) It should be collected in sterile and pyrogen-free containers.
        f) It should be used within a day of collection.

Figure 7.1 represents the method by which potable water can be converted into water for injection:

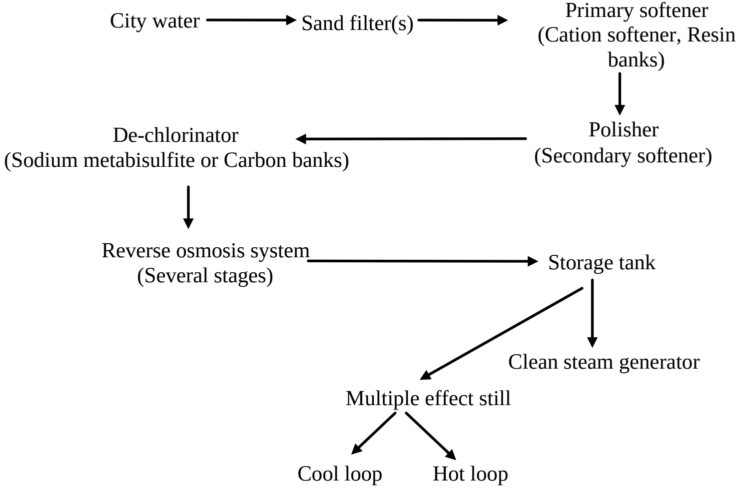


Figure 7.1: Water for Injection System

ii) **Sterile Water for Injection U.S.P.**
   a) It is packed in single-dose containers of 1 litre capacity.
   b) It should be free from pyrogens and should have endotoxin in acceptable level, i.e., up to 0.25 U.S.P. endotoxin units per millilitre.
   c) It should not be present with any antimicrobial agent or other added substance.
   d) However, its total solids content may be slightly higher than that in water for injection; because during sterilisation of water for injection U.S.P. leaching of solids occurs from the glass-lined tanks.
   e) It should be used as a vehicle for already sterilised and packed injectables.
   f) It is used for reconstitution of antibiotics. It is aseptically added to the vial (containing drug) to prepare the desired injection. **For example,** a suitable injection may be prepared using the sterile dry powder ampicillin sodium U.S.P. by aseptically adding sterile water for injection.

iii) **Bacteriostatic Water for Injection U.S.P.**
   a) It is sterile water for injection containing suitable antimicrobial agents.
   b) It is packed in prefilled syringes or in vials containing up to 30ml of water.
   c) It should be labelled with the names and proportions of antimicrobial agents present in it.
   d) Due to the presence of antimicrobial agents, it should be used only in parenteral preparations administered in small volumes.
   e) It is used in small volume parenteral preparations as a sterile vehicle.
   f) It should be added with bacteriostatic agents in multiple-dose parenteral preparations. The added bacteriostatic agents should be chemically compatible with the medicinal agent being dissolved or suspended.
   g) It should be avoided in neonates.

iv) **Sodium Chloride Injection U.S.P.**
   a) It is a sterile isotonic solution of sodium chloride in water for injection.
   b) It has no antimicrobial agents but contains 154mEq each of sodium and chloride ions per litre.
   c) It is used as a sterile vehicle in solutions or suspensions of drugs intended for parenteral administration.
   d) It is often used as a catheter or intravenous line flush for infusing fluids and intravenous medications and for drawing blood for laboratory analysis. About 2ml is generally used to flush the line after each use or after every 8 hours if the line is not used.

v) **Bacteriostatic Sodium Chloride Injection U.S.P.**
   a) It is a sterile isotonic solution of sodium chloride in water for injection.
   b) It should be labelled with the names of antimicrobial agents present in it.
   c) Sodium chloride present in 0.9% concentration makes the solution isotonic.
   d) While using this isotonic solution as a vehicle, it should be made sure that the drug is compatible with the preservative and sodium chloride.
   e) It is also used to flush a catheter or intravenous line in order to maintain its potency.
   f) It should be avoided in neonates.

vi) **Ringer's Injection U.S.P.**
   a) It is a sterile solution of sodium chloride, potassium chloride, and calcium chloride in water for injection.
   b) The concentration of sodium chloride, potassium chloride, and calcium chloride is similar to those of physiologic fluids.

  - c) This injection is either used as a vehicle for other drugs or alone as an electrolyte replenisher and plasma volume expander.
  - d) **Lactated Ringer's injection U.S.P.** is a sterile solution of sodium chloride, potassium chloride, calcium chloride, and sodium lactate in water for injection.
  - e) It is used as a fluid and electrolyte replenisher and as a systemic alkaliser.

2) **Non-Aqueous Vehicles:** An aqueous vehicle cannot be used for an injection, if the added drug has limited water solubility or is prone to hydrolysis. Due to these physical or chemical factors, aqueous vehicles are used limitedly, and non-aqueous vehicles are the only alternative. The non-aqueous vehicles ideally should possess the following features:
   - i) They should be non-irritating.
   - ii) They should be non-toxic.
   - iii) They should be pharmacologically inert.
   - iv) They should fluidise over a wide range of temperature.
   - v) They should be non-sensitising.
   - vi) They should metabolise easily.
   - vii) They should be less viscous to allow syringability.
   - viii) They should have a high boiling point to permit heat sterilisation.

   The **examples** of commonly used non-aqueous vehicles are fixed oils or vegetable oils (like corn, olive, peanuts, soybean, cotton seed, sesame, and persic oils). Ethyl oleate, isopropyl myristate, benzyl benzoate, and dimethylacetamide are some other non-aqueous vehicles used occasionally. Non-aqueous vehicles are also used for steroidal hormones and oil-soluble vitamins. The use of mineral oil is avoided as it cannot metabolise in the body.

7.1.6.3. Additives

The following high quality solutes should be used in the formulation of parenteral products:

1) **Medicaments:** These are the active ingredients, and are sterilised before adding to the formulations.

2) **Additives:** The following additives are added to increase the utility and stability of parenteral products:
   - i) **Solubilisers:** These are added to maintain the solubility of slightly soluble drugs by increasing their solubility. Dimethylacetamide, ethyl alcohol, polysorbates (20, 40, and 80), lecithin, PEG 300, PEG 40, and castor oil are the **examples** of commonly used solubilisers.
   - ii) **Antioxidants:** Many drugs in solution degrade by oxidation reactions (addition of oxygen or removal of hydrogen) mediated by free radicals or molecular oxygen. Metal, hydrogen, and hydroxyl ions catalyse such oxidative decomposition. Drugs with a favourable oxidation potential are more susceptible to oxidation.

     For example, drugs like epinephrine, morphine, ascorbic acid, menadione, etc. are formulated in their reduced form and get easily oxidised. Oxidation can be minimised by increasing the drug's oxidation potential. Salts of sulphur dioxide (such as bisulfite, metabisulfite, and sulphite) are most commonly used as antioxidants in aqueous parenterals. They keep the product stable by getting oxidised and gradually get consumed through its shelf-life. Some common **examples** of antioxidants are given in **table 7.1**:

Table 7.1: Antioxidants Used in Parenteral Formulations

Additives	Concentration Range (%)
Reducing Agents:	
Ascorbic acid	0.02-0.1
Sodium bisulphite	0.1-0.15
Sodium metabisulphite	0.1-0.15
Sodium formaldehyde sulphoxide	0.1-0.15
Thiourea	0.005
Blocking Agents:	
Ascorbic acid esters	0.01-0.015
Butyl Hydroxy Toluene (BHT)	0.005-0.02
Tocopherols	0.05-0.075
Synergist Agents:	
Ascorbic acid	0.01-0.05
Citric acid	0.005-0.01
Citraconic acid	0.03-0.45
Phosphoric acid	0.005-0.01
Tartaric acid	0.01-0.02
Chelating Agents:	
EDTA	0.01-0.075

iii) **Chelating Agents:** These agents form complexes with the metal ion and dissolve in the solvent, thus preventing the metal ions from interfering in the manufacturing process. Some common **examples** of chelating agen ts are given in **table 7.2**:

Table 7.2: Chelating Agents Used in Parenteral Formulations

Additives	Concentration Range (%)
Edetate disodium	0.00368-0.05
Edetate calcium disodium	0.04
Edetate tetrasodium	001

iv) **Buffers:** These are added to maintain the form ulation pH, as a change in pH results in product degradation. Either a weak base and its salt or a weak acid and its salt are used as a buffer in parenterals. Some common **examples** of buffers are given in **table 7.3**:

Table 7.3: Buffers Used in Parenteral Formulations

Additives	Concentration Range (%)
Acetic acid	0.22
Adipic acid	1.0
Benzoic acid and sodium benzoate	5.0
Citric acid	0.5
Lactic acid	0.1
Maleic acid	1.6
Potassium phosphate	0.1
Sodium phosphate monobasic	1.7
Sodium phosphate dibasic	0.71
Sodium acetate	0.8
Sodium bicarbonate	0.115
Sodium carbonate	0.06
Sodium citrate	4.0
Sodium tartrate	1.2
Tartaric acid	0.65

v) **Stabilisers:** These are added to formulations which can undergo rapid oxidation. Some common **examples** of stabilisers are given in **table 7.4**:

Table 7.4: Stabilisers Used in Parenteral Formulations

Additives	Concentration Range (%)
Creatinine	0.5-0.8
Glycine	1.5-2.25
Niacinamide	1.25-2.5
Sodium caprylate	0.4
Sodium saccharin	0.03

vi) **Surfactants:** These are used for disposing a water-insoluble drug as a colloidal dispersion, for wetting powder, for preventing crystal growth in a suspension, for providing acceptable syringability, and for solubilising steroids and fat-soluble vitamins. Some common **examples** of surfactants are given in **table 7.5**:

Table 7.5: Surfactants Used in Parenteral Formulations

Additives	Concentration Range (%)
Polyethylene	0.1-0.5
Sorbitan monooleate	0.05-0.25

vii) **Preservatives:** These are included in the formulation to maintain the sterility of solution when a multiple dose package is used. Some common **examples** of preservatives are given in **table 7.6**:

Table 7.6: Preservatives Used in Parenteral Formulations

Additives	Concentration Range (%)
Benzalkonium chloride	0.01
Benzethonium chloride	0.01
Benzyl alcohol	0.5-10.0
Butyl paraben	0.015
Chlorobutanol	0.25-0.5
Metacresol	0.1-0.25
Methyl paraben	0.01-0.18
Phenol	0.065-0.5
Phenylmercuric nitrate	0.001
Propyl paraben	0.005-0.035
Thimerosal	0.001-0.02

viii) **Protectants:** These are mainly used in protein formulation to provide protection against loss of activity due to stress and to prevent loss of active ingredients by adsorption to process equipment or to primary packaging materials. Some common **examples** of protectants are given in **table 7.7**:

Table 7.7: Protectants Used in Parenteral Formulations

Additives	Concentration Range (%)
Sucrose	2-5
Glucose	2-5
Lactose	2-5
Maltose	2-5
Trehalose	2-5
Human serum albumin	0.1-1.0

ix) **Tonicity Adjusting Agents:** These are used to ease parenteral administration by reducing pain or tissue irritation. Some common **examples** of tonicity adjusting agents are given in **table 7.8**:

Table 7.8: Tonicity Adjusting Agents

Additives	Concentration Range (%)
Gelatin	1.6-2.25
Lactose	0.14-5.0
Mannitol	0.4-2.5
Dextrose	3.75-5.0
Sodium chloride	Varies
Sodium sulphate	1.1
Sorbitol	2.0

7.1.6.4. Importance of Isotonicity

Isotonicity is important for parenteral formulations because if the solution is isotonic with blood, the possibility of the product penetrating the RBCs and causing haemolysis is reduced. Solution having less osmotic pressure than the blood plasma is **hypotonic** and solution having more osmotic pressure than the blood plasma is **hypertonic**. In hypotonic solution, water diffuses into the RBCs causing them to swell and finally burst, i.e., haemolysis. In hypertonic solution, water diffuses out of the RBCs causing them to shrink. In isotonic solution (**e.g.,** 0.9% sodium chloride), the RBCs maintain their tonicity.

7.1.7. Production Procedure – Aseptic Processing

The general procedure for manufacturing parenterals include planning and scheduling of equipments, material managements, and manufacturing requirements like ingredients, drugs, etc. An overview of the manufacturing process of parenterals is shown in **figure 7.2**:

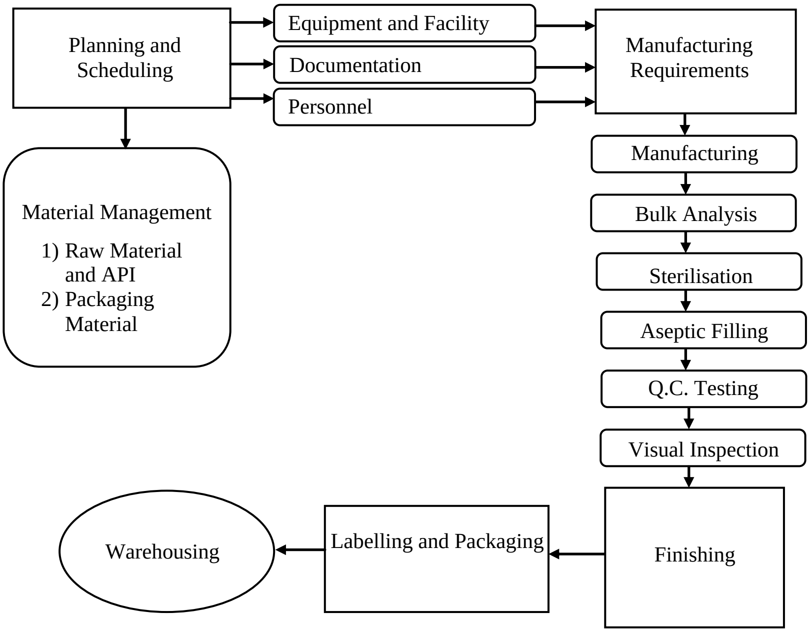


Figure 7.2: Flow Chart of Manufacturing Process of Parenterals

The manufacturing of parenterals involves the following **steps**:
1) Cleaning and washing of containers and closures,
2) Preparation of solutions,
3) Sterilisation,
4) Filling and sealing, and
5) Packaging and labeling.

7.1.7.1. Cleaning and Washing of Containers and Closures

The vials are soaked in detergent solution overnight. This removes any sticking particles, grease, etc. from them. Then the vials are washed three to four times with tap water to remove the soap solution. The vials are washed with 1.0% hydrochloric acid and then again with tap water to remove surface alkalinity. The vials are finally rinsed with de-ionised water followed with distilled water and sterilised for 4 hours at 200°C temperature. Rubber closures are boiled with 1.0% detergent solution for 30 minutes followed by washing with tap water to remove the detergent. Then they are again boiled for 30 minutes with 1.0% hydrochloric acid solution and washed with tap water. Then they are boiled with 1.0% sodium carbonate and again washed. Thereafter the closures are treated with a bacteriostatic solution, washed three to four times with pyrogen free water, and sterilised by autoclaving for 30 minutes at 115°C temperature.

7.1.7.2. Preparation of Solution

The active pharmaceutical ingredient is completely dissolved in water for injection with constant stirring. Then the other excipients are added one at a time with stirring to make them dissolve. The desired pH is adjusted by using buffering agents like sodium hydroxide and hydrochloric acid. The volume is made up with water for injection, and the pH is re-adjusted if required.

7.1.7.3. Sterilisation

Parenteral products, except those containing thermolabile substances, after being filled and sealed in the final containers are sterilised, and this process is termed **terminal sterilisation**.

So for sterilising thermolabile products, non-thermal methods are used. These methods involve **filtration through bacteria-proof filters**. In some thermolabile preparations (**e.g.,** colloids, oleaginous solutions, suspensions, and emulsions), each component is sterilised separately and the product is formulated and processed aseptically. **Sterilisation by radiation** is a non-thermal method. Dry solids (**e.g.,** penicillin, streptomycin, polyvitamins, and some hormones) are effectively sterilised by ionised radiations. **Gaseous sterilisation** is not preferred when a glass container or other impermeable barrier may prevent the permeation of gas into the material.

Dry heat sterilisation also has limited application as the materials being sterilised should not get affected by the elevated temperatures. Another method of sterilisation is **lyophilisation** (also known as freeze drying).

Autoclaving involves pressurised steam which is the most useful and the most effective sterilisation method for aqueous liquids or substances through which steam can easily penetrate. This method is however not effective under anhydrous conditions, **e.g.,** a sealed ampoule containing an anhydrous oil or a dry solid. To prevent the contamination following sterilisation, materials which have been autoclaved are covered; however, this is not required in parenteral solutions as they are already sealed. The effectiveness of a sterilisation method should be verified on a routine basis using biological indicators.

7.1.7.4. Filling and Sealing of Ampoules

The steps given below are followed to fill the ampoules manually:

1) A little more than 1.1ml of the drug solution is gently drawn into the syringe to avoid large numbers of air bubbles in the liquid.
2) The syringe is inverted so that the air rises towards the needle, and then the plunger is pushed up to expel the bubble and leave 1.1ml in the barrel.
3) The needle is wiped with a cellulose film disc, unlike filter paper or a cloth, so that no fibres are left on the needle.
4) The ampoule is inverted over the needle. Since the needle surface is dry, no liquid will be put on the ampoule neck. If the ampoule is held straight and the syringe is reverted for filling, the weight of the plunger may force a drop of solution from the needle tip, thus contaminating the neck.
5) Once the ampoule is settled over the needle, both (the ampoule and the syringe) are reverted together and the liquid is gently expelled to prevent splashing into the neck.
6) Finally, the needle tip is touched against the constriction at the bottom of the neck to dislodge the last drop of liquid and then the needle is withdrawn without touching the neck.

After filling the ampoules they should be immediately sealed to prevent the contamination of contents. They are sealed by melting a portion of the glass neck. The following **two types of seals** are employed:

1) **Tip- or Bead -Seals:** This type of seals is made by melting glass using a high-temperature gas-oxygen flame at the tip of the ampoule neck to form a bead that closes the opening. A uniform bead can be produced if the ampoule neck is heated uniformly on all sides either by using burners on opposite sides of stationary ampoules or by rotating the ampoule over a single flame.

   The flame temperature and the interval of heating to completely close the opening with a glass bead should be carefully determined. Excessive heating will lead to expansion of gases within the ampoule against the soft bead seal and formation of a bubble. If this bubble bursts, the ampoule is no more sealed; and if it does not, the wall of the bubble will be thin and fragile. On the other hand, insufficient heating will leave an open capillary through the centre of the bead. An ampoule that is incompletely sealed is called a leaker.

2) **Pull-Seals:** This type of seals is made by heating the ampoule neck below the tip. By holding the tip with forceps or other mechanical devices, the ampoule is rotated over the flame from a single burner. When the glass softens, the tip is grasped firmly and pulled away from the ampoule body while rotating it continually. The small capillary tube so formed is twisted closed. Pull-sealing is a slow process than tip-sealing, but more sure.

   Pull-sealing is suitable for powder ampoules or other types having a wide opening. If the ampoule necks become wet during filling, they fracture at the time of sealing. Wet ampoule necks also increase the frequency of bubble formation and carbon deposition in case of organic product.

   Product decomposition in an ampoule can be prevented by displacing the air in the space above the product. This is done by introducing a stream of inert gas (such as nitrogen or carbon dioxide) during or after filling. Immediately after filling the ampoule is sealed so that the gas does not diffuse out. This process should be validated to ensure adequate displacement of air by the gas in each container.

7.1.7.5. Filling and Sealing of Vials

The filling procedure for glass vials is the same as that for ampoules. In vials containing a fixed number of dose units, an excess volume is required to allow the withdrawal of specified number of doses. The vial openings are **sealed with rubber closures** held in place by an aluminium sealing. A hand crimper is used to put the rubber closures and aluminium sealing onto the vials.

The vials are more at risk of contamination since their openings are larger than those of ampoules. Thus, the rubber closures should be sealed on the vials immediately after filling. During the critical exposure time, the open containers should be protected from contamination using a blanket of HEPA-filtered laminar airflow.

The rubber closure should tightly fit the vial mouth so that its elasticity will seal rigid to slight irregularities in the vial lip and neck. However, the closure should not fit so tightly that it cannot be introduced into the vial neck. Closures are inserted mechanically via automated process, especially with high-speed processing. By halogenating or treating the closure surfaces with silicone, friction is reduced enabling the closure to slide easily through a chute and into the container opening. The closure is positioned at the insertion site and pushed mechanically into the container opening. In case of small batches, the vials are stoppered manually with forceps; however, manual process poses greater risk of contamination than automated process.

Container-closure integrity testing measures the sealability between the glass or plastic container opening and the rubber closure to remain tight and fit and to resist any microbial contamination throughout the product shelf-life.

Rubber closures are positioned over the vial openings with tamper-proof aluminium caps. They cover the closure and are crimped under the vial lip to hold them in place. A closure can be removed only by destroying the aluminium cap; therefore, an intact aluminium cap is a proof that the closure has not been removed intentionally or unintentionally. This confirmation ensures the integrity of the contents with respect to sterility and other aspects of quality.

The outer layer of double-layered aluminium caps or the centre of single-layered caps can be removed to expose the centre of the rubber closure without disturbing the band that holds the closure in the container. Rubber closures used in intravenous administration sets have a permanent hole. In such cases, a thin rubber disk overlayed with a solid aluminium disk is placed between the inner and outer aluminium cap, providing a seal of the hole through the closure.

Single-layered aluminium caps are applied using a hand crimper, known as **Fermpress**. Double- or triple-layered caps are applied using heavy-duty mechanical crimpers.

7.1.7.6. Filling of Infusion Fluids

Parenteral solutions are prepared in an asepsis room or a laminar flow cabinet to reduce the possibility of contamination with particulate matter, to reduce the number of microorganisms in the preparation, and to increase the safety factor in the sterilisation process. A 500ml infusion bottle is considered suitable for preparation of parenteral solutions. It is assumed that the bottle has been stored with a double cap protecting the mouth. The outer cap is discarded and the inner cap is removed. After ensuring that the bottle neck is not chipped, the solution is poured in and immediately the inner cap is replaced.

Using a forceps, a plug-type closure is removed from its storage container. The cap is lifted from the bottle and the plug is pushed into the neck carefully without touching the part that goes into the bottle. A ring-type metal cap obtained from its storage tin is tightly screwed on the bottle after inspecting it to be free from deformities. The plug or liner stored in sterile water should be washed with filtered solvent prior to use because the particles may separate, cling to the closure and later contaminate the injection.

7.1.7.7. Packaging and Labelling - Containers and Closures Selection

Parenteral formulations are packed in containers of glass or plastic. Container systems meant for packaging of parenteral products include ampoules, vials, syringes, cartridges, bottles, and bags. **Ampoules** are made up of glass and **bags** are made up of plastic. The other containers are either made up of glass or plastic and should have rubber materials, like rubber stoppers for **vials** and **bottles** and rubber plungers and rubber seals for **syringes** and **cartridges**. **For example,** irrigation solutions are packed in glass bottles having aluminium screw caps.

Glass is widely used as a container material for parenteral products. These containers are sealed or closed with rubber stoppers. Type I glass containers are used for aqueous preparations. Interaction of the product with glass surface can be prevented by the process of **siliconisation**, in which a thin film of silicone is applied to coat the inside surface of the vials and ampoules. The process minimises adsorption of active ingredients from homogeneous solutions, prevents adsorption of solids from suspensions, and prevents aggregation at the glass surface in colloidal preparations.

Plastics used for packaging parenteral products are polyethylene or polypropylene. Use of plastic containers is limited than that of glass containers, but the former is being used increasingly for intravenous fluids. The polypropylene containers can be sterilised by autoclaving. Many plastics allow selective passage of chemical molecules and are permeable to gases. Plastics are widely used for containers of administration sets, of disposable type particularly.

Rubber is mainly used for closures for multiple-dose vials, intravenous fluids bottles, plugs for disposable syringes, and bulbs for ophthalmic pipettes. Rubber closures allow the needle of a hypodermic syringe to penetrate the multiple-dose vials and resealing of the vial after withdrawing the needle. An aluminium band is used to keep the rubber closure in place. Some rubber closures are made up of many ingredients and thus its basic structure is a linear unsaturated hydrocarbon, isoprene. Sometimes a part or the entire natural polymer is replaced with various synthetic rubber polymers.

Rubber closures may also include a **vulcanising agent** (sulphur), an **accelerator** (2-mercaptobenzothiazole), an **activator** (zinc oxide), **fillers** (carbon black or limestone), **antioxidants**, **lubricants**, etc. These substances can leach into the product or undergo chemical interaction; this can be minimised by applying lacquer or plastic coating on the surface of the rubber closures in contact with product. **Coring** (generation of rubber particles, known as cores, from the closures when needles are inserted) is another common problem of rubber closures, which can be minimised by the proper selection and use of gauge needle.

The **label** of an injectable preparation should include all the information necessary for the physician and users to ensure safe and proper use of the product. All the information cannot be put on the container in a readable format, so an add-on printed matter should be supplied.

The word **labelling** is used to indicate all labels and other written, printed, or graphic matter on an immediate container or on any package or cover in which the product is enclosed. The label should not be put on the outer shipping container.

Label comprises of the following **details**:
1) Name of the preparation,
2) Percentage content of the drug in a liquid preparation,
3) Quantity of active ingredient in a dry preparation,
4) Volume of liquid need to be added for preparing an injection or suspension from a dry preparation,
5) Route of administration,
6) Storage conditions,
7) Expiry date,
8) Name of the vehicle and the proportions of each constituent if the product is a mixture,
9) Names and proportions of all substances added for increasing the product stability, and
10) Name of the manufacturer or distributor and an identifying lot number which provides the complete manufacturing history of the package.

The label should be arranged such that adequate area of the container remains uncovered for its full length or circumference for allowing proper examination of the product.

The labels prepared for dialysis, haemofiltration, or irrigation solutions should fulfil the requirements for injections, other than those relating to volume. They should also mention that they are not meant for intravenous injection. The injections for veterinary use should also be labelled.

7.1.8. Production Facilities and Controls

The facilities for manufacturing sterile products should be designed to maintain desired cleanliness for each step. Almost perfect cleanliness should be maintained in aseptic filling rooms. The surrounding areas should provide a buffer area with the cleanliness standards slightly lower than those for the aseptic rooms. Prevention of contamination should be the prime aim in the design of these facilities.

Such exceptional design and construction standards can be obtained by combining the knowledge of the purpose of the facility with the utilisation of best construction materials. Ceiling, walls, and floors should be constructed with easily cleanable and non-porous materials, so that accumulation of debris and moisture can be prevented.

One of the best finishes for rigid surfaces is the **spray-on-tile**, which is a ceramic epoxy finish applied on the ceiling and walls by spraying or painting to form a continuous, smooth, seal coating. Although, this epoxy finish can degrade, wear or peel due to the rigorous effects of continuous washing with detergents and disinfectants.

Flooring is done with **ceramic-plastic cement** applied as a thick coat over the rigid floor to form a continuous, sealed surface. Another flooring material which is in use in areas of less heavy traffic is **sheet vinyl with heat-welded seams**, covered to the side walls and applied by adhesives on underlying surfaces. **Movable metal partitions** are also used to provide flexibility of room arrangement, but they have seams and joints sealed with much difficulty.

Glass is used in partitions to facilitate supervisory view of the operation, and also to provide pleasant, better lighted, and less confining surroundings for the personnel. Lighting fixtures should be recessed and presence of exposed piping or other dirt-collecting surfaces should be avoided. Furniture should be of non-porous, hard-surfaced materials, especially of stainless steel. The walls should have suspended counters.

The equipment which cannot be sterilised or are sterilised with difficulty are kept out of the aseptic areas. If they are to be used in the aseptic area, they should not be taken out and should be exposed to disinfecting processes continuously. The operating machinery parts when not in use should be enclosed in stainless steel housing.

The electrical, gas, water, air ventilation, and other utilities lying in these areas, need proper mechanical servicing. This can be effectively done by providing a floor above, space underneath, or corridor along with the side of production area where all service connections are made available and are properly maintained. This prevents any kind of disruption in production and also contamination of the production area by regulating the operations and personnel.

HEPA-filtered laminar airflow is added to the basic design and construction of aseptic area. Commonly, laminar air-flow is added to a clean room for better environmental control in a local area, like in workbench enclosure or over a filling line.

7.1.8.1. Personnel

The personnel working in the production and manufacturing unit of parenteral products should be neat, orderly, and reliable. Their **health condition** should be good and they should not have any dermatological infections which might increase the microbial load. If the personnel are suffering from influenza, allergies, or similar illness, their entry should be restricted in the aseptic area until their complete recovery.

But, healthy personnel with adequate personal hygiene will also shed a large number of viable and non-viable particles from their body surface. This results in continuous problems even when the personnel are present in clean rooms. Proper **training and gowning of the personnel** can only reduce (and not eliminate) the problem of particle shedding.

The operators in an aseptic area should be provided with proper formal **training in the principles of aseptic processing and techniques** to be used. Also, the acquired knowledge and skills of the personnel should be evaluated to make sure that the training has been effective before they are allowed to involve in the preparation process. **Re-training** should be given on a regular schedule to enhance the maintenance of the required level of expertise. An effort should be made to make the operators realise their essential role in determining the reliability and safety of the final sterile product. This is especially required for supervisors, who not only understand the requirements of aseptic procedures but also regulate the full involvement of other employees to fulfil the aseptic requirements.

The **uniforms of personnel** should be designed such that they restrict the shedding of particles from their body; this prevents the entry of these contaminants into the production environment. The uniforms of personnel working in aseptic areas should be sterile. Whenever the personnel return to the aseptic area or after every break period, fresh, sterile uniforms should be used. In plants where the product is to be sterilised in its final container, this is not required.

Uniforms consist of coveralls, hoods for covering hair, face masks, and Dacron or plastic boots for both men and women. Sterile rubber or latex-free gloves are also worn during aseptic operations, after scrubbing the hands thoroughly with a disinfectant soap. Two pairs of gloves are worn; one at the beginning of the gowning procedure and the other after all other apparel has been put on. Goggles are worn to complete the coverage of all skin areas. Uniforms are mainly of Dacron or Tyvek, and are effective barriers to the viable and non-viable particles shedding from the personnel's body. The uniforms are lint-free and comfortable. Air showers are sometimes recommended to the personnel before entering the processing area to blow away the loose lint from the uniforms.

Gowning rooms should be designed to improve pre-gowning and gowning procedures by the trained personnel. This ensures continued sterility of the exterior surfaces of the sterile gowning components. A **separate exit room** should be used for de-gowning.

7.1.8.2. Functional Areas

There are many functional production areas such as warehousing or procurement, compounding or formulation, material (containers, closures, and equipment) preparation, filtration and sterile receiving, aseptic filling, stoppering, lyophilisation, and packaging, labelling and quarantine. These areas are involved for attaining the aim of manufacturing a sterile product of high quality.

Some additional requirements for the aseptic area are designed to provide an uncontaminated environment to which a sterile fluid may be exposed for a short-term while transferring a portion of it from the bulk container to individual-dose containers. Dust, lint, other particles, and microorganisms are found floating in the air, lying on counters or other surfaces, on clothing and body surfaces of personnel, in the respired air of personnel, and accumulated on the floor. Therefore, for reducing the presence of these contaminants, the aseptic area is designed and controlled in such a manner that they are no longer hazardous for the aseptic filling of preparations.

For the effective flow of components, the aseptic area should be just adjacent to the support areas. Also barriers (like sealed walls, manual or automatic doors, airlock, pass-through, ports of various types, or plastic curtains) should be provided to reduce the entry of contaminants in the aseptic area.

Flow Plan

1) Firstly, the flow of parenteral components after release is either from the warehouse to the compounding area (as for the formula ingredients) or to materials support area (as for the containers and equipment).
2) After proper processing in these areas, the components flow into the aseptic area for filling the product in a suitable container.
3) Then, the product passes into the quarantine and packaging area for performing all the required tests.
4) In case the product is to be sterilised in the final container, its flow is interrupted after it leaves the aseptic area for performing sterilisation.
5) After obtaining the tests report, the batch records are reviewed to ensure that the product fulfils the release specifications.
6) Then the product is passed to the finishing area for final release for shipment.
7) Sometimes, changes are observed in this flow plan for fulfilling the needs of an individual product or to follow the existing facilities.
8) The automated operations have larger capacity and can transport the components from one area to another with slight or no handling by operators.

7.1.8.3. Layout of Sterile Products Area

The sterile product area should be free from microbial contamination. Particles of size not more than 0.5 µm should be present in this area. The particle count should not exceed a total of 100 particles/ft^3. This complete area is divided into clean-up area, preparation area, aseptic area, quarantine area, and the finishing and packaging area. These areas should be constructed and designed such that they can be effectively cleaned, operations can be carried out efficiently, and also the personnel feel comfortable in the environment. **Figure 7.3** shows a floor plan of a sterile product area, and **figure 7.4** shows the flow of materials in this area:

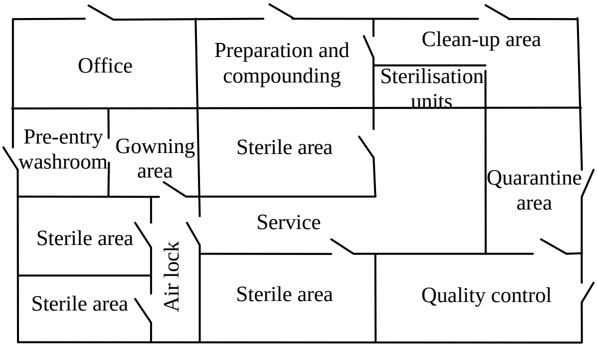


Figure 7.3: Floor Plan of Sterile Products with its Services

The **clean-up area** should withstand moisture, steam, and detergents. Inward air leaks and dirt collecting crevices, corners, and projections should not be present in the area so that accumulation of dust and microbes can be prevented. Ceiling and walls should be coated with epoxy and vinyl polymeric continuous film coating materials.

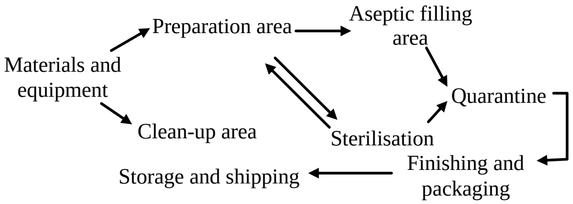


Figure 7.4: Scheme for Flow of Materials

In the **preparation area**, the formulation is compounded and preparations for filling operations are done (such as assembling equipment). Thus, the controls maintained for this area should be stricter in comparison to those for clean-up area. Cabinets and counters should be made up of stainless steel and should not have any catch area where dirt can accumulate. The area should also have a sink and a counter space. Ceiling, walls, and floors should be sealed.

The **aseptic area** should have maximum security as it is the major part of processing the sterile products. An ultra-clean environment should be maintained in this area. The ceiling, walls, and floors should be painted with germicidal paint (**e.g.,** Fungi Check). The walls should have glass panels built on it to facilitate visibility and supervision from a non-sterile area.

All the fixtures should be buried in the ceiling walls to eliminate ledges, joints, and other locations where dust and dirt may accumulate. All the counters should be made up of stainless steel and should be hung from walls. All the operating parts of mechanical equipment should be completely sealed within a stainless steel cabinet.

Small-scale operations should be carried out under an aseptic hood. The personnel should enter the aseptic area through an air-lock. The personnel should wear sterile dresses, masks, caps, foot-covers, etc. Minimum movement should be undergone in the aseptic area. The air in the aseptic area should be made free from fibres, dust, and microbes by fitting **High Efficiency Particulate Air (HEPA) filters**. These filters can efficiently remove 99.97% or more of particles up to 0.3 μm size.

HEPA filters are used in laminar air flow benches in which air moves with uniform velocity along parallel lines with minimum eddies. The air flow is either horizontal or vertical. The minimum effective air velocity is 100±10 ft/minute.

Air being the greatest sources of contamination should be clean in **sterile product area**. It should be made to pass through a pre-filter (of glass wool, cloth, or shredded plastics) to remove large particles.

Then it should be passed through an electrostatic precipitator to remove the particles in air (on which an electrical charge is induced), which attract to the oppositely charged plates. This treated air is finally passed through HEPA filters. UV lamps are also installed to produce a disinfectant action on directly irradiated surfaces between the antibacterial UV rays.

The aseptic area should be maintained carefully and the total viable count of bacteria should be routinely determined in sterile product area to make sure the area is free from microbial contaminants.

7.1.8.4. Clean Room Classified Area

The **clean** or **buffer room** is the secondary engineering control. It houses the primary engineering controls (the LAFH, BSC, or CAI) where the aseptic compounding is actually performed. The clean room is a specially constructed enclosed area, which contains one or more clean zones, where the concentration of airborne particles is controlled using HEPA filters, continuous air circulation, and a physical barrier to non-filtered (or outside) air.

Clean rooms establish appropriate environmental levels for airborne particulates, temperature, humidity, air pressure, and airflow patterns. Clean rooms are categorised by their constant air quality or class. Clean rooms are rated as given in **table 7.9**:

Table 7.9: Classes of Clean Rooms and their Properties

Clean Room	Properties
Class 10,000 (ISO class 7)	10,000 or less particles of 0.5μ and larger size exist in a given cubic foot of air.
Class 1,000 (ISO class 6)	1,000 or less particles of 0.5μ and larger size exist in a given cubic foot of air.
Class 100 (ISO class 5)	100 or less particles of 0.5μ and larger size exist in a given cubic foot of air.

Lower the classification number, cleaner is the air.

Clean rooms are divided into different classes in standards. **Table 7.10** lists the equivalence of classes from different international standards. For manufacturing sterile products, a certain classification (**table 7.11**) with grades A to D are characterised to activity category (**tables 7.11** and **7.12**) used.

Table 7.10: Class Limits for Federal 209D and ISO Standards

Classes		Measured Particle Size (Micrometers)					
Federal 209D	ISO	0.1	0.2	0.3	0.5 (a)	1.0	5.0
1	3	1000	237	102	1	8	
10	4	10000	2370	1020	10	83	
100	5	100000	23370	10200	100	832	29
1000	6	1000000	237000	102000	1000	8320	293
10000	7				10000	832000	2930
100000	8				100000	8320000	293000

(a): Particle count for this particular size is per ft^3 while others are per m^3.

Table 7.11: Air Particle Classification System for the Manufacturing of Sterile Products

Grades	Maximum Permitted Number of Particles per m^3 Equal to or Above			
	At Rest (b)		In Operation (b)	
	0.5µm (d)	5µm	05µm (d)	5µm
A	3500	0	3500	0
B (a)	3500	0	350000	2000
C (a)	350000	2000	3500000	20000
D (a)	3500000	20000	Not defined (c)	Not defined (c)

Remarks

1) In order to reach the air grades B, C, and D, the number of air changes should be related to the room size, and the equipment and personnel in the room. The air system should be provided with HEPA filters for grades A, B, and C.
2) After 15 -20 minutes of clean-up period, an unmanned state (no manual activity) should be received.
3) Appropriate alert and action limits should be fixed for particulate and microbiological monitoring results. A corrective action in the operating procedures should be taken in case these limits are exceeded.

The need for other parameters (like temperature, relative humidity, etc.) depends on the nature of product and manufacturing procedure. These parameters do not have any relation with the purifying classes.

Table 7.12: Terminally Sterilised Products

Grades	Examples of Operation
A	Filling of products, when unusually at risk.
C	Preparation of solutions, when unusually at risk. Filling of product.
D	Preparation of solutions and components for subsequent filling.

Most products should be prepared in grade D environment; while grade C environment should be used in case of an unusual risk.

Table 7.13: Aseptic Parameters

Grades	Examples of Operation
A	Aseptic preparation and filling.
C	Preparation of solutions to be filtered.
D	Handling of components after washing.

The components after washing should be handled in grade D environment. The sterile starting material should be handled in grade A environment with grade B background. Solutions to be sterile filtered should be prepared in grade C environment; while if not filtered, the preparation should be done in grade A environment with grade B background. The aseptically prepared products should be handled and filled in grade A environment with grade B background.

The sterile ointments, creams, suspensions, and emulsions should be prepared and filled in grade A environment with grade B background, when the product is exposed and is not subsequently filtered. Control of purity of zones by the particles in operation state and microbial control at an aseptic production area is required; and the recommended levels are listed in **table 7.14**:

Table 7.14: Recommended Limits for Microbial Contamination in the Operation State (Average Values)

Grades	**Air Sample (cfu/m^3)**	**Settle Plates (Diameter 90mm), cfu/4 hours (a)**	**Contact Plates (Diameter 55mm), cfu/plate**	**Glove Print, 5 Fingers cfu/glove**
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

(a): Individual settle plates are exposed for 4 hours or less; **cfu:** colony-forming unit.

Warning limitation and action for contamination by particles and microbes depend on the controlling results. Also corrective action should be provided in case of exceeding the above limits.

7.1.8.5. Air Control

The air should be exchanged at recurrent intervals in areas engaged by personnel. Fresh outside or recycled air should be filtered first for eliminating the gross particulate matter by using a spun glass, cloth, or shredded polyethylene filter. To provide a gradation of particle size removal from highly contaminated air, a series of prefilter is used, in which the first is of larger pore size and the next is of smaller.

HEPA filter made up of glass fibres and fillers or electrostatic precipitators is used for removing at least 99.97% particles of 0.3 µm size and larger. Air passing through HEPA filters is made free of foreign matter. Another air cleaning system is used to wash the air with a disinfectant and control humidity simultaneously.

Blowers should be installed upstream to the filters in the air ventilation system so that all dirt-producing devices are ahead of the filters.

The clean air is disseminated to the specific areas through stainless steel ducts. It is not possible to keep these ducts clean all the time; thus a HEPA filter is installed at the point from where clean air enters the controlled room. Another alternative is to replace the ducts with a room (a plenum) above the production area into which the clean air is blown and then distributed to all the controlled rooms through the provided openings. Through this, the whole plenum remains clean and aseptic. The clean, aseptic air flows into the maximum security rooms at the greatest volume flow rate, and in these areas, a positive pressure is formed. Due to this pressure, the unclean air is prohibited from entering the aseptic area through cracks, temporarily opened doors, or other openings.

7.1.8.6. Environmental Control

The level of effective physical and biological environmental control somewhat depends on the facility type. The standards for environmental control vary from plant to plant, and also depend on the topographic location, the area involved (clean-up, packaging, compounding, or filling), and the type of product being prepared. Therefore, the standards should be flexible, and seasonal conditions should also be considered. The area used for manufacturing aseptic products not requiring terminal sterilisation should be maintained under rigid biological control. On the contrary, the compounding and filling areas should be under less rigid biological control if the products are to be terminally sterilised. The standards of cleanliness and daily disinfection for the clean-up and packaging areas should be rigid.

7.1.8.7. Traffic Control

An effective environmental control can be easily maintained if the personnel and supplies are not moved from one place to another. Therefore, the aseptic areas should be designed in a manner to control and limit traffic. Only the personnel's wash rooms, the non-sterile manufacturing area, and the packaging area should have a direct access from the outside. The personnel's access to the aseptic corridor should be through an airlock. **Pass-through openings** and **double-ended sterilisers** should be provided for controlled passage of supplies from non-septic to aseptic areas.

Personnel should enter the aseptic areas after following rigidly prescribed protocol that includes washing their hands, and removing their street clothing, donning gowns, hats, shoes, facemasks, gloves and other prescribed attire. On entering the aseptic area, the personnel should not move in and out of the area without re-dressing. Personnel assigned for cleaning and packaging should not enter these areas. Unofficial personnel should not enter the aseptic area.

7.1.8.8. Laminar Flow Benches

The aseptic area environment can be controlled by using laminar airflow originating from HEPA filter, which occupies one side of the limited space completely. Hence, the total space is rinsed with very clean air to remove all the contaminants. The orientation of the airflow direction can be **horizontal** (**figure 7.5**) or **vertical** (**figure 7.6**) and occupy either a limited area (like a workbench) or an entire room.

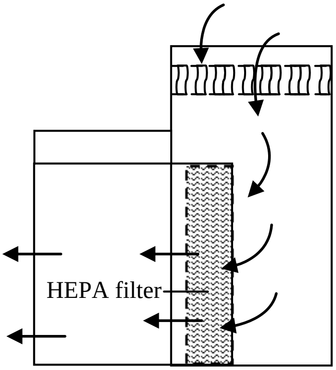


Figure 7.5: Horizontal Laminar Airflow Hood

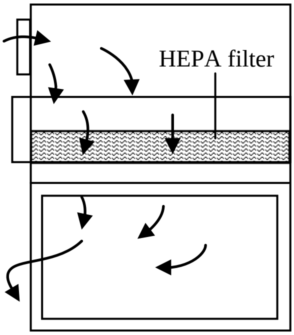


Figure 7.6: Vertical Laminar Airflow Hood

At the present time, this is the only way by which a Class 100 clean room (in which the particle count in the air is not more than 100 per cubic foot of 0.5 µm and larger in size) can be attained. The air coming from HEPA filter is uniformly blown out of the entire back or top of a workbench, or entire side or ceiling of a room. The airflow should have a uniform velocity (100 ± 20ft/min) and direction throughout the given cross-sectional area. Contamination is controlled because it is brushed away with the airflow. Contaminants entering downstream from the filter can get transferred to working areas beyond the downstream by improper setting of supplies, handling of personnel, or discharge from equipment. The risk of contamination through these situations is less when the air flows vertically from the ceiling-mounted HEPA filters. Thus, vertical flow is often employed to protect critical sections of processing lines and similar actions. Horizontal flow is often used for workbenches for providing protection to the processing lines.

7.1.8.9. Materials Support Area

Materials support area is a **Class 100,000 clean room**, designed to resist moisture, steam, and detergents. The ceiling, walls, and floor should be of impermeable materials so that they do not retain moisture. **Coating of vinyl** or **epoxy-sealing** provides a continuous surface with no holes or crevices. These surfaces can be washed thoroughly at regular time intervals. These areas are exhausted sufficiently for removing the heat and humidity which provide comfort to personnel. Due to high humidity and heat, microbial growth may occur which should be prevented. Precautions should be taken to prevent dust accumulation.

Material support area is utilised for filling operations, like cleaning and assembling of equipment. There should be sink and counter space in the area. This area should be cleanable and microbial load should be checked and controlled routinely. There should be no deposition of dust or other contaminants on clean containers and equipment. To prevent dust accumulation, the containers should be packed in boxes or wrapped preliminary for sterilisation and depyrogenation process.

7.1.8.10. Compounding Area

This area as the name suggests is used for compounding formulation. The steps taken to control microorganisms and particulate matter in this area should be more firm than for the materials support area. Required measures should be taken to regulate dust generated from weighing and compounding operations. **Stainless steel** should be used for the construction of cabinets and counters, which should be fitted well to the walls and other furniture. This prevents the accumulation of dirt. The ceiling, walls, and floor should be same as in the materials support area.

7.1.8.11. Aseptic Area

Aseptic area should be designed in such a manner that it controls the growth of microbes and particulate matter. The ceiling, walls, and floor should be sealed so that they can be easily washed and sanitised with a disinfectant. **Stainless steel** should be used for constructing the counters and they should have no legs (and need to be hung from the wall) so that dirt cannot collect in the areas where they are placed on the floors.

The light fixtures, utility service lines, and ventilation fixtures should be fitted in the walls or ceiling to prevent the accumulation of dust and dirt in ledges, joints, and other locations. Tanks with the compounded product should remain outside the aseptic filling area and the product is fed into the area through hose lines.

If the tanks are moved in, proper sanitisation is needed. Large mechanical equipment in the aseptic area should be stored inside a stainless steel cabinet to seal their operating parts and dirt-forming tendencies from the aseptic environment. All these equipment parts should be kept below the filling line. Mechanical parts that will be in contact with the parenteral product should be demountable for cleaning and sterilisation.

Entering of personnel in the aseptic area should be done by an airlock. They should wear sterile coveralls with sterile hats, masks, goggles, and foot covers. Movement inside the aseptic room should be negligible and in-and-out movement should be restricted during a filling process. If the product is to be sterilised terminally in a sealed container, the necessities of room preparation and the personnel can be fairly relaxed. However, a single standard procedure is required for fulfilling all the desired standards.

7.1.8.12. Isolation Barrier Technology

Isolation barrier technology is used for **isolating aseptic operations** from personnel and the neighbouring environment. Using this technology in sterility testing has given positive results. In European circles, favourable results have also been reported from use in hospital IV admixture programs. Because of such results, experimental efforts in adapting automated, large-scale, aseptic filling operations to isolators have gained momentum.

The operations are performed in windowed, sealed walls with operators working through glove ports. The sealed enclosures are pre-sterilised using peracetic acid, hydrogen peroxide vapour, or steam. Sterile supplies are introduced from sterilisable movable modules through specially designed transfer ports or directly from attached sterilisers, including autoclaves and hot-air sterilising tunnels. The results obtained are very promising, and provides enhanced control over aseptic environment.

7.1.9. Quality Control Tests of Parenteral Products

Parenteral products should undergo the most stringent quality control tests as they are meant to be used within the body. These products are monitored for sterility and pyrogens to make sure that they possess the required features. The tests performed for the quality control of parenteral products are:

1) Leaker testing,
2) Clarity testing,
3) Pyrogen test,
4) Sterility testing, and
5) Particulate matter monitoring.

7.1.9.1. Leaker Testing

Ampoules are sealed by tip sealing and pull sealing methods. Due to improper handling, there are chances that the ampoules are incompletely sealed and cracks may appear around the seal or at the base during the process of sealing. Therefore, the leak test is used for **identifying improper filling and sealing of ampoules**, and if found any they are rejected.

In this test, sample ampoules are immersed in a deeply coloured dye solution (0.5-1.0% methylene blue) and negative pressure of 27 inches Hg or more is applied in a vacuum chamber for 30 minutes. After this period, vacuum is released and the dye under the influence of atmospheric pressure penetrates the ampoules through any opening present. The ampoules are then washed externally and visually observed to check any change in the product colour due to the penetrated dye.

The leak test can be carried out during the cycles of autoclaving by immersing the ampoules in a dye bath. This method achieves two objectives, firstly it evaluates the **presence of any leakage** and secondly it **sterilises the product**. The leak test is **not suitable for vials and bottles** because they have rubber closures which are not rigid.

7.1.9.2. Clarity Testing

Clarity test is required for preventing the distribution and use of parenteral products having particulate matter. Clarity is a factor that needs to be considered seriously in parenteral preparations. Clarity testing is mainly performed through **human visual inspection of the containers in a direct light against a black and a white background**. As a result, the transparent particles are visible against black background and the coloured particles are visible against the white background.

The method of visual inspection has some limitations. Due to this reason, the particulate matter can also be identified by passing the solution through a filter and then examining the filter under a microscope. Many **automatic image analysis devices** are developed (such as **Quantimat 720 system 20**), which focus image of particles on a TV screen and concurrently a permanent record is also formed. There are some other devices available for identifying the particulate contamination; such devices are based on light absorption, light scattering, or change in electrical resistance. **Coulter counter method** is also used for detecting particulate matter.

7.1.9.3. Pyrogen Test

Pyrogens are endotoxin metabolites of microorganisms that increase the body temperature when parenteral preparations contaminated with them are administered. The pyrogen test is carried out as flows:

1) **Rabbit Test:** For this test, healthy rabbits maintained under suitable environment and diet before the test, are used. Normal or control temperatures are selected for each animal and are used as the base for easily determining any increase in temperature when the test solution is injected. Three rabbits whose temperature differs from each other by not more than 1 °C and whose body temperatures are also normal are selected. The test solution (obtained from the product to be tested) is warmed up to 37±2°C and injected in the marginal ear vein of each rabbit, completing each injection within 10 minutes of the start of administration. The temperature should be monitored at intervals of 30 minutes for 1-3 hours after the injection. The product is considered to fulfil the requirements for the absence of pyrogens if **no rabbits show a rise in temperature of 0.5°C or more**; on the other hand if any of the three rabbits show a rise in temperature of 0.5 °C or more, the test is continued using five more rabbits. Now if not more than three out of the eight rabbits show a rise in temperature, the product is considered to meet the requirements for the absence of pyrogens.

2) **Limulus Amebocyte Lysate (LAL) Test:** This *in vitro* test method for detecting pyrogens in the product utilises the **gelling property of the lysate of the amebocyte of *Limulus polyphemus*** (the horseshoe crab). If the pyrogenic endotoxins from gram-negative bacteria are present in the product, a firm gel is formed within 60 minutes on incubating the product at 37 °C. The LAL test is 5-10 times more sensitive than the rabbit test; and with the use of serial dilutions, it is assumed to be **semi-quantitative**.

7.1.9.4. Sterility Testing

Sterility test is a **confirmatory test for sterilisation process**. Parenteral preparations such as injectables, ophthalmic products, and absorbent cotton are tested by this test, which is performed aseptically to avoid product contamination during the test.

Principle

Sterility test works on the principle that on supplying microorganisms with nutrient medium and incubating them under favourable temperature, they start growing and multiplying, and their presence can be detected by the appearance of turbidity in the clear medium.

Preparation of Culture Media

The culture media used for sterility testing should stimulate the growth of various aerobic and anaerobic microorganisms such as bacteria and fungi. **Two types** of culture media that can be used are:

1) **Fluid Thioglycollate Medium:** This medium supports anaerobic as well as aerobic bacterial growth. **Table 7.15** enlists the ingredients and their quantities used for preparing this medium:

Table 7.15: Composition of Fluid Thioglycollate Medium

Ingredients	Quantity (for 100ml)
L-cysteine	0.5gm
Sodium chloride (NaCl)	2.5gm
Dextrose	5.5gm
Agar	0.75gm
Yeast extract	5.0gm
Pancreatic digest of casein	15.0gm
Sodium thioglycolate	0.5gm
Resazurin (0.1% fresh solution)	1.0ml
Distilled water (q.s.)	1000ml

2) **Soybean-Casein Digest Medium:** This medium supports aerobic bacterial growth and fungal growth. **Table 7.16** enlists the ingredients and their quantities used for preparing this medium:

Table 7.16: Composition of Soybean-Casein Digest Medium

Ingredients	Quantity (for 1000 ml)
Pancreatic digest of casein	17.0gm
Peptic digest of soybean meal	3.0gm
Sodium chloride	5.0gm
Dibasic potassium phosphate (K_2HPO_4)	2.5gm
Dextrose	2.5gm
Distilled water (q.s.)	1000ml

Sampling (Selection of the Sample Sizes)

The sample itself and their number should be procured from the given batch of sterile product. The material should be thoroughly mixed if the sample is to be obtained from the bulk. The sample is withdrawn randomly from the batch of final containers.

Test Methods

1) **Membrane Filtration Method:** This method is used when the test substance is:
   i) An oily preparation,
   ii) An ointment that can be placed in the solution,
   iii) A soluble powder or a liquid with antimicrobial properties,
   iv) A solid with no antimicrobial properties and not readily soluble in the culture media, and
   v) A liquid product whose volume in a container is 100ml or more.

   Procedure: Sterility test utilises membrane filters having pore size not greater than 0.45μm and diameter 47mm. These filters should retain microbes. The filtration system and the membrane should be sterilised and the substances are membrane filtered under aseptic conditions.

The membrane is washed thrice with 100ml of sterile solvent if the substances have antimicrobial properties. Then the membrane is aseptically cut into two equal halves. One half is immersed in soybean-casein digest medium (100ml) and incubated at 20-25°C. The other half is immersed in fluid thioglycollate medium (100 ml) and incubated at 30-35°C for a week.

2) **Direct Inoculation Method:** The test substance to be used in each culture medium is directly transferred or inoculated into the culture media aseptically. This inoculated liquid is mixed with the medium. If the test substance contains antimicrobial properties, it is neutralised with the addition of inactivating substances (**e.g.,** penicillinase in case of penicillin) to the medium. The inoculated medium is incubated at 20-25°C with soybean-casein digest medium and at 30-35°C with fluid thioglycolate medium for a week.

3) **Positive Control Test:** This test is performed to make sure that the prepared culture media and the environment conditions maintained during the test period support the microbial growth. The culture media is streaked under aseptic conditions with the causative test microorganism and then the method discussed above is adopted. On completion of the test growth or multiplication, the microbial load should be observed.

4) **Negative Control Test:** This test is performed to make sure that proper sterile conditions have been maintained in the test area. The sterilised culture media is exposed to the test area and incubated. At the end of the study, there should not be any growth in the culture media, thereby proving the sterility and absence of microorganisms in the working area; an **example** is the laminar airflow unit.

Observation and Interpretation of Results

At intervals during the incubation period and on its completion, the media are examined for the presence of growth of microorganisms. If the material under test makes the medium turbid, detection of microbial growth by visual inspection becomes difficult. Two weeks after the beginning of incubation, 1ml portions of each medium are transferred to fresh vessels containing the same medium. Then, the original and transfer vessels are incubated for 4 days.

If no microbial growth occurs, the preparation is considered to pass the sterility test, while if microbial growth is observed, the preparation fails the test. The sterility test is not repeated unless it can be proved that the test was invalid for reasons unrelated to the preparation being tested.

If the test is declared to be invalid, it is repeated using the same number of units as in the original test. If no microbial growth is observed in the repeat test, the preparation passes the sterility test, while if microbial growth is observed which is even confirmed microscopically, the preparation fails the test.

7.1.9.5. Particulate Matter Monitoring

The presence of particulate matter in a solution to be administered intravenously is considered harmful. Till now limited data has been procured related to the extent of damage caused by particulate matter, although **Garvan** and **Gunner** have shown in **1964** that particles of rubber, insoluble chemical, lint, and other foreign chemicals can produce emboli in the vital organs of animal and man. Particulate matter in infusion fluids causes infusion phlebitis. Erythrocytes have a diameter of 4.5 µm, thus particles of more than 5µm size should form the basis of evaluation. By using Tyndall effect for analysis, particles of 10µm size can be viewed.

The **methods** employed for particulate matter monitoring are as follows:

1) **Visual Inspection:** The U.S.P. has specified that each final container of an injection should be visually inspected and those having visible particles should be discarded. Thus, all the products from the production line undergo separate inspection under good light and against black and white background. Visual inspection however has some **drawbacks** like particle size limitation (that can be seen with naked eyes), the visual opinion may vary from inspector to inspector as their emotional state, eyes strains, fatigue and other personal factors may affect the evaluation.

2) **Microscopic Method:** Particles of size smaller than 50 μm cannot be detected by visual inspection. Thus, a microscopic method has been developed by the U.S.P. for detecting large volumes of intravenous solutions. This method has a limit of not more than 50 particles/ml of size 10μm and large and not more than 5 particles/ml of size 25 μm and large. In this method, a measured volume of sample solution is filtered through a membrane filter under aseptic conditions and then the particles on the surface of the filter are counted microscopically using oblique light at 40x and 100x magnification.

3) **Shadow Cast Method:** The U.S.P. has established standards for small-volume parenterals meant for intravenous administration, using an electronic instrument which measures particle size by mode of a shadow cast by the particles, as it passes through high-intensity light beams. The prescribed limits are not more than 10,000 particles/container of size ≥ 10μm and not more than 1000 particles/container of size ≥ 25μm. These specifications were laid on the assumption that five products can be added to a 1L bottle of a large-volume parenteral and they should not contribute to more than the overall limits of particles prescribed for large-volume parenteral.

4) **Electronic Particle Counter:** Some other methods are also available for determining the presence of particulate matter. Many electronic particle counters are available, which utilise the principle of light scattering for counting particles in a liquid sample.

5) **Thermocouple Conductivity Method:** Some instruments, **e.g.,** the Coulter Counter, are available for counting and sizing particles by measuring the resistance effect between two electrodes when the particle passes between them.

All of these methods require aseptic preparation techniques to achieve accuracy in counting and sizing the practices present in solution, and not those introduced accidentally during sample preparation or testing procedure. These procedures are also quite destructive, and can be performed using only those samples withdrawn from a production lot.

7.1.10. Formulation of Sterile Powders

The processing and filling of sterile powders is a difficult task in the conduct of simulation as the equipment used cannot easily accommodate the liquid media generally used for the simulation. In most of the cases in the simulation process, sterile liquid media and a sterile powder placebo are added to the container. The order of addition and the extent to which the powder filling process is adapted to accommodate the liquid fill can make this a difficult simulation.

As liquid filling on a powder line is a rare event, some firms fill a number of liquid containers along with the powder fill to establish that this activity is not the cause of any contamination. The sterilising filtration for sterile powders is conducted in a separate facility (or by a separate firm), therefore simulation concerns at the filling site are restricted to the activities performed there, including milling and blending.

Methods of Preparing a Sterile Drug Powder

1) **Sterile Re-Crystallisation:** In this method, the drug is dissolved in a solvent, the solution obtained is sterilised by passing through a 0.22 μm membrane filter, and finally a sterile anti-solvent is added to crystallise the drug particles, which are filtered and dried aseptically.

   Advantage

   This method is flexible and economic.

   Disadvantage

   This method represents variations from batch to batch and contamination.

2) **Lyophilisation:** In this method, a solid substance is separated from solution by freezing the solvent and evaporating the ice under vacuum. The obtained drug solution is sterile filtered into sterile trays, which are then aseptically loaded into a freeze dryer. The solution is then frozen at –50°C and then dried by vacuum to separate the drug powder.

   Advantage

   This method involves removal of water at low temperatures.

   Disadvantages

   i) In this method, the biological molecules are damaged by the stress associated with freezing and drying.
   ii) This method is expensive and time consuming.

3) **Spray Drying:** In this method, the drug solution is sprayed into a dry chamber where it comes in contact with a hot steam of a sterile gas at 80-100°C temperature.

   Advantages

   i) This method is simple, economic, scalable, and faster.
   ii) This method involves coating of particles during drying prolonged release.

   Disadvantages

   i) In this method, the high processing temperatures and high shear forces can damage the drugs.
   ii) In this method, higher levels of drug are lost in comparison to freeze drying.
   iii) This method has a limited solvent choice for a given drug.
   iv) In this method, product cannot be prepared directly in vials or plates.

7.1.11. Formulation of Large Volume Parenterals

Large volume parenterals are sterile aqueous solutions or emulsions having water for injection as its main component. They are formulated as single-dose injections administered by intravenous infusion. They are packed and administered in large volumes. They should be free of particles. Before administration, sometimes additional drugs are added to them by either injecting small volume parenterals to the **administration sets** or by the **piggyback method** (smaller volume infusion of an additional drug is added to the intravenous delivery system). Large-volume parenteral products include:

1) Infusion fluids,
2) Total Parenteral Nutrition (TPN) solutions,
3) Intravenous antibiotics,
4) Patient-controlled analgesia,
5) Dialysis fluids, and
6) Irrigation solutions.

Large volume parenterals should be **terminally heat sterilised**. Apart from water for injection as the main component, other **ingredients** that should be included are carbohydrates (**e.g.,** dextrose, sucrose and dextran), amino acids, lipid emulsions (containing vegetable or semi-synthetic oil), electrolytes (**e.g.,** sodium chloride), and polyols, including glycerol, sorbitol and mannitol.

The large volume parenterals are mostly clear aqueous solutions, except for the oil-in-water emulsions. The emulsions for infusion are produced by highly specialised method as they are destabilised by heat. This results in many difficulties during production, thus the size of oil droplets should be controlled during heat sterilisation.

Production of Large-Volume Parenterals

The manufacturing and filling of large volume parenteral fluids into containers are carried out in a **high-standard clean room environment**. High standards are required to prevent these products from getting contaminated with organisms, pyrogens, and particulate matter. The quality of products can be ensured by strictly following the quality assurance procedures.

In commercial manufacturing facilities, large volumes of fluids are used in the production of a product batch. The fluids from a bulk container are filled into the product container using **high-speed filling machines**. Before filling the fluid into the container, it is passed through an in-line membrane filter to remove the particulate matter. After filling, the neck of each glass bottle is immediately sealed with a tight-fitting rubber closure held in place with a crimped aluminium cap. The outer cap is also of aluminium and an outer tamper-evident closure is used.

In case plastic bags are used, the pre-formed plastic bags are aseptically filled and heat sealed immediately. A **blow-fill-seal system** can also be used that involves melting the plastic, forming the bag, and filling and sealing in a high-quality clean room environment. Blow-fill-seal system minimises the problems with product handling, cleaning and particulate contamination. After the product is filled into containers, they are checked for particulate matter and the integrity of container closures is established.

The large volume parenteral products, including irrigation solutions and dialysis fluids, should be **moist heat sterilised** immediately after the containers are filled. Plastic containers should be sterilised with an over-pressure during the sterilisation cycle so that they do not burst.

7.1.12. Formulation of Lyophilized Products

Lyophilised or freeze dried products are prepared by freeze drying, and this process is known as **lyophilisation** or **cryodesiccation**. It is a dehydration process used for preserving a perishable material or making the material more convenient for transport. Freeze-drying works by freezing the material and then reducing the surrounding pressure so that the frozen water in the material directly sublimes from the solid phase to the gas phase.

The **four stages** involved in the freeze drying process are:

1) **Pre-Treatment:** In this stage, the product prior to freezing is either concentrated, the formulation is revised (i.e., adding new components to increase the stability and/or improve the processing), a high vapour pressure solvent is decreased, or the surface area is increased. In many cases, pre-treatment is based on the theoretical knowledge of freeze-drying and its requirements, or is demanded by cycle time or product quality considerations.

The **methods** of pre-treatment are:

i) Freeze concentration,
ii) Solution phase concentration,
iii) Formulation to preserve product appearance,
iv) Formulation to stabilise reactive products,
v) Formulation to increase the surface area, and
vi) Decreasing high vapour pressure solvents.

2) **Freezing:** On a smaller scale in this stage, the material is placed in a freeze-drying flask that is rotated in a bath (called a shell freezer) cooled by mechanical refrigeration, dry ice and methanol, or liquid nitrogen. On a larger scale, a freeze-drying machine is used for freezing. The material is cooled below its triple point (the lowest temperature at which the solid and liquid phases of the material can coexist) to ensure that the material will not melt but sublime in the subsequent steps. Larger crystals can be easily freeze dried; thus larger crystals should be produced by freezing the product slowly or by annealing (cycling the product up and down in temperature).

3) **Primary Drying:** In this stage, the pressure is lowered (up to a few millibars) and heat is supplied to the material so that the water sublimes. The amount of heat required is determined by using the latent heat of sublimation of sublimating molecules. 95% of the water in the material sublimes in this initial drying phase. This phase is slow because on adding excessive heat the material's structure gets altered.

   The pressure in this phase is controlled by applying partial vacuum that speeds up sublimation. A cold condenser chamber and/or condenser plates (maintained at −50 °C temperature) provide a surface on which the water vapour re-solidifies. This condenser has no role in keeping the material frozen; but, it prevents water vapour from reaching the vacuum pump, or else the pump's performance will be degraded.

4) **Secondary Drying:** In this stage, the unfrozen water molecules are removed, since the ice was removed during primary drying. This stage of freeze-drying is governed by the material's adsorption isotherms. In secondary drying, the temperature is increased more than in the primary drying phase, and can even be above 0°C, to break any physicochemical interactions between the water molecules and the frozen material. The pressure is also lowered (in the range of microbars or fractions of a Pascal) to facilitate desorption. However, some products are benefitted from increased pressure.

   After completing the freeze-drying process, the vacuum is broken with an inert gas (such as nitrogen) and the material is sealed. In the final product, the residual water content is extremely low (around 1-4%).

7.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) The term **parenteral** has been derived from the Greek word ***para enteron*** which means **outside the intestine**.

2) Thus, parenteral preparations (par + enteral) as the name suggests are **administered from other than enteral routes** (i.e., oesophagus, stomach, intestines are bypassed by the parenteral drugs).

3) **Transfusion Fluids** are parenteral solutions administered by intravenous route.

4) **Solutions or Emulsions of Medicaments for Injections** are used as injections and available in single dose or multiple dose containers.
5) **Lyophilised Powders for Injections** are converted into solutions or suspensions after reconstitution for administration.
6) **Colloidal Solutions** are homogeneous solutions in which the particles are dispersed in the liquid phase.
7) **Injectable Emulsions** are liquid preparations in which the drug substances are dissolved or dispersed in a suitable emulsion medium.
8) **Injectable Suspensions** are liquid preparations in which the solids are suspended in a liquid medium.
9) **Implants** are sterile solids implanted in the tissues to release the active ingredient for prolong periods.
10) **Sterile Solids** are dry sterile solids dissolved in a solvent and then administered in the body.
11) Parenteral dosage forms include solutions, suspensions, and sterile solids for reconstitution.
12) **Thermo Gravimetric Analysis** (TGA) is another thermal analytical method used for detecting the existence and stability of solvated drug molecules.
13) **Potentiometric pH titration** or **pH-solubility analysis** is used for determining the pka value.
14) **Medicaments** are the active ingredients, and are sterilised before adding to the formulations.
15) **Tonicity Adjusting Agents** are used to ease parenteral administration by reducing pain or tissue irritation.
16) Solution having less osmotic pressure than the blood plasma is **hypotonic.**
17) Solution having more osmotic pressure than the blood plasma is **hypertonic**.
18) In hypotonic solution, water diffuses into the RBCs causing them to swell and finally burst.
19) In hypertonic solution, water diffuses out of the RBCs causing them to shrink.
20) In isotonic solution (**e.g.,** 0.9% sodium chloride), the RBCs maintain their tonicity.
21) Parenteral products, except those containing thermolabile substances, after being filled and sealed in the final containers are sterilised, and this process is termed **terminal sterilisation**.
22) Single-layered aluminium caps are applied using a hand crimper, known as **Fermpress**.
23) The air in the aseptic area should be made free from fibres, dust, and microbes by fitting **High Efficiency Particulate Air (HEPA) filters**.
24) Clarity testing is mainly performed through **human visual inspection of the containers in a direct light against a black and a white background**.
25) Lyophilised or freeze dried products are prepared by freeze drying, and this process is known as **lyophilisation** or **cryodesiccation**.

7.3. EXERCISE

7.3.1. True or False

1) The term parenteral has been derived from the Greek word *para enteron*.
2) Injectable suspensions are sterile solids implanted in the tissues to release the active ingredient for prolong periods.
3) Solution having less osmotic pressure than the blood plasma is hypertonic.
4) Solution having more osmotic pressure than the blood plasma is isotonic.
5) Tonicity Adjusting Agents are used to ease parenteral administration by reducing pain or tissue irritation.
6) Transfusion Fluids are parenteral solutions administered by intravenous route.

7.3.2. Fill in the Blanks

7) Solution having less osmotic pressure than the blood plasma is __________.
8) Solution having more osmotic pressure than the blood plasma is _________.
9) In hypotonic solution, water diffuses into the RBCs causing them to ______.
10) Single-layered aluminium caps are applied using a hand crimper, known as__________.
11) ___________ are homogeneous solutions in which the particles are dispersed in the liquid phase.

Answers

1) True
2) False
3) False
4) False
5) True
6) True
7) Hypotonic
8) Hypertonic
9) Swell
10) Fermpress
11) Colloidal Solutions

7.3.3. Very Short Answer Type Questions

1) Write a short note on parenteral preparations.
2) Discuss the limitations of parenteral formulations.
3) What is the importance of isotonicity?
4) Discuss environmental control for parenteral production facilities.
5) Discuss the buffers used in parenteral procedures.

7.3.4. Short Answer Type Questions

1) Write a short note on various types of parenteral preparations.
2) Discuss the process of sterilisation for parenteral preparations.
3) Write a short note on packaging and labeling of parenteral preparations.
4) Give the layout of sterile product area.

7.3.5. Long Answer Type Questions

1) Discuss the quality control tests for parenteral products.
2) Give a detailed note on formulation of injections.
3) Explain the production facilities and controls required for parenteral preparations.

CHAPTER 8

Ophthalmic Preparations

8.1. OPHTHALMIC PREPARATIONS

8.1.1. Introduction

Ophthalmic or eye preparations are sterile liquid, semi-solid, or solid preparations containing one or more active pharmaceutical ingredient and meant to be applied on the conjunctiva, conjunctival sac, or eyelids.

These specialised dosage forms are intended for topical application on the external surface of the eye, for administration inside (intraocular) or adjacent (periocular) to the eye, or for using along with an ophthalmic device. The ophthalmic dosage forms are mainly available in the form of solutions, suspensions, and ointments. At the present time, the dosage forms for delivering ophthalmic drugs are gels, gel-forming solutions, ocular inserts, intravitreal injections, and implants.

Advantages

1) They can be easily administered by the nurse.
2) They can be easily administered by the patients themselves.
3) They undergo quick absorption and thus produce a quick effect.
4) They produce less systemic side effects.
5) They have increased shelf-life.
6) They show better patient compliance.

Disadvantages

1) They stay for a very short time at the eye surface.
2) They have poor bioavailability.
3) The dissolved drug shows instability.
4) They need a preservative.

8.1.2. Formulation Considerations

Discussed below are the special formulation considerations for ophthalmic preparations:

1) **Clarity:** Ophthalmic solutions should not have any undissolved ingredients and foreign particles. In some solutions, the clarity can be improved by filtration using clean and well-rinsed equipment so that the solution does not get contaminated with particulate matter (that may be present in the filtration equipment).

   Clear solutions with no foreign particles can be obtained by preparing them in clean surroundings, using laminar-flow hoods, and wearing non-shedding garments. In some cases, clarity and sterility is achieved during filtration only. If the preparation contains viscosity-imparting polymers, a polish-filtering step should be carried out before the final filtration.

2) **Stability:** Drug stability in an ophthalmic preparation depends on the drug's chemical nature (whether it is in solution or suspension form), product's pH, preparation method (particularly temperature exposure), solution additives, and

packaging type. For achieving the desired stability, some compromises are made in the formulation, packaging, and preparation of the final product. The product pH most commonly is the stability-controlling factor for many drugs. **For example,** pilocarpine and physostigmine are active and comfortable in the eyes at pH 6.8; but, at this pH chemical stability or instability is measured in days or months; either pilocarpine or physostigmine will undergo a loss in chemical stability in less than a year; while, both the drugs remain stable for several years at pH 5.

Along with optimal pH, if oxygen sensitivity is also a factor, the desired stability can be obtained by adding an antioxidant or by special packaging. Plastic packaging (i.e., low-density polyethylene containers such as the Drop-Tainer representing a patient convenience) may affect the product stability by allowing oxygen permeation which causes oxidative decomposition of the drug.

Pharmaceutical manufacturers carry out complete stability programs to make sure that each product remains stable till the assigned expiration date. The chemical and physical stability of the pharmaceutical ingredient as well as of the preservative is monitored chemically or by challenging the preservative efficacy with test organisms.

3) **Buffer and pH:** The pH of ophthalmic preparations should be equal to the pH of tear fluid, i.e., 7.4; however, this requirement can be attained rarely. The active ingredients used in ophthalmology are mostly salts of weak bases, while others are stable at an acidic pH. This can be extended to suspensions of insoluble corticosteroids, and these suspensions are most stable at low pH. It is accepted that an acidic pH will not cause stinging or discomfort when the product is instilled into eyes. If after the product application, the overall pH of tears goes back to pH 7.4, minimum discomfort occurs.

   On the other hand, if the buffer capacity can resist adjustment by tear fluid and the overall eye pH remains acidic for a considerable time period, stinging and discomfort can occur. So, buffer capacity should be adequate for stability, but minimised to allow the overall pH of the tear fluid to be disrupted momentarily. Special care regarding the pH and buffer capacity should be taken while formulating intraocular products.

4) **Tonicity:** It is the osmotic pressure exerted by the salts in aqueous solution. An ophthalmic solution is isotonic when the colligative properties of the solution have equal magnitudes. An ophthalmic solution is isotonic when its tonicity is equal to that of a 0.9% sodium chloride solution (290mOsm). The osmotic pressure of aqueous intraocular fluid is slightly higher than that of tears measuring about 305mOsm. The external eye can tolerate solutions equivalent to a range of 0.5-1.8% sodium chloride. Isotonicity is desirable and important in intraocular solutions; but in some cases a non-isotonic topical product is desirable.

   Tear fluid of dry eye in some cases is hypertonic, and this condition can be neutralised with a hypotonic artificial tear product. Hypertonic ophthalmic products available as solutions and ointments containing 2-5% sodium chloride are used for relieving corneal oedema.

5) **Viscosity:** Ophthalmic solution and suspension eye drops contain viscosity-imparting polymers to thicken the tear film and increase corneal contact time by reducing the rate of tear fluid drainage. For suspensions, the increased viscosity delays the settling of particles between uses and at the same time maintains their

suspension for uniform dosing. Increased viscosity makes initial re-suspension difficult, mostly in a suspension which can undergo caking during storage. The **examples** of hydrophilic polymers used commonly are methylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, and polyvinyl alcohol. They are used in concentrations which produce viscosities in the range of about 5-100 cps.

In new ophthalmic dosage forms (like gel-forming solutions and semi-solid aqueous gels), viscosity and gel elasticity is increased to enhance drug bioavailability and duration of action. These improvements help in reducing the dosing frequency and thus improving patient compliance.

6) **Additives:** These are used as inactive ingredients in most of the ophthalmic dosage forms. They are however used limitedly in intraocular products for tissue compatibility. Vehicle is the most common inactive ingredient. Purified Water U.S.P. is used for topical products. Water for Injection U.S.P. is used in intraocular products for non-pyrogenicity. Mineral oil and petrolatum are used in combined form as a vehicle for ophthalmic ointments. Non-aqueous liquids are used limitedly in topical eye drops as they can cause ocular irritation and poor patient tolerance. Some mineral and vegetable oils are used for moisture-sensitive or poorly water-soluble drugs.

Microbiological preservatives are used in multiple dose topical ophthalmic products. Other additives of topical eye products are substances which maintain and **buffer** the pH, and substances which adjust the tonicity. Usually same substances are used for both the purposes (i.e., pH and tonicity adjustment) in parenteral products. **Antioxidants** (**e.g.,** sodium bisulphite, ascorbic acid, and acetyl cysteine) are used less commonly.

Surfactants are added in topical eye products in very small concentration (as they can cause irritation to sensitive ocular tissues) for the dispersion of insoluble ingredients or for solubilisation. Non-ionic surfactants are frequently used as they are comparatively less irritating. Polysorbate 80 is added in the formulation of ophthalmic emulsions. Polyoxyl 40 stearate and polyethylene glycol are used to solubilise a drug in an anhydrous ointment so that it can be sterilised by filtration.

8.1.2.1. Formulation of Eye Drops

An eye drop formulation comprises of the following:

1) Active ingredient(s) to produce the desired therapeutic effect.
2) Vehicle (aqueous or oily).
3) Inert antimicrobial preservatives to prevent microbial contamination and to maintain sterility.
4) Inert adjuvants for adjusting tonicity, viscosity or pH to increase the stability of active ingredient(s).
5) Suitable container to maintain the preparation in a stable form and provide protection against contamination during preparation, storage, and use.

The most important requirement of eye drops is that they should be sterile. In history, some eye drops were found to be contaminated with *Pseudomonas aeruginosa*, which is difficult to treat and can cause loss of vision.

Antimicrobial Preservatives

Multiple-dose eye drops are added with an effective antimicrobial preservative system (a single substance cannot be successfully used as a preservative in ophthalmic solutions) that should pass the test for efficacy of antimicrobial preservatives. This ensures that the eye drops are sterile and non-contaminated. Healthy eyes can efficiently prevent the penetration of microorganisms, but colonies of microorganisms can develop in the eyes having damaged epithelia. The lack of vascularity of cornea and some other internal structures of eyes make them highly prone to infections and thus should be treated at once. A preservative should not be added to eye drops formulated to be used during intraocular surgery, because there is a risk of damage to the internal surfaces of the eye. Preservatives that can be added to eye drops are given in **table 8.1**:

Table 8.1: Preservatives Suitable for Specific Eye Drops

Benzalkonium Chloride (0.01% w/v)	**Chlorhexidine Acetate (0.01% w/v)**	**Phenylmercuric Nitrate[a] (0.002% w/v)**
Atropine sulphate	Cocaine	Tetracaine
Carbachol	Cocaine and homatropine	Chloramphenicol
Cyclopentolate		Fluorescein[b]
Homatropine		Hydrocortisone and neomycin
Hyoscine		Lachesine
Hypromellose		Neomycin
Phenylephrine		Sulphacetamide
Physostigmine		Zinc sulphate
Pilocarpine		Zinc sulphate and adrenaline
Prednisolone		

[a] The acetate may also be used.
[b] This is preferably used as single dose preparations.

8.1.2.2. Formulation of Eye Ointments

The following bases can be used for the preparation of eye ointments:

1) Yellow soft paraffin (80gm),
2) Liquid paraffin (10gm), or
3) Wool fat (10gm).

White soft paraffin is prepared by bleaching the yellow soft paraffin, thus is not used. Some of the bleaching agents used stick to the base even after thorough washing and irritate the eyes on application. **Wool fat** is used for specific emulsification of the solution and helps in the absorption of active ingredient. **Liquid paraffin** is used for reducing the viscosity of base, so that it can be easily expelled from collapsible tubes when required to be applied on eyes.

8.1.2.3. Formulation of Eye Lotions

Eye lotions are undiluted aqueous solutions used for first aid purposes. They allow a large volume of fluid to quickly flow over the eyes. They are iso-osmotic to tears as they make the lachrymal fluid much more dilute than the eye drops. However, they may cause discomfort if not adjusted. Thus, their preparations should be very simple and should contain a sterile normal saline.

An **ideal eye lotion** should have the following **properties**:

1) It should be sterile and should contain no preservative.
2) It should be iso-osmotic to lachrymal fluid.
3) It should have a neutral pH.
4) It should be of large volume but not greater than 200ml.
5) It should be non-irritant to ocular tissue.

8.1.3. Methods of Preparation

Preparation of Eye Drops

1) **Preparation of the Solution:** The aqueous eye drop vehicle containing suitable preservative, antioxidant, stabiliser, tonicity modifier, viscosity modifier, or buffer should be prepared, and added with the active ingredient and the vehicle to make up the volume.

2) **Clarification:** Sintered glass filters or membrane filters having 0.45 -1.2µm pore sizes should be used. The clarified solution is either filled directly into the final containers which are sealed before heat sterilisation or is temporarily filled into a suitable container before filtration. Clarified vehicle is used to prepare eye drop suspensions filled into final containers and sealed before sterilisation.

3) **Sterilisation:** This can be achieved by autoclaving at 115°C temperature for 30 minutes or 121°C temperature for 15 minutes. Filtration into sterile containers through a membrane filter having 0.22 µm pore size is also a suitable method for sterilisation. Dry heat sterilisation at 160°C temperature for 2 hours is best suited for non-aqueous preparations such as liquid paraffin eye drops.

4) After sterilisation, the eye drop containers should be covered with a readily break-able seal to distinguish between opened and unopened containers.

Preparation of Eye Ointments

Wool fat and yellow soft paraffin are melted on a heated water bath. Liquid paraffin is added to the melted mixture and filtered through a coarse filter paper (**e.g.,** Whatman 54) placed in a heated funnel. The obtained mixture is sterilised at 160°C temperature for 2 hours. The medicament is added with eye ointment base, and the final mixture is packed in a sterile container.

Preparation of Eye Lotions

The British Pharmaceutical Codex has defined eye lotions as “sterile aqueous solutions containing no bactericide for first-aid purposes over a maximum period of 24 hours” or “aqueous solutions containing a bactericide for intermittent domiciliary administration for up to 7 days”.

In the older times, an eye lotion comprises of a solution which the patient had to dilute with an equal volume of water before application. If such preparations are prescribed at the present time, they should be issued as sterile solutions even though the patient cannot maintain the sterility of the preparation during use. An **example** of this type of eye lotion is given by the following **prescription**:

Prescription for Eye Lotion
R_X
Boric acid 2%
Zinc sulphate 0.4%
Purified water to 100ml

Send 200ml

Label: Use with equal volume of warm water in an eye bath

Zinc sulphate and boric acid are dissolved in purified water. The resultant solution is clarified by filtration and transferred to a fluted bottle, which is closed with a screw-cap and sterilised in an autoclave. The patient should avoid contaminating the solution during use.

8.1.4. Containers

The containers of **eye drops** should provide protection against microbial contamination, moisture, and air. The container materials should neither leach into the solution, nor should they absorb or adsorb any eye drop ingredient. Before sterilising the product in the final container, all the container parts should be sterilised.

The eye drop containers are made up of glass or plastic and may be single- or multiple-dose containers (the latter should not contain more than 10ml):

1) **Single-Dose Containers:** These containers consist of an injection-moulded polypropylene container which is sealed at its base and has a nozzle sealed with a screw cap. These containers are autoclaved in an outer heat-sealed pouch with peel-off paper backing.

2) **Plastic Bottles:** The commercially prepared eye drops are mostly dispensed in plastic dropper bottles **(figure 8.1)** made up of polyethylene or polypropylene. These bottles are sterilised using ionising radiation before they are filled under aseptic conditions.

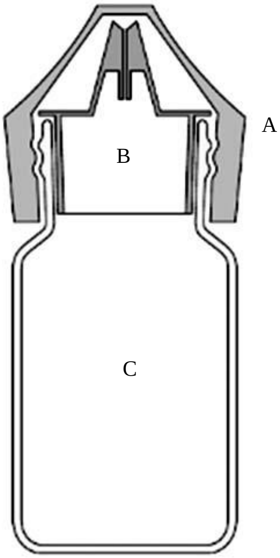


Figure 8.1: Plastic Eye Drop Bottle. (A) Rigid Plastic Cap. (B) Polythene Friction Plug Containing Baffle that Produces uniform Drops. (C) Polythene Bottle

3) **Glass Bottles:** Most extemporaneously prepared eye drops are supplied in 10ml amber coloured partially ribbed glass bottles. These bottles can be made up of **neutral glass** and can be autoclaved more than once. They can also be of **soda glass** with treated internal surfaces (during manufacture) to reduce the release of alkali on coming in contact with aqueous solutions, but these glass bottles can be autoclaved only once.

   The **teats** are made of natural or synthetic rubber. The **teats of natural rubber** withstand autoclaving for 30 minutes at 115 °C temperature but not at high temperatures of dry heat sterilisation; while the **teats of silicone rubber** withstand dry heat sterilisation and are used with oily eye drops.

   Since silicone rubber is permeable to water vapour, aqueous eye drops in bottles having silicone rubber teats have a shelf-life of only 3 months. This can be however extended by dispensing the sterile eye drops in bottles sealed with an ordinary screw cap together with a separately wrapped and sterilised silicone rubber dropper unit.

Teats and caps are used once only. All the components should be thoroughly washed with filtered distilled or deionised water, dried and stored in a clean area until required.

Rubber teats absorb preservatives and antioxidants during autoclaving and storage. Thus, it is necessary that individual studies should be carried out during formulation to prevent preservative and antioxidant loss.

The components of an eye drop bottle are shown in the **figure 8.2**:

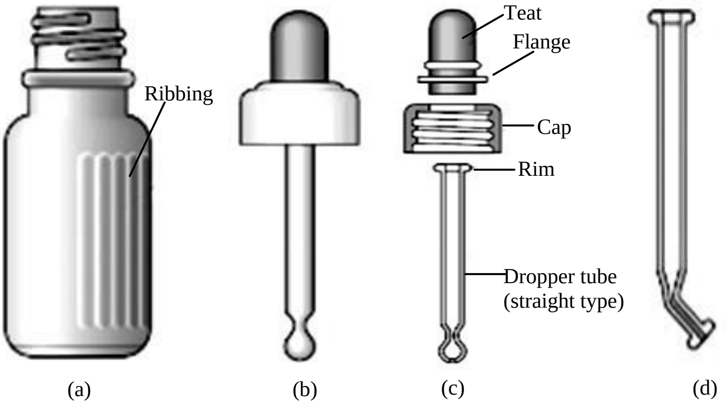


Figure 8.2: Eye Dropper Bottle. (a) Bottle (b) Assembled Closure (c) Components of Closure (d) Dropper Tube (Angled Type)

Eye ointments should be packed in collapsible metal (aluminium) or plastic (polyvinyl chloride) tubes or in single-dose containers. Any dust or metal particles should be removed from the collapsible metal tubes before use by blowing the tubes out with a powerful jet of filtered, dust free air. Some patented eye ointments are supplied in single-dose containers, which are elongated, flexible, and like gelatin capsule with one end constricted. They are opened by cutting this constricted end with sterile scissors. The eye ointment containers which are not extemporaneously dispensed should be enclosed in a readily breakable, sealed package to indicate that it has not been opened.

Eye lotions are dispensed in coloured fluted bottles closed with a metal or plastic screw cap. The liner of the screw cap should not be made of cork as it may result in microbial contamination. Rubber or plastic liners should be suitably used. Uncoloured or non-fluted bottles should be used if a suitable coloured, fluted bottle is not available.

8.1.5. Labelling

The label for ophthalmic products should include:

1) The product name,
2) The name(s) of active ingredient(s) and their concentration,
3) The name(s) and concentration(s) of antimicrobial agent(s) and/or antioxidant(s) added,
4) The amount or volume of preparation in the container,
5) The batch (lot) number as assigned by the manufacturer,
6) The expiry date,
7) Special storage conditions or handling precautions (if any),
8) The period of use after opening the container,
9) Directions for use, warnings, and precautions,
10) The manufacturer's name and address, and
11) The statement "This preparation is sterile".

For single-dose containers, the following information should be provided on the container:

1) The name(s) of the active ingredient(s) and their concentration(s),
2) The volume of preparation in the container,
3) The manufacturer's name, and
4) The type of preparation.

8.1.6. Evaluation of Ophthalmic Preparations

Ophthalmic preparations are evaluated as follows:

1) **Sterility:** The ophthalmic products should meet the standard requirements. If the ingredients used do not lend themselves to routine sterilisation, ingredients that meet the sterility requirements should be used. The container for ophthalmic preparations should be sterilised at the time of filling and closing. They should be sealed and tamper-proof to maintain their sterility.

2) **Antimicrobial Preservatives:** These should be added to multiple-dose containers, unless there are different directions provided in the individual monograph for multiple product withdrawal, the substance contains a radionuclide with a physical half-life of less than 24 hours, the product itself is sufficiently microbicidal, or the added ingredients meet the requirements of antimicrobial agent content. Thus, acceptance criteria for the content of antimicrobial preservative in multiple-unit products should be established.

3) **Uniformity of Dosage Units:** This test should be performed for single-dose containers to evaluate the mass of the dosage form as well as the content of the drug substance(s) in the dosage form. The test is performed by either content uniformity or weight variation.

4) **Uniformity in Containers:** Semisolid drug products undergo physical separation during manufacturing and/or during the storage period. To ensure the drug product integrity, the uniformity of the finished product at the time of batch release and throughout its shelf-life should be evaluated.

5) **Leachables and Extractables:** The packaging system and the preparation should not undergo any physical or chemical interaction to alter the strength, quality, or purity of the drug product. The packaging system should meet the requirements in elastomeric closures for injection, and glass or plastic containers.

6) **Container Closure Integrity:** The packaging system should be closed or sealed to prevent contamination or loss of contents. It should also be tamper-proof. Validation of container integrity should demonstrate no penetration of microbial, chemical or physical contaminants.

7) **Viscosity:** The residence time of the product in eyes increases with increase in viscosity; but, the diffusion of drug from the formulation into the eye is inhibited. The ophthalmic ointments have a very high viscosity to prolong their residence time in the eyes.

8) **Antioxidant Content:** The content of antioxidants (if added in the drug product) should be established unless oxidative degradation can be detected by another test method such as impurity testing. Acceptance criteria for antioxidant content should also be established based on the levels of antioxidant required to keep the product stable throughout its shelf-life.

9) **Resuspendibility/Redispersibility:** A good physical stability of a suspension should be established. If the particles settle down and form a cake at the container bottom, they should get redispersed when shaken at the time of use to achieve dosage uniformity.

10) **Particle Size and Particle Size Distribution:** The potential for any changes in the particle size of ophthalmic suspensions and emulsions should be evaluated through stability testing. The drop size for ophthalmic drops ranges from 20-70μL. However, the drop size should be controlled and maintained throughout the product shelf-life. Suitable substances should be added to the ophthalmic products to increase their stability, provided they do not cause any harm in the amounts administered and do not interfere with the therapeutic efficacy or responses to the specified assays and tests.

8.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) **Ophthalmic** or **eye preparations** are sterile liquid, semi-solid, or solid preparations containing one or more active pharmaceutical ingredient and meant to be applied on the conjunctiva, conjunctival sac, or eyelids.
2) **Ophthalmic solutions** should not have any undissolved ingredients and foreign particles.
3) The pH of ophthalmic preparations should be equal to the pH of tear fluid, i.e., 7.4; however, this requirement can be attained rarely.
4) **Tonicity** is the osmotic pressure exerted by the salts in aqueous solution.
5) **Eye lotions** are undiluted aqueous solutions used for first aid purposes.
6) The containers of **eye drops** should provide protection against microbial contamination, moisture, and air.
7) **Eye ointments** should be packed in collapsible metal (aluminium) or plastic (polyvinyl chloride) tubes or in single-dose containers.
8) **Eye lotions** are dispensed in coloured fluted bottles closed with a metal or plastic screw cap.
9) **Single-Dose Containers** consist of an injection-moulded polypropylene container which is sealed at its base and has a nozzle sealed with a screw cap.
10) **Additives** are used as inactive ingredients in most of the ophthalmic dosage forms.

8.3. EXERCISE

8.3.1. True or False

1) Ophthalmic or eye preparations are non-sterile liquid, semi-solid, or solid preparations.
2) Tonicity is the osmotic pressure exerted by the salts in aqueous solution.
3) Eye ointments are packed in non-collapsible metal (aluminium) or plastic (polyvinyl chloride) tubes.
4) Eye lotions are undiluted aqueous solutions used for first aid purposes.
5) Eye lotions are dispensed in coloured fluted bottles closed with a metal or plastic screw cap.

8.3.2. Fill in the Blanks

6) _______ is the osmotic pressure exerted by the salts in aqueous solution.
7) __________ are undiluted aqueous solutions used for first aid purposes.
8) __________are packed in non-collapsible metal (aluminium) or plastic (polyvinyl chloride) tubes.
9) _______ are used as inactive ingredients in most of the ophthalmic dosage forms.
10) The pH of ophthalmic preparations should be equal to the pH of tear fluid, i.e., ______.

Answers

1) False
2) True
3) False
4) True
5) True
6) Tonicity
7) Eye lotions
8) Eye ointments
9) Additives
10) 7.4

8.3.3. Very Short Answer Type Questions

1) Write a short note on ophthalmic preparations.
2) Give the advantages and disadvantages of ophthalmic preparations.
3) Give the formulation of eye lotions.
4) Discuss the formulation of eye ointments.
5) Give the labelling requirements for ophthalmic preparations.

8.3.4. Short Answer Type Questions

1) Discuss the formulation of eye drops.
2) Discuss formulation of eye ointments and eye lotions.
3) Give the method of preparation for eye drops.
4) Write a note on containers used for ophthalmic preparations.

8.3.5. Long Answer Type Questions

1) Give the formulation considerations for ophthalmic preparations.
2) Discuss evaluation of ophthalmic preparations.
3) What are the labelling requirements for ophthalmic preparations? Also discuss the containers used for their storage.

CHAPTER
9

Cosmetics

9.1. COSMETICS

9.1.1. Introduction

The word **cosmetic** has been derived from a Greek word which means **to adorn**. Cosmetic is a substance that comes in contact with various parts of human body like skin , hair, nail, lips, teeth, etc.

It helps in improving or changing the external appearance of the human body, masks the body odour, and protects the skin and keeps it in good condition. In other words, cosmetic is an external preparation applied on the external body parts. A cosmetic product can also be applied on the mucous membrane of oral cavity or teeth to clean or perfume them.

Cosmetic can also be defined as a substance that is applied on the human body by rubbing, sprinkling or any other similar method with the aim to promote attractiveness, clean, beautify, and alter the external appearance. The mild cosmetics act to keep the skin and hair healthy.

9.1.2. Lipsticks

Lipsticks are colouring matter dispersed in a base containing a suitable blend of oils, fats, waxes, perfumes, and flavours, and moulded in the form of sticks to impart an attractive colour and shine to the lips. Lipsticks on application provide a moist appearance to the lips, thus highlighting them and concealing their defects.

An **ideal lipstick** should have the following **properties**:

1) It should cover the lips effectively, impart shine, and last for long.
2) It should make the lips soft.
3) It should adhere to the lips and should not be brittle and tacky.
4) It should be indelible.
5) It should retain the colour intensity without changing its shade.
6) It should be free of gritty particles.
7) It should be non-drying.
8) It should not cause irritation to the lips.
9) It should have a desirable degree of plasticity.
10) It should have an acceptable odour and flavour.

9.1.2.1. Formulation

The lipstick base is prepared by mixing varying proportions of oils and waxes to obtain a desirable viscosity and melting point. The ingredients used in the formulation of lipsticks are enlisted in **table 9.1**:

Table 9.1: Ingredients used in the Formulation of Lipsticks

Ingredients	Examples
1) Solid components/waxes i) Hydrocarbon waxes ii) Mineral waxes iii) Hard waxes iv) Microcrystalline waxes	 White bees wax. Ozokerite wax and ceresin wax. Carnauba wax, candelilla wax, and hard paraffin.
2) Liquid components	Mineral oils, vegetable oils, castor oils, butylstearate, glycol, water, silicon-fluids, and isopropyl maleate.
3) Softening components	Anhydrous lanolin, lanolin cocoa butter, lecithin, and petrolatum.
4) Colouring agents	Carmine, dyestuff stain, pigmented stain, lakes, etc.
5) Pearlescent pigments	Guanine crystals and bismuth oxychloride
6) Opacifying agents	Titanium dioxide
7) Perfumeries	Rose oil, cinnamon oil, lavender oil, etc.
8) Miscellaneous agents i) Preservatives	 Parabens
ii) Antioxidants	BHA, BHT, tocopherol, etc.
iii) Flavouring agents	Cinnamon oil, spearmint oil, etc.

The following raw materials are used in the formulation of lipsticks:

1) **Solid Components:** These components solidify the liquid matrix to make up the final structure of the product. The solid components used in manufacturing lipsticks include natural waxes. **Types** of solid waxes are:
    i) **Hydrocarbon Waxes:** A popular **example** is white bees wax obtained naturally from the honey combs of honey bee, *Apis mellifera*. It forms the oil base in the formulation of lipsticks.

    Advantages
    a) It is compatible with waxes obtained from vegetables, minerals, and animals.
    b) It can be moulded into the desired form.

    Disadvantage: When used in more than 20% concentration, it forms a dull film on the lips. To avoid this, it is mixed with ozokerite wax, carnauba wax, or candelilla wax.

    ii) **Mineral Waxes:** These are not popularly used and have been replaced with the microcrystalline waxes. Some **examples** of mineral waxes are:
    a) **Ozokerite Wax:** It is an amorphous hydrocarbon obtained naturally from bituminous products.

    Advantage: It is available in various grades.

    Disadvantage: It may undergo adulteration.

    b) **Ceresine Wax:** It is also obtained naturally from the bituminous products.

    iii) **Hard Waxes:** These impart the desired shape and hardness to the lipsticks. They include the following waxes:
    a) **Candelilla Wax:** It is obtained from *Euphorbia cerifera* and *Euphorbia antisyphilitica* plants of Euphorbiaceae family. It is extracted out by plunging the plant in boiling water containing sulphuric acid and then skimming off the wax that rises to the surface.

    b) **Carnauba Wax:** It is obtained as exudates from the pores of the leaves of *Copernicia prunifera* (Brazilian wax palm tree). It is extracted out by cutting, drying, and heating the leaves.

       Disadvantage: It has a high melting point, thus is not miscible with other waxes and remains as a separate solid phase.

    c) **Hard Paraffin:** It is present as a purified blend of some solid hydrocarbon bases obtained from petroleum.

       Disadvantage: It is limitedly soluble in castor oil, thus does not dissolve and provide a greasy appearance.

  iv) **Microcrystalline Waxes:** These hydrocarbons contain a long carbon chain.

      Disadvantage: They exhibit a low solubility in castor oil.

2) **Liquid Components:** The commonly used liquid components are:
   i) **Mineral Oils:** They are a blend of hydrocarbons obtained from petroleum. They are available as light or heavy mineral oils. They impart gloss to the product. They are used in less than 5% concentrations and are not rancid.

   ii) **Vegetable Oils:** Sesame oil and olive oil are the commonly used vegetable oils. They provide low solubility towards staining dyes and hence are less in use.

   iii) **Castor Oil:** It is obtained from the seeds of the castor plant, *Ricinus communis*. It is the most valuable lipstick base, and is used in 40-50% concentration. It has a high viscosity and a good dissolving power. It is stable towards oxidation, and compatible with other ingredients.

   iv) **Butyl Stearates:** They possess less solubility, still are used for dispersing the colouring matter. They wet the colouring pigments readily. They do not have any odour and are non-rancid.

   v) **Propylene Glycol:** It is non-toxic and sweet in taste. It has a good wetting property towards high colouring stains. It is used along with other monoesters of propylene glycol.

   vi) **Water:** It is not used as a solvent, but is used in minor quantities to dissolve the colouring matter.

   vii) **Silicone Fluid:** It is used in minor quantities to aid in mould release and to prevent the rub-out of the wax.

   viii) **Isopropyl Maleate (IPM):** It acts as a co-solvent and is used in 2.3% concentration with mineral oil to impart shine.

3) **Softening Agents:** These agents increase the spreadability of lipsticks by softening them. The commonly used softening agents are:
   i) **Anhydrous Lanolin or Wool Fat or Wool Wax:** It is used in 0.25% concentration to impart shine, softness, emolliency, and protection to the lips.

   ii) **Lanolin or Hydrous Wool Fat:** It is used in minor quantities to improve the covering properties of film. It contains 25-30% of water and result in sticky and greasy products. It helps in dispersing the coloured pigments.

   iii) **Lanolin Derivatives:** Ethers, esters, and lanolin oils are some commonly used derivatives. They are non-drying and provide a non-greasy appearance to the film. They are also used as blending agents or plasticisers.

   iv) **Cocoa Butter:** It has a good emollient property and was used earlier. It imparts an oily look on the lips and thus makes them appear glossy. However, at the current time, it is no more in use due to rancidity and surface crystallisation.

   v) **Petrolatum:** It is an odourless and tasteless hydrocarbon obtained from petroleum. It is used to enhance the shine.

   vi) **Lecithin:** It is smooth and has an emollient property. It is used in minor quantities to increase the ease of application.

4) **Colouring Agents:** Colour is imparted to the lips by staining them with a dye stuff colour or by covering them with colouring layers. The colours commonly used in the formulation of lipsticks are:
   i) **Soluble Colours:** These are dye stuff agents that are easily soluble in oil, water, and alcohol.

   ii) **Insoluble Colours:** These are insoluble organic or inorganic pigments.

   The commonly used colouring agents are:
   i) **Carmine:** It is obtained from the cochineal insects by extracting them with ammonia. The carminic acid obtained is precipitated with alum and dried for use. However, carmine was used earlier.

   ii) **Dye Stuff Stains:** These stains provide a long lasting effect on the lips by retaining the colour on the lip cells. They are:
      a) **Eosin Dye:** It imparts orange red colour to the lips.

      b) **Acid Eosin Dye:** It is orange in colour and changes to intense red colour at acidic pH of 4. But it may produce toxic effects like allergic reactions or cheilitis (inflammation of lips) and thus used along with bromo acids.

   iii) **Pigmented Stains:** These organic or inorganic stains form dispersion in the solvent base. They are used along with metallic lakes to improve the colour intensity.

   iv) **Lakes:** These are potential pigments that adsorb on aluminium hydroxides, barium oxides, calcium oxides, etc. They are used in 8-10% concentrations. Aluminium, barium, calcium or strontium lakes are some common examples.

5) **Pearlescent Pigments:** These pigments impart nacreous or a pearl-like appearance to the product. Guanine crystals obtained from fish scales are the natural pearlescent pigments. Bismuth oxychloride in 70% castor oil is also an **example** that provides a lustrous look.

6) **Opacifying Agents:** These agents are used for opacifying or whitening of lipsticks. They can also change the pigment shade by varying the proportions. Titanium dioxide is a common **example** of opacifying agent.

7) **Preservatives:** These are added to increase the life period of the lipsticks by reducing microbial growth. The common **examples** are methyl paraben and propyl paraben. They are anhydrous and should not be used in more than 0.1% concentration.

8) **Antioxidants:** These are added to prevent product degradation from oxidation, since some of the ingredients added in the formulation may be susceptible to oxidation. The **examples** of commonly used antioxidants are Butylated Hydroxyl Anisole (BHM), Butylated Hydroxyl Toluene (BHT), tocopherol, propyl gallate, butylated hydroxyl quinines, etc.

9) **Perfumeries:** Light floral fragrances, **e.g.,** rose oil, cinnamon oil, lavender oil, etc. are used in lipsticks. The fruity flavours that mask the fatty odour of the oily waxes can also be used. The perfumeries used in lipsticks should be tasteless, non-irritating, and compatible.

10) **Flavouring Agents:** These agents, **e.g.,** spearmint oil, cinnamon oil, etc. are added to impart a good flavour to the lipsticks. Sodium saccharin and ammonium glycyrrhizate can also be added along with them to improve the taste.

9.1.2.2. Preparation

Lipsticks can be manufactured by following the **three steps**:

1) Melting and mixing of ingredients,
2) Pouring the ingredient mixture in tube, and
3) Packaging and dispatching the product for sale.

The ingredients of lipstick are mixed and stored to be used later. It is not necessary to mix the ingredients while pouring:

1) **Melting and Mixing:** First the ingredients are separately melted and then mixed due to the variation in its ingredients. One portion comprises of solvents, the second comprises of oils, and the third comprises of lipid materials like fats and waxes. These portions are heated in either stainless steel or ceramic containers.

   Solution of solvent and liquid oils is mixed with colour pigments. The oil and pigment mixture is subjected to roller mill to remove gritty particles. Milling introduces air into the mixture, which is removed by constant stirring for a few hours or by applying vacuum. The pigment mass obtained is mixed with hot wax till the required shade and consistency is achieved, and the mixture is agitated to bubble out any trapped air. This mixture is poured into the moulds, cooled, demoulded, visually inspected, and sent for packaging or are stored for later use.

   In case of immediate use of fluid lipstick, the mixture is maintained in its molten state and agitated to remove air. A previously stored mixture should be re-heated to check its colour and consistency (easily pourable), and should be adjusted as per the standards if not found to be satisfied. Lipsticks should be prepared in batches to avoid colour variation in the final products.

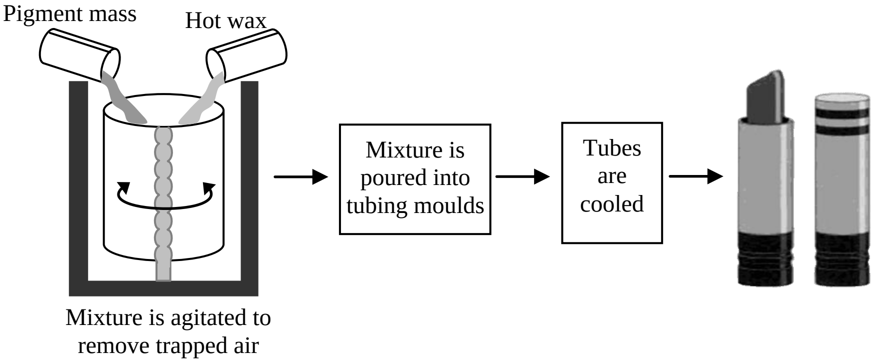


Figure 9.1: Melting and Mixing

2) **Moulding:** After removing air from the mixture, it is poured in tubes using many available machines. In case of large scale production, the mixture is kept in molten state throughout the process by using a melter; while in case of small scale production, the mixture is maintained at appropriate temperature and agitated manually.

The molten mixture is poured into the moulds, the bottom portion of which is made up of metal or a plastic tube and the shaping part fits exactly on the tube. At the time of moulding, the mixture should be poured in an inverted manner to get a proper shape. Any excess of mass is scrapped off. The moulds are kept in refrigeration unit to cool the lipstick mass. Then they are demoulded, sealed from the bottom, and passed through a flaming unit (or manually flamed) to seal the pinholes. A final touch is given by removing any lines, air holes, or blemishes; however, this should not be done as air removal in the later stages becomes difficult. Thus, it is recommended to correct the defects manually with the help of a spatula.

9.1.3. Shampoos

Shampoos are viscous preparations containing synthetic detergent used for washing hair. They aim to clean the scalp by removing sebum and foreign substances, and to make the hair shiny. In the previous times, hair were washed using detergent soaps; however, now shampoos are used. Detergent and other ingredients of shampoo should be non-toxic. Shampoos are used for cleaning as well as for medicinal purpose (for which medicated shampoos are available).

An **ideal shampoo** should have the following **properties**:

1) It should be of optimum viscosity so that it can be easily applied.
2) It should be easy to spread.
3) It should produce sufficient lather with both hot and cold water.
4) It should remove waste materials such as debris, soil, sebum, dead cells, salts (due to sweat), etc., from the scalp.
5) It should not form any film on scalp.
6) It should not produce irritation or itching to the scalp.
7) It should not support any microbial growth.
8) It should be rinsed out completely when washed.
9) It should facilitate combing after shampooing.
10) It should not make the hair rough after drying.
11) It should make the hair shiny.
12) It should impart a good odour to the hair.
13) It should have a half-life of about 2-3 years.
14) It should be economical.

9.1.3.1. Formulation

The ingredients used in the formulation of shampoos are enlisted in **table 9.2**:

Table 9.2: Ingredients used in the Formulation of Shampoos

Ingredients	Examples
1) Surfactants	
i) Anionic surfactants	Alkyl sulphates and alkyl ether sulphate
ii) Non-ionic surfactants	Alkanolamides
iii) Cationic surfactants	Alkyl amines and alkyl imidazolines
iv) Amphoteric surfactant	Acyl amino acids
2) Foam booster	Monoethanolamides, lauramides DEA, and cocamide DEA.
3) Germicide and anti-dandruff agent	Benzalkonium chloride, cetrimide, selenium sulphide, and cadmium sulphide.
4) Conditioning agent	Lanolin, egg, and amino acids.

5) Pearlescent agent	4-methyl-7-diethylamino coumarin and 4-methyl-5-7-dihydrocoumarin.
6) Sequestrants	EDTA, citric acid, and tripolyphosphate.
7) Thickeners	Alginates, polyvinyl alcohol, and methyl cellulose.
8) Perfuming agent	Herbal fruits and floral fragrance.
9) Preservatives	*p*-Hydroxyl benzoic acid and phenyl mercuric nitrate.
10) Colour	FD and C dye.

The following raw materials are used in the formulation of shampoos:

1) **Surfactants:** These agents are used to produce foam and clean the scalp. They are of **four types**:
   i) **Anionic Surfactants:** These have a good foaming property, hence are the principal surfactant and the main ingredient of shampoos.

   ii) **Non-Ionic Surfactant:** These are the secondary surfactants. They are not used to produce foam because they have less foaming power; however, they are used as viscosity inducers, emulsion stabilisers, and opacifiers.

   iii) **Cationic Surfactants:** These contain a positive charge. They are considered as both principle and secondary surfactants as they have a good foaming and cleaning properties but are also toxic to eyes (thus, used in low concentrations).

   iv) **Amphoteric Surfactants:** These possess both cationic and anionic charges with respect to the acidic and basic media. When the media pH is neutral, they form Zwitter ions. They are used as secondary surfactants as they produce mild actions, are compatible with other surfactants, and exhibit excellent hair conditioning property.

2) **Foam Boosters:** These agents, **e.g.,** fatty acid alkanolamides and amine oxides, are used to stabilise or strengthen the foam produced by the surfactants. They make the foam dense so that they remain for a long duration. They are added in 2-5% concentration. Fatty acids and fatty alcohols in 0.25-0.50% concentrations can also be used as foam boosters.

3) **Germicide and Anti-Dandruff Agents:** These agents prevent the microbial growth on the scalp and removes dandruff.

4) **Conditioning Agents:** These agents, **e.g.,** lanolin, oils, herbal extracts, egg, amino acids, etc., improve the hair condition. They reduce the electric charges on the hair, thus making them shiny and easily manageable. They also exhibit a bactericidal effect. Amino acids are most commonly used as they provide an efficient conditioning effect.

5) **Pearlescent Agents:** These agents, **e.g.,** alkanolamides and coumarins like 4-methyl-7-diethyl amino coumarin, 4-methyl-5, 7-dihydrocoumarin, etc., are added as adjuvants to the conditioning agents as they improve the conditioning property and also impart brightness to hair. They are also called as opacifying agents as they make the preparation transparent or opaque. Alcohols and phosphates may also be used as they improve transparent solubilisation.

6) **Sequestrants:** Surfactants form complexes with the metals present in water, i.e., calcium and magnesium. These agents, **e.g.,** EDTA, citric acid, etc., prevent the complex formation between metal and surfactant and themselves form complexes with the metal ions. This prevents the formation of film on the scalp, i.e., the film formed by surfactant and metal ions.

7) **Thickening Agents:** These agents, **e.g.,** methyl cellulose, alginates polyvinyl alcohol, polyethylene glycol, etc., make the preparation viscous to facilitate ease of handling and prevent wastage during application.

8) **Perfumes:** These agents are obtained from natural sources such as flowers, fruits, herbs, etc. They mask the undesirable odour of other ingredients and impart a good fragrance to the shampoo. The selected perfumes should retain a good odour for a fixed time period even after shampooing. They should not affect the solubility and stability of the product.

9) **Preservatives:** These agents, **e.g.,** *p*-hydroxybenzoic acid and phenyl mercuric acetate, prevent microbial growth and maintain the product stability for a desired time period. Since shampoo is a wet preparation, it provides a media for various microorganisms and should be added with appropriate preservatives.

10) **Colours:** These agents impart a pleasant appearance to the shampoos. They should be water-soluble and should not impart any colour to hair or scalp.

9.1.3.2. Preparation

Originally, a single method was available for the preparation of shampoos. Later this basic method was modified to obtain different types of shampoos like cream, gel, aerosol, etc.

General Methods for Preparation of Different Types of Shampoos

1) **Liquid Shampoo:** It is prepared as follows:
   i) The detergent to be used is converted to its solution form and half of this solution is taken in a container.
   ii) Alkanolamide (a secondary surfactant) is dissolved by stirring or sometimes by gently heating the detergent solution.
   iii) A suitable amount of perfuming agent is dissolved in the remaining half of the detergent solution.
   iv) The perfume solution so obtained is added to the alkanolamide solution [prepared in step (ii)].
   v) Colour and preservatives are first dissolved in a sufficient volume of water and then added to the obtained solution.
   vi) The entire solution is mixed well by gentle stirring as excessive stirring form bubbles.
   vii) The final volume of the preparation is made by adding clear sterile waste to obtain a clear liquid shampoo.
   viii) If the preparation contains lauryl alcohol ether sulphate, the viscosity of shampoo should be adjusted with an electrolyte solution. Generally, sodium chloride solution is added with constant stirring.

2) **Cream Shampoo:** The cream shampoo having glycol stearate is prepared by following the same steps as discussed above. However, **cream shampoo containing wax** is prepared as follows:
   i) A detergent solution and water are heated at 80°C temperature.
   ii) Wax is heated in a separate container at the same temperature to melt it.
   iii) Both the solutions maintained at 80°C temperature are mixed uniformly by constant and gentle stirring.
   iv) The obtained solution is cooled at 40-45°C temperature.
   v) The other ingredients like colours, perfumes, and preservatives are added with stirring.
   vi) Under warm conditions, the mixture obtained is transferred to a suitable container and packed.

3) **Gel Shampoo:** It is prepared in the same way as liquid shampoo. The obtained shampoo is treated with a thickening or gelling agent (**e.g.,** hydroxy propyl methyl cellulose) to obtain a gel-like consistency. However, formation of gels can also be facilitated by adding anionic and amphoteric surfactants in appropriate amount.

4) **Aerosol Shampoo:** It is prepared in the same way as liquid shampoo. The obtained shampoo is added with a non-reactive propellant, and packed in an aerosol container. The propellant creates a pressure within the container to achieve spraying action and the product (shampoo) is sprayed in the form of foam.

5) **Powder Shampoo:** It is prepared by simple blending. All the ingredients are powdered to a suitable degree of fineness and blended. Two separate solutions of perfume and colour are prepared using alcohol or water as solvents. The obtained solutions are sprayed onto the blended mixture. The wet mixture is dried and packed, or else the ingredients will get internally soaked into the solutions of colour and perfume.

9.1.4. Cold Cream

Cold creams are water-in-oil or oil-in-water type emulsions added with certain fats (generally beeswax) and perfuming agents. These are applied on skin to provide smoothness and remove makeup. Cold creams are named so due to the cooling effect they impart on application.

An **ideal cold cream** should have the following **properties**:

1) It should have a low sensitisation index.
2) It should be elegant in appearance.
3) It should be non-dehydrating.
4) It should provide a smooth texture.
5) It should be non-greasy and non-staining.
6) It should not cause irritation to the skin.
7) It should not alter the membrane or skin functioning.
8) It should be miscible with skin secretion.

9.1.4.1. Formulation

The ingredients used in the formulation of a cold cream are enlisted in **table 9.3**:

Table 9.3: Ingredients used in a Formulation of Cold Cream

Formula	Quantity for 100gm
White beeswax (emollient)	20gm
Mineral oil (lubricant)	50gm
Distilled water (vehicle)	28.8gm
Borax (buffer)	0.7gm
Perfume (odour)	0.5gm

9.1.4.2. Preparation

The cold creams are prepared by the following steps:

1) Beeswax is melted in a container on a water bath maintained at 70°C temperature and added with mineral oil; this is mixture A (oily phase).
2) Water is heated in another container at the same temperature and added with borax; this is mixture B (aqueous phase).
3) Mixture B is slowly added to the mixture A with stirring to form a creamy emulsion.
4) In the last step, the preparation is brought down to 40°C temperature and added with a suitable perfume.

9.1.5. Vanishing Cream

Vanishing creams are also known as **day creams** as they are applied in the day times. These creams provide emollient and protective action to the skin against environmental conditions by forming a neither greasy nor oily semi-occlusive residual film. Vanishing creams are oil-in-water type emulsions. They are named so as they spread as thin oil-less film when applied on the skin and this film is not visible to the naked eye. They are used to hold powder on the skin and to improve adhesion.

Properties

1) It should have a high melting point.
2) It should be pure white in colour.
3) It should possess a very slight odour.
4) It should have a less amount of iodine.

9.1.5.1. Formulation

The ingredients used in the formulation of vanishing creams are enlisted in **table 9.4**:

Table 9.4: Ingredients used in the Formulation of Vanishing Creams

Ingredients	Uses
1) **Main Ingredient** **Example:** Stearic acid	It controls the cream consistency and imparts pearlescent property by forming crystals.
2) **Humectants** **Example:** Glycerine, sorbitol, and propylene glycol.	
3) **Alkalis** **Examples:** i) Potassium hydroxide	It imparts fine texture and consistency without providing harshness.
ii) Sodium hydroxide	It is used with potassium hydroxide, since if used alone it makes the cream hard.
iii) Carbonates, i.e., potassium and sodium carbonate	They are used because they liberate carbon dioxide and make the creams spongy.
iv) Ammonia	It is effective, but difficult to handle. Because of its odour and volatility, it is also to make cream yellow in colour with age.
v) Borax	It is used with potassium hydroxide to produce a white emulsion.
4) **Emulsifying Agent** **Example:** Triethanolamine soap, amino glycol soap or glyceryl monostearate.	
5) **Purified Water (i.e., Distilled and Deionised)**	It provides stability to the cream. If hard water is used, it forms soap of lime and magnesium, which causes inversion of emulsion and hence reduces stability.
6) **Preservatives** **Example:** Methyl paraben and propyl paraben	They prevent deterioration caused by bacteria or fungi.
7) **Perfume**, i.e., perfume solvent or perfume dissolved in alcohol. They should be added when the cream attains 40°C temperature. **Example:** Geranium, sandal wood, lavender oil, terpineol, etc.	It provides odour to the cream and also has aesthetic value.

9.1.5.2. Preparation

The methods of preparation of different formulations of vanishing creams are given below:

Formula 1:

Formula	%
Stearic acid	24.0
Potassium hydroxide	1.0
Water	64.0
Glycerine	10.5
Perfume	0.5
	100.0

Method: Stearic acid is melted by heating on a water bath. Potassium hydroxide is dissolved in water, glycerine is added, and the mixture is heated at 75°C temperature. This heated mixture is slowly added to the melted stearic acid with constant stirring. The obtained mixture is maintained at 40°C temperature and added with a suitable perfume.

Formula 2:

Formula	%
Stearic acid	17.0
Sodium carbonate	0.5
Potassium hydroxide	0.5
Glycerine	6.0
Water	71.0
Alcohol	4.5
Perfume	0.5
	100.00

Method: Stearic acid is melted . A solution of alkalis is prepared in water and added with glycerine. This solution is added to the melted stearic acid with steady agitation. Stirring is continued till the temperature of mixture drops down to 40°C. A suitable perfume is dissolved in alcohol and added to the final solution. This batch is left undisturbed for a day before filling.

Formula 3:

Formula	%
Triethanolamine	2.0
Stearic acid	17.0
Lanolin	1.0
Borax	4.0
Glycerine	5.0
Water	70.5
Perfume	0.5
	100.00

Method: Lanolin and stearic acid are melted. A hot solution of borax, triethanolamine, glycerine, and water is prepared. The alkali solution is added to stearic acid and stirred to emulsify. When the temperature drops down to 40°C, a suitable perfume is added.

9.1.6. Toothpastes

Toothpastes are used for removing stains from the teeth and to impart freshness to the mouth and breath. These purposes are solved as the toothpastes are added with mild abrasives and some flavours. They are the most popular form of dentifrices.

9.1.6.1. Formulation

The ingredients used in the formulation of toothpastes are enlisted in **table 9.5**:

Table 9.5: Ingredients used in the Formulation of Toothpastes

Ingredients	Examples
Agents responsible for cleansing action: 1) Polishing agents/abrasive agents	i) Precipitated calcium carbonate. ii) Phosphates of calcium. iii) Dental graded silica/polymers of silica $(SiO_2)n$. iv) Trihydrated alumina.
2) Foaming agents/surfactants	i) Sodium lauryl sulphate $(ROSO_3Na)$. ii) Sodium lauryl sarcosinate.
Agents responsible for the formation of toothpastes: 1) Humectants	i) Sorbitol 70 ii) Glycerine iii) Propylene glycol
2) Ceiling agents/binding agents	i) Sodium Carboxy Methyl Cellulose (SCMC). ii) Cellulose ethers.
Agents responsible for improving palatability 1) Sweetening agents 2) Flavouring agents	i) Sodium saccharin ii) Chloroform iii) Cinnamon bark iv) Spearmint oil
Miscellaneous agents 1) Colouring agents 2) Whitening agents 3) Preservatives 4) Therapeutic agents	

The following raw materials are used in the formulation of toothpastes:

1) **Polishing or Abrasive Agents:** These agents polish the teeth and remove food debris from their surface. They are used in 20-50% concentration of the total formulation.

   Some common **examples** of abrasive agents are:

   i) **Precipitated Calcium Carbonate ($CaCO_3$) or Precipitated Chalk:** It is available in a number of grades. Its crystalline form is available as:
      a) **Calcite:** It contains rhombohedral crystals.
      b) **Aragonite:** It contains orthorhombic crystals.

   ii) **Phosphates of Calcium:** Various insoluble calcium phosphates are available:
      a) **Dicalcium Phosphate (DCP) Dihydrate ($CaHPO_4.2H_2O$):** It is a commonly used abrasive agent among the phosphates of calcium.
      b) **Dental Grade Silica/Polymer of Silica $(SiO_2)_n$:** It is a silica polymer commonly used as abrasive agent in large quantities in toothpaste gels.

2) **Foaming or Wetting Agents or Surfactants:** They serve the purpose of cleansing by reducing the surface tension at the interface of the adhered material and teeth enamel. They facilitate the abrasive action by wetting the teeth surface. They easily diffuse into the narrow spaces, and enhance the cleansing action.

   An **ideal surfactant** should have the following **properties**:
   i) It should be compatible with other ingredients.
   ii) It should have a good surface active property.
   iii) It should be non-toxic and non-irritant to the oral mucosa.
   iv) It should impart no taste to the formulation.

   Some common **examples** of surfactants are:
   i) **Sodium Lauryl Sulphate ($ROSO_3Na$):** It is used in 0.5 -2% concentrations to provide the required foaming action.
   ii) **Sodium Lauryl Sarcosinate:** It is the most preferred surfactant for oral products.

3) **Humectants:** These agents prevent rapid drying of the product by preventing excessive moisture loss. They also impart plasticity to the product. They are used in 20-40% concentration in the formulation.

   Some common **examples** of humectants are:
   i) **Sorbitol 70:** It is used in 70% w/v concentration of the sorbitol solution.
   ii) **Glycerine:** It is used in 5-10% concentration.
   iii) **Propylene Glycol:** It is rarely in use as it has been replaced with sorbitol.

4) **Ceiling or Binding Agents:** These agents, **e.g.,** Carboxy Methyl Cellulose (CMC), Sodium CMC, hydroxyethyl cellulose, cellulose ethers, etc., hold the solid and the liquid components together to form a smooth paste and to retain this property during storage. They prevent bleeding from the paste and also add up to the body and viscosity of the product.

5) **Sweetening Agents:** These agents, **e.g.,** saccharin sodium, chloroform, aspartame, cyclamates and potassium acesulfame, improve the sweetening properties and mask the bitter taste of other ingredients like surfactants, binders, etc. They promote the acceptance of the product on oral administration.

6) **Flavouring Agents:** These agents are a mixture of edible volatile oils having spearmint and peppermint oil as major components. Some other components like thymol, anethole, eucalyptol, aniseed oil, oil of winter green, etc. may also be added. Flavouring agents are used in 0.5 -1.5% concentration and constitute the most costly part of the formulation.

7) **Colouring Agents:** These agents are used in less than 0.01% concentration as permitted by the EEC Cosmetics Directive. They can be used in combination with a portion of a white creamy base. They influence the consumer preferences and increase the purchase intent.

8) **Whitening Agents:** These agents, **e.g.,** titanium dioxide (TiO_2) should be added to provide additional whiteness and brilliance to the product.

9) **Preservatives:** These agents maintain the properties of the product during their storage and improve the shelf-life. A mixture of methyl paraben (5%) and propyl paraben (0.02%) is most effectively and commonly used. Sodium benzoate is not used due to its incompatibility with other therapeutic agents of the product.

10) **Therapeutic Agents:** These agents provide additional beneficial effects apart from normal cleansing properties.

    Examples:
    - i) **Anticaries Agents:** Fluoride derivatives like NaF, Na_2FPO_3, etc.
    - ii) **Antiplaque Agents:** Chlorhexidine, Triclosan, etc.
    - iii) **Antitartar Agents that prevent the Colouring of Teeth:** Zn salts, Pyrophosphate ions, Tetra sodium pyrophosphate, and Disodium dihydrophosphate.
    - iv) **Sensitive Dentine Agents:** Strontium chloride, Strontium acetate, Formaldehyde, etc.
    - v) **Optical Brightness:** Substituted coumarins in long chain alkyl amines.
    - vi) **Bleaching Agents:** Hydrogen peroxide and Sodium peroxide.
    - vii) **pH Regulators:** Zirconium silicate.

9.1.6.2. Preparation

Toothpastes can be prepared by any of the following two methods:

1) **Dry Gum Method:** The steps involved are:
    - i) Apart from the surfactants, the remaining solid components, like abrasive agent, binding agent, etc., are mixed together in a dry mixer (an agitation mixer with slow rotating blades).
    - ii) The liquid components, like humectants and water are added to the dry mixture obtained.
    - iii) All these ingredients are mixed till a smooth paste is obtained.
    - iv) Finally, the surfactants and flavouring agents are added to the homogenous paste under vacuum.
2) **Wet Gum Method:** The steps involved are:
    - i) The liquid components are mixed together to form a liquid phase.
    - ii) The binding agent is added to the liquid phase obtained with uniform stirring to form a mucilage.
    - iii) Thereafter, the solid ingredients except the surfactants are uniformly mixed with the mucilage in an agitation mixer to form a homogenous paste.
    - iv) Finally, the surfactants, flavouring agents, and colouring agents are added to the homogenous paste under vacuum.

Based on the principle involved in the above two methods, the following techniques have been proposed for manufacturing toothpastes:

1) **Cold Compression Technique:** The steps involved in the preparation of toothpastes by this technique are:
    - i) The humectant, like sorbitol (70% w/v) or glycerine is taken in the mixer bowl.
    - ii) The binding agent is sprinkled over the humectant under agitation for uniform dispersion.
    - iii) The liquid components, like water, sweetener, and preservatives are mixed separately to form a separate liquid phase.
    - iv) Therapeutic ingredients (if required) are added to the liquid phase obtained.
    - v) Thereafter, the liquid phase is added to the humectant-binder mixture in the mixer bowl and mixed for 5 minutes to remove air from the thick gelatinous liquid phase.

vi) Vacuum supply is stopped and the abrasive agents are added with constant mixing to dissolve them completely.

vii) Vacuum is reapplied and mixing is continued for half an hour.

viii) Surfactants and the flavouring agents are dispersed separately in 5% humectant.

ix) The obtained mixture is added to the vacuum at the end and mixed for another 5 minutes to obtain an air free smooth paste.

2) **Multiple Liquid Phase Technique:** This technique is used for formulations using combination of CMC and magnesium aluminium silicate. It is also suitable for preparing clear-gel dentifrices. The steps involved in the preparation of toothpastes by this technique are:

   i) Hot water is taken in a mixer bowl and magnesium aluminium silicate is added to it.

   ii) Humectant, flavouring agent, binding agent, and preservative are mixed separately to form a liquid phase.

   iii) This liquid phase is added to the mixer and the final volume is made up with the humectant.

   iv) Vacuum is applied into the bowl to remove air from the liquid mixture.

   v) Thereafter, the vacuum supply is removed and the abrasive agents are added.

   vi) Vacuum is again introduced and the ingredients are mixed for 30 minutes.

   vii) Finally, the surfactants are added with constant mixing for 5 minutes.

3) **Hot Liquid Phase Technique:** The steps involved in the preparation of toothpastes by this technique are:

   i) The abrasive agent, binding agent, and preservative are mixed separately in a dry mixer to obtain a dry powder.

   ii) The humectant, sweetener, and water are mixed separately to obtain a liquid phase.

   iii) This liquid phase is heated and slowly added to dry powder with constant mixing.

   iv) The obtained mass is mixed under vacuum for 30 minutes.

   v) Finally, flavouring agent and surfactant solution is added under vacuum and mixed for 5 minutes to obtain a clear and homogeneous paste.

9.1.7. Hair Dyes - Formulation and Preparation

Hair dyes or colourants are used by both the genders to change the natural hair colour or to mask grey hair. An **ideal hair dye** should have the following **properties**:

1) It should have a stable formulation.
2) It should colour the hair uniformly.
3) It should impart a stable colour to the hair.
4) It should not result in the loss of natural shine of hair.
5) It should not result in the loss of natural moisture of hair.
6) It should not damage the hair shaft.
7) It should be non-irritant, non-toxic, and non-sensitising.
8) The coloured hair should not get affected by air, water, sunlight, sweat, friction, shampoos, lotions, gels, oils, etc.

Hair dyes are classified as follows:

1) Temporary hair colourants.
2) Semi-permanent hair colourants/direct dyes.

3) Oxidative dyeing systems:
    i) Semi-permanent hair colourants, and
    ii) Permanent hair colourants.
4) Gradual hair colourants.
5) Natural dyes.

9.1.7.1. Temporary Hair Colourants

Temporary hair colourants are leave-in preparations, i.e., after their application the hairs are not washed. These colourants get easily removed by washing the hair once with shampoo because they are only absorbed into the cuticles and do not enter the hair cortex.

Temporary hair colourants comprise of dye stuffs, **e.g.,** acid dyes, basic dyes, metalised dyes, and disperse dyes. Chemically, the dye stuffs are azo dyes, anthraquinone dyes, benzoquinone imine dyes, triphenylmethane dyes, phenazanic dyes, and xanthenic dyes.

Temporary hair colourants are available in different formulations, like powders, crayons, liquids, and shampoos. The common ones are discussed below:

1) **Powder Formulations:** These colourants consist of dye stuffs and acids (like citric acid or tartaric acid). They are used in theoretical make up and masquerades. They are available in sachets. For application, the powder is dissolved in 250ml of water and then applied on wet hair after shampooing.

Formula	Quantity for 100gm
Certified colour	5gm
Tartaric acid (buffer)	95gm

2) **Crayon Formulations:** These colourants consist of soap, waxes, dyes, or pigments. They are applied between the applications of permanent hair colourants. They colour the newly growing hair. They are available in many different shades.

Formula	Quantity for 100gm
Stearic acid (anionic surfactant)	15gm
Triethanolamine (surfactant)	7gm
Beeswax (wax)	50gm
Carnauba wax(wax)	13gm
Ozokerite (wax)	7gm
Glyceryl mono stearate (surfactant)	6gm
Tragacanth (gum)	2gm
Colour	q.s.

Method

i) Triethanolamine, glyceryl monostearate, and tragacanth are heated at 70°C temperature.
ii) Stearic acid is added to the obtained mixture and heated at 75°C temperature.
iii) Beeswax and carnauba wax are separately melted at 70-80°C temperature.
iv) The obtained molten waxes are added to and stirred well with the above mixture [obtained in (ii)].
v) Colour is properly mixed with the resultant mixture by stirring.
vi) This mixture is poured into the moulds.

9.1.7.2. Semi-Permanent Hair Colourants/Direct Dyes

Semi-permanent hair colourants on application leave a long lasting colour in comparison to other colour shampoos. They produce a stronger colour. They produce dark colours; however, they do not contain H_2O_2. This offers an advantage that the semi-permanent hair colourants do not bleach but only mask the hair melanin.

The colour obtained on the grey hair is different than that on the black (pigmented) hair, and thus the hair appears highlighted. The colour produced by these colourants is not lost in one wash with shampoo, but loses gradually in 5-8 washes. These colourants may be added with fragrance.

Ingredients

The semi-permanent hair colourants are composed of:

1) Dye,
2) Water,
3) Organic solvent like alcohol or glycol derivatives,
4) Fatty acid and fatty acid amide,
5) Thickener,
6) Surfactant,
7) Perfume, and
8) Aliphatic primary amines as co-solvent and buffer.

Formula	Quantity for 100gm
Quaternary ammonium compound (colour)	10-12g
Anionic surfactant (surfactant)	8-10gm
Acid (buffer)	6-8gm
Alkanolamide (surfactant)	4-6gm
Dye stuff (colour)	1-2gm
Water (solvent)	To make 100gm

Method

1) Alkanolamide and the anionic surfactant are mixed.
2) Dye is dissolved in the obtained mixture.
3) Acid and the quaternary ammonium compound are dissolved in water.
4) This aqueous solution is added to the dye solution [obtained in (2)] with stirring.
5) This dye is investigated for the effects of quaternary ammonium compounds, pH, aldehydes, and alcohols additions.
6) The dye viscosity is adjusted by adding hydrophilic colloids like methylcellulose, natural gum, etc.
7) The colourant viscosity is increased by adding non-ionic thickener in its composition.
8) Amphoteric surfactant is added to the colourant followed by basic dyes.

9.1.7.3. Oxidative Dyeing Systems

Oxidative dyes are also called **para dyes**. They are colourless when applied on the hair, but turn to the particular colour after undergoing chemical reactions (oxidation, coupling, and condensation).

Ingredients

1) **Bases:** These are primary intermediates and aromatic compounds.
2) **Couplers:** These are aromatic compounds, **e.g.,** 2,4-diaminoanisole, resorcinol, *m*-chlororesorcinol, and *m*-phenylenediamine, and are referred to as **modifiers**. They are benzene derivatives that show $-NH_2$ and –OH substitutions at *meta*-position. Their oxidation with hydrogen peroxide is difficult.
3) **Oxidising Agents:** The most common oxidising agent is hydrogen peroxide.

Formulation of Oxidative Dyeing Systems

The following factors are considered during the formulation of oxidative dyes:

1) **Formulation Bases:** These are used as dye vehicles and modifiers. The vehicle facilitates uniform distribution of the colourant mixture on the hair. Some **examples** of vehicles are a mixture of water (48 -79%), ethyl alcohol (20 -50%), and glycerine (0.5-2%) for amino dyes as they have a low aqueous solubility; for an emulsion type product, cream or lotion (instead of a solution) is used. **The emulsion type preparations** are of the following **two types**:
    i) **Foaming Type Creams:** These are emulsified by adding surfactants, like monoethanolamine lauryl sulphate and ethylene glycol monostearate.

Formula	Quantity for 100gm
Monoethanolamine lauryl sulphate (surfactant)	10gm
Ethylene glycol monostearate (surfactant)	1gm
Preservative	q.s
Water (solvent)	To make 100gm

    ii) **Non-Foaming Type Creams:** These are emulsified by adding mineral oils, cetyl alcohol, and non-ionic emulsifiers.

Formula	Quantity for 100gm
Mineral oil (emulsifying agent + emollient)	1.5gm
Cetyl alcohol (emulsifying agent + emollient)	5gm
Non-ionic emulsifier (emulsifying agent)	3-5gm
Preservative	q. s
Water (solvent)	To make 100gm

2) **Dye Components:**
    i) **Oxidation Bases:** Varying concentrations of *p*-phenylenediamine or *p*-toluene diamine are used to obtain different shades of colour.

Percent of Oxidation Base	Shade Obtained
0.3	Light brown
0.45	Medium brown
0.5	Brown
0.9	Black

    iii) **Coupling Agents:** These agents modify the shade and stabilise it.
3) **Alkalis:** Since the oxidative dyes serve well in alkaline medium, an alkali is added in their composition. **Ammonium hydroxide** (in 1-2% concentration) is the preferred one as it leaves no remnants on the hair. However, it has a strong odour due to which it has been replaced with ammonium carbonate, monoethanolamine, guanidine or arginine derivatives, diethanolamine, triethanolamine, alkanolamide, etc.

4) **Oxidising Agents:** Amino dyes when exposed to air turn black; thus, an oxidising agent, **e.g.,** hydrogen peroxide (the preferred one), ferric chloride, potassium permanganate, potassium dichromate, etc., is added to achieve the desired colour. Hydrogen peroxide is used in 5-6% concentration and generates 20 volumes of oxygen. It develops colour on the hair. It is sold in a package containing two containers. One container contains dye and the other contains the developer.

5) **Antioxidants:** While preparing amino dyes, a nitrogen atmosphere is maintained to prevent the darkening of dyes. Also a chemical antioxidant like sodium sulphite can be added in the formulation instead of maintaining a nitrogen atmosphere. The total amount of base and the coupling agent added in the formulation gives the amount of sodium sulphite to be used. If darker shades are desired, sodium sulphite is added in increased amount.

Types

1) **Semi-Permanent Hair Colourants:** These differ in the extent of giving light colour shades to the hair.

2) **Permanent Hair Colourants:** They produce colour that lasts longer than that produced by the semi-permanent colourants. It is the precursor of dye (and not the dye itself) which on application to the hair undergoes chemical changes to form the colour. Permanent hair colourants are available in light colour to dark colour shades. The colour does not fade away, however the growth of hair demands the need to re-dye. This results in stripped appearance of the hair.

Both these classes of oxidative dyeing system comprise of the following constituents:

1) **Alkalising Agents:** These agents, **e.g.,** ammonia and monoethanolamine, are added to increase the formulation pH upto an optimal level, to generate active oxidisers from hydrogen peroxide, and to swell the hair fibres for absorption of dye.

2) **Oxidants:** These are added to generate active species (like *p*-phenylenediamine and benzoquinone monoamine) for coupling. They bleach the hair melanin. Light colour shades are obtained when the grey and pigmented hair are coloured evenly by using semi-permanent colourants.

3) **Dyes:** These impart the desired colour shade to the hair.

4) **Solvents:** These are used to dissolve the water-insoluble constituents of the colourants to obtain a homogenous preparation.

5) **Surfactants:** These reduce the surface tension between the different ingredients to obtain a homogeneous preparation.

9.1.7.4. Gradual Colourant

Gradual colourants colour the hair gradually on several applications. These products contain the solutions of the salt forms of heavy metals, like lead or bismuth. Since gradual colourants include heavy metals, they offer some negative effects on the health. Thus, the use of these colourants has been declined.

9.1.7.5. Natural Dyes

Plant materials are regarded as the beneficial sources for various ailments and other purposes from the ancient times. The parts of following plants are used as natural dyes or colourants:

1) **Henna:** The henna leaves are non-toxic and non-sensitizing. Its active constituent is **lawsone**, which chemically is 2-hydroxy-14-napthoquinone, and imparts colour. Indigo leaves or synthetic indigo is added to henna to change the colour. Pyrogallic

acid and metallic salts (like copper sulphate) are also added. By increasing the level of pyrogallic acid, darker shades can be obtained. The henna leaves are available in powdered form, which is mixed with hot water to form a paste. This paste is directly applied on hair and a warm towel is wrapped around the head to enhance the colouring effect. A reddish colour is imparted to the hair.

Formula	Quantity for 100gm
Powdered henna (colour)	89gm
Pyrogallic acid (colour)	6gm
Copper sulphate (colour)	5gm

2) **Camomile:** The camomile flowers are used to impart colour. It is also available in powdered form, which is mixed with hot water to form a paste. This paste is applied on hair and a warm towel is wrapped around the head to enhance the colouring effect. The colour achieved is due to the **navy blue volatile oil** present in the flowers. Kaolin (2 parts) or fuller's earth (11 parts) is added to camomile powder to form a cohesive composition. Henna can also be mixed with it to modify the colour.

Formula	Quantity for 100gm	
	(1)	(2)
Powdered camomile (colour)	70gm	30gm
Powdered henna (colour)	30gm	70gm

9.1.8. Sun Screens - Formulation and Preparation

Sunscreens are products that absorb or reflect some of the sun's UV rays on the skin (exposed to sunlight), thus they provide protection against sunburns. They are available in the form of lotions, sprays, gels, or creams. They are also added in skin lightening products because light skin is more susceptible to sun damage than darker skin. Many sunscreens on the other hand are added with tanning power to help the skin to darken or tan.

An **ideal sunscreen** should have the following **properties**:
1) It should absorb UV rays over the range of 280-320nm.
2) It should be stable to heat, light, and perspiration.
3) It should be non-toxic and non-irritant.
4) It should not get rapidly absorbed.
5) It should be neutral.
6) It should be readily soluble in suitable vehicles.

Sunscreens contain the following **ingredients**:
1) Organic chemical compounds that absorb UV light.
2) Inorganic particulates, **e.g.,** titanium dioxide, zinc oxide, or a combination of both, that reflect, scatter, and absorb UV light.
3) Organic particulates containing multiple chromophores that absorb light like the organic chemical compounds but reflect and scatter light like inorganic particulates.

Sunscreen preparations are important in the cosmetic field. **Suntan preparations** are of three classes, i.e., **preventive**, **simulatory**, and **therapeutic**. Sunburns can be prevented by shading the exposed body surface and by using chemicals that screen out some fraction of UV rays from the sun. These chemicals are either **salts of quinines** (**e.g.,** quinine hydrochloride, quinine sulphate, quinine bisulphate, and quinine oleate) or substances like **ethyl *p*-amino benzoate** and **isobutyl *p*-amino benzoates**. Some **salicylates**, **e.g.,**

paraphenyl salicylate, triethanolamine salicylate, benzyl salicylate, phenyl salicylate, ethylene glycol monosalicylate, etc., are also effectively used as sunscreen agents. Acetanilide, esculin, ethyl umbelliferone, menthyl anthranilate, benzophenones, kaolin, talc, magnesium oxide, and titanium dioxide are other agents used. The sunscreen products are available as protective powders, sticks, lotions, or creams that shut out the burning rays of the sunlight without stopping the action of the tan producing rays.

Formulation

Some **examples** of common sunscreen preparations, their formulation and method of preparation are given below:

Sunscreen Lotion (SPF 25)

Formula	% W/W
Phase A	
Dimethicone	1.50
Wheatgerm oil	3.00
Octyl palmitate	4.50
Isohexadecane	6.00
Cetyl dimethicone copolyol	2.00
Cyclomethicone [and] aluminium/magnesium hydroxide stearate	10.00
Candelilla wax	1.00
Phase B	
Sodium chloride	0.50
Water, pure	51.30
Phase C	
Titanium dioxide [and] C12-15 alkyl benzoate	20.00

Method: Phase A and B are heated separately at 75°C temperature. Phase C is heated at more than 60°C temperature. The heated phase C is allowed to cool up to 45°C temperature and added to the mixture of phases A and B. Phase D is also heated at the same temperature, cooled upto 25-30°C temperature, and added to the above mixture with continuous stirring to form a homogenous system.

Sunscreen Moisturiser

Formula	%
Part A	
Stearic acid	3.0
Glyceryl stearate	3.0
Isopropyl myristate, isopropyl palmitate (mixture)	10.00
Octyl hydroxyl stearate	6.0
Lauryl lactate	1.8
Mineral oil (light)	6.2
Octyl dimethyl PABA	2.0
Part B	
Distilled water	55.12
Methyl paraben	0.20
Propyl paraben	0.10
Disodium EDTA	0.05
Triethanolamine (99%)	1.03
Part C	
Aloe vera gel	11.00
Soluble collagen	1.0
	100.0

Method: The oily phase A is heated at 70-80°C temperature and stirred well to get a clear and homogeneous mixture. The temperature of this mixture is maintained at 75°C. The aqueous phase B is heated in a separate vessel at 75°C temperature. Both the mixtures are mixed for 10 minutes and cooled up to 45°C temperature. Aloe vera gel is added and mixed well. When the temperature reaches to 40 °C, soluble collagen is mixed well to obtain a homogeneous system.

Sunscreen Cream

Formula	**%**
Quinine bisulphate	2.5
Cholesterin absorption base	25.0
Mineral oil	12.5
Alcohol	10.0
Water	49.5
Perfume	0.5
	100.00

Method: Quinine bisulphate is dissolved in alcohol. The absorption base and the mineral oil are melted together. Water is heated at the same temperature and added to the melted fat with continuous stirring till the temperature drops to 45°C. Thereafter, quinine solution and perfume are added with stirring until a cold and homogenous product is obtained.

Sunscreen Stick

Formula	**%**
C_{10}-C_{30} carboxylic acid sterol ester	42.5
Oleyl alcohol	7.0
C_{18}-C_{36} triglyceride	14.0
C_{18}-C_{36} glycol ester	3.5
Cyclomethicone	2.80
Oleyl dimethyl PABA	5.0
	100.00

Method: Triglyceride and sterol ester are melted together. Oleyl alcohol is added to the melted mixture and the temperature is raised to 75-80°C to obtain a clear mixture. Cyclomethicone is finally added and the resultant mixture is filled in the moulds.

Sunscreen Powder

Formula	**%**
Quinine bisulphate	3.0
Zinc stearate	10.0
Titanium dioxide	7.0
Talc	58.0
Colloidal clay	13.0
Precipitated chalk	5.0
Suntan colour base	4.0
	100.00

Method: Quinine bisulphate is dissolved in a small quantity of alcohol and the obtained solution is rubbed on colloidal clay. The alcohol is allowed to evaporate, after which other ingredients are added and prepared as ordinary face powder.

9.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) The word **cosmetic** has been derived from a Greek word which means **to adorn**.
2) Cosmetic helps in improving or changing the external appearance of the human body, masks the body odour, and protects the skin and keeps it in good condition.
3) Cosmetic can also be defined as a substance that is applied on the human body by rubbing, sprinkling or any other similar method with the aim to promote attractiveness, clean, beautify, and alter the external appearance.
4) **Lipsticks** are colouring matter dispersed in a base containing a suitable blend of oils, fats, waxes, perfumes, and flavours, and moulded in the form of sticks to impart an attractive colour and shine to the lips.
5) **Hard Waxes** impart the desired shape and hardness to the lipsticks.
6) **Microcrystalline Waxes** are hydrocarbons containing a long carbon chain.
7) **Softening Agents** increase the spreadability of lipsticks by softening them.
8) **Colouring Agents** are used for imparting colour to the lips by staining them with a dye stuff colour or by covering them with colouring layers.
9) **Pearlescent Pigments** impart nacreous or a pearl-like appearance to lipsticks.
10) **Shampoos** are viscous preparations containing synthetic detergent used for washing hair.
11) **Surfactants** are used in shampoos to produce foam and clean the scalp.
12) **Germicide and Anti-Dandruff Agents** are used in shampoos to prevent the microbial growth on the scalp and removes dandruff.
13) **Cold creams** are water-in-oil or oil-in-water type emulsions added with certain fats (generally beeswax) and perfuming agents.
14) **Vanishing creams** are also known as **day creams** as they are applied in the day times.
15) **Toothpastes** are used for removing stains from the teeth and to impart freshness to the mouth and breath.
16) **Hair dyes** or colourants are used by both the genders to change the natural hair colour or to mask grey hair.
17) **Temporary hair colourants** are leave-in preparations, i.e., after their application the hairs are not washed.
18) **Semi-permanent hair colourants** on application leave a long lasting colour in comparison to other colour shampoos.
19) **Oxidative dyes** are also called **para dyes**. They are colourless when applied on the hair, but turn to the particular colour after undergoing chemical reactions (oxidation, coupling, and condensation).
20) **Gradual colourants** colour the hair gradually on several applications.
21) The henna leaves are non-toxic and non-sensitizing. Its active constituent is **lawsone**, which chemically is 2-hydroxy-14-napthoquinone, and imparts colour.
22) **Sunscreens** are products that absorb or reflect some of the sun's UV rays on the skin (exposed to sunlight), thus they provide protection against sunburns.
23) The **camomile flowers** are used to impart colour. It is also available in powdered form, which is mixed with hot water to form a paste.

9.3. EXERCISE

9.3.1. True or False

1) The active constituent of henna is lawsone.
2) The camomile leaves are used to impart colour.
3) Oxidative dyes are also called para dyes.
4) Cold creams are also known as day creams.
5) Hard Waxes impart the desired shape and hardness to the lipsticks.
6) Pearlescent pigments increase the spreadability of lipsticks by softening them.

9.3.2. Fill in the Blanks

7) __________ is the active constituent of henna.
8) __________ are leave -in preparations, i.e., after their application the hair is not washed.
9) __________ are products that absorb or reflect some of the sun's UV rays on the skin.
10) __________ are used in shampoos to produce foam and clean the scalp.
11) __________ are used for removing stains from the teeth.

Answers

1) True
2) False
3) True
4) True
5) True
6) True
7) Lawsone
8) Temporary hair colourants
9) Sunscreens
10) Surfactants
11) Toothpastes

9.3.3. Very Short Answer Type Questions

1) Write a short note on cosmetics.
2) Define lipsticks and give its ideal properties.
3) What are ideal properties of shampoos?
4) Write a short note on cold cream.
5) Define hair dyes and give its types.
6) Discuss vanishing cream.

9.3.4. Short Answer Type Questions

1) Discuss the preparation of lipsticks.
2) Give the method of preparation of vanishing cream.
3) Write a short note on temporary hair colourants.
4) Give the preparation of shampoos.
5) Discuss oxidative dyeing systems.

9.3.5. Long Answer Type Questions

1) Give the formulation and preparation of lipsticks.
2) Define shampoos. Give its preparation.
3) Write a detailed note on toothpastes.
4) Give a detailed note on sunscreens.

CHAPTER 10

Pharmaceutical Aerosols

10.1. PHARMACEUTICAL AEROSOLS

10.1.1. Introduction and Definition

An aerosol is **a disperse phase system**, consisting of very fine solid drug particles or liquid droplets dispersed in the continuous phase, i.e., the propellant (gas). Aerosol can also be defined as a **system which expels the contents from the container depending on the pressure developed by compressed or liquefied gas**; or a **pressurised dosage form containing one or more therapeutic active ingredients which when actuated emit a fine dispersion of liquid and/or solid materials (smaller than 50 µm in size) contained in a gaseous medium**.

When the valve assembly of aerosol system is activated, pressure is applied by one or more liquefied or gaseous propellants. Under the influence of this pressure, the contents of aerosol container are forced out through the valve opening. These aerosol products were designed for topical administration for treating burns, minor cuts, bruises, infections, and various dermatologic conditions. Aerosol products are also designed to exert local activity in the respiratory tract.

10.1.2. Advantages

Aerosols have the following advantages:

1) A dose can be removed without contaminating the remaining contents; this is important in delivery of sterile dosage forms, **e.g.,** sterile saline aerosols used for cleaning of wounds.
2) Medicaments susceptible to oxygen and moisture remain stable as they are provided with sufficient protection.
3) The aerosol container closure system is tamper proof.
4) Medication can be directly delivered to the affected area in the form of spray, stream, quick breaking foam, or stable foam. Further handling of the medicament is not required.
5) A metering valve can be used for delivering medications in accurate dose.
6) The required particle size of the medicament can be delivered to the desired sites (such as nasal or buccal).
7) Irritation which may occur by the mechanical application of topical medication is reduced or eliminated. This is because manual application of topical medicament on the affected area is eliminated. The medication can be applied in a thin layer.
8) A pressure package can be easily and conveniently used.

10.1.3. Disadvantages

Aerosols have the following disadvantages:

1) Their limitations are mostly related to the propellants used.
2) The propellants used are highly inflammable.
3) Empty aerosol containers may contain propellant residues, thus should be carefully disposed.

4) In MDIs, a proper coordination isrequired between the valve actuation and inhalation.
5) If used inaccurately, pharyngeal deposition increases; and in case of inhaled corticosteroid, oral candidiasis, hoarseness, and increased blood absorption occurs.
6) Topical application leads to sudden cooling, which may cause further damage to the injured skin.

10.1.4. Components

An aerosol system consists of the following components:

1) Containers,
2) Value and actuator,
3) Concentrate containing the active ingredients(s), and
4) Propellant.

Particle size distribution, dose uniformity (for metered values), delivery rate, spray pattern, spray velocity, wetness, spray temperature, fluid viscosity, and foam density are the different characteristics determined by the nature of aerosol components

10.1.4.1. Containers

Aerosol containers are available in the following types:

1) **Metal**
    i) Tin-plated steel,
    ii) Tin-free steel,
    iii) Aluminium, and
    iv) Stainless steel.
2) **Glass**
    i) Uncoated glass, and
    ii) Plastic-coated glass.

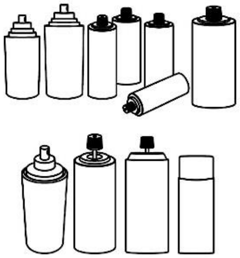


Figure 10.1: Tin-Plated Steel Containers

Tin-Plated Steel Containers

These are steel containers plated with a tin sheet on both sides. The thickness of tin plating is denoted by numbers like #25, #50, and #100. The container size is indicated by a measure of its diameter and height.

Tin-plated steel containers are light in weight and economical. To prevent the inside of the container from getting corroded by the product, special protective coatings (like oleoresin, phenolic, vinyl, or epoxy coatings) are applied to the tin sheets before fabrication. Tin-plated steel containers (**figure 10.1**) are used for topical aerosols.

Tin-Free Steel Containers

TFS, also termed **electrolytic chromium/chromium oxide coated steel**, consists of mild steel base coated with chromium-chromium oxide. This coating provides protection to the steel base from corrosion before fabrication.

TFS containers can be made resistant to corrosion by applying additional protective coatings (like enamels and lacquers) to their inside as well as outside. TFS is used for making the bottoms and tops of aerosol containers.

Figure 10.2: Aluminium Containers

Aluminium Containers

These containers are light in weight. Being less reactive, these containers result in less compatibility problems and also are strongly resistant to corrosion. On applying with further coatings of phenolic, vinyl, or epoxy resins, they can be made more corrosion-resistant. A stable coating of aluminium oxide can be formed on aluminium containers by anodisation. Aluminium containers are produced seamless by impact extrusion process; thus they have greater safety against leakage, corrosion, and incompatibility. Aluminium containers (**figure 10.2**) are used in metered dose inhalers. Containers having neck finishes ranging from 15-20mm are also used for other special purposes. Aluminium containers are available in size ranging from 10-1,000ml.

Stainless Steel Containers

These containers are smaller due to the production problems and costs involved. They are very strong and resistant to wide range of materials. These containers do not require any internal coating. Stainless steel containers (**figure 10.3**) are best used for inhalation aerosols.

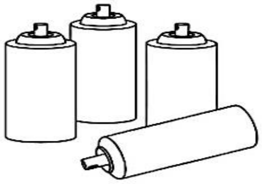


Figure 10.3: Containers Made of Stainless Steel

Glass Containers

Glass containers can also be used for aerosol packaging. They either have or do not have a plastic coating, which may be totally adhered or non-adhered and vented. Plastic coating provides greater resistance to breakage, aids in identification, provides UV protection, and absorbs shock from production operations like crimping. These containers show less compatibility problems, and have nil corrosion problems. Glass containers provide easy visual inspection of the content level. Glass is used for products having lower pressures and for lower percentage of propellants. Glass also enables easy designing of containers. Glass containers are used for small volume solution aerosols, which operate at low pressures

10.1.4.2. Valves

The flow of therapeutic agents and propellant from the containers is regulated by the valves. The spray characteristics of aerosol are determined by the diameter, location, and number of orifices. Aerosols for topical use provide continuous spray operations, whereas those for oral and nasal use utilise metered-dose valves to deliver a uniform quantity of product when activated.

Materials compatible with the formulations should be used for manufacturing valve. Plastic, rubber, aluminium, and stainless steel valve components are usually used.

The valves are of the following **two types**:

1) Continuous spray valve, and
2) Metering valves.

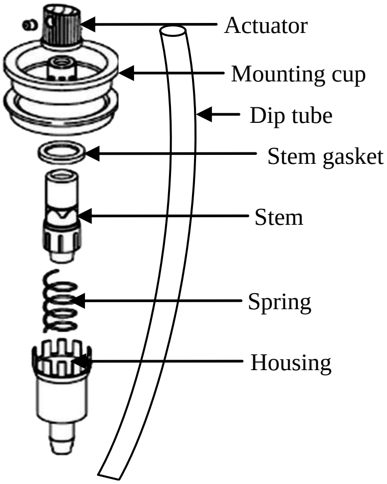


Figure 10.4: Aerosol Valve Components

An aerosol valve contains the following components (**figure 10.4**):

1) Actuator,
2) Stem,

3) Stem gasket,
4) Spring,
5) Housing,
6) Dip tube, and
7) Ferrule or mounting cup.

The different parts of an aerosol valve, along with their functions are discussed below.

Actuator

Actuators are buttons specially designed for easy opening and closing of the valve. Actuator is fitted to the valve stem. The types of product discharge (whether in spray or foam or solid stream form) depend on the propellant type and quantity, and also on the actuator design and dimension. In pharmaceutical and medicinal aerosols, special actuators are used to dispense products into the mouth, nose, throat, vagina, or eye.

Actuators are of the following **types** (**figure 10.5**), based on the type of product discharge:

1) **Spray Actuators:** These actuators can dispense the product concentrate and propellant in a stream of small particles. The stream is passed through one or three orifices. Propellant vaporisation, actuator orifice, and internal channels work together to deliver the spray in desired range of particle size.
2) **Non-Mechanical Break Up Actuators:** In these actuators, the propellant concentration should be high so that the product can be dispensed in spray form.
3) **Mechanical Break Up Actuators:** In these actuators, the propellant concentration should be less than 50%, that mechanically break up the stream into spray by swirling through various channels in the actuator.

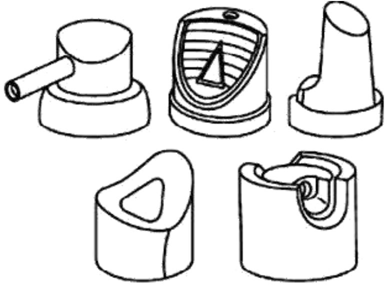


Figure 10.5: Different Types of Actuators

4) **Foam Actuators:** These actuators consist of large orifices of size ranging from 0.070-0.125 inch and greater. The product enters a large chamber by passing through the orifices; in the chamber the product is expanded and dispensed through a large orifice.
5) **Solid Stream Actuators:** These actuators are similar to foam actuators. It has an orifice which is large so that semi-solid products (like ointments) can be dispensed.
6) **Special Actuators:** These actuators are specially designed for delivering the medicament to target sites (like throat, nose, eyes, or vaginal tract).

Stem

Stem (**figure 10.6**) is a part of the valve assembly meant for controlling the product flow. It has one to four orifices of size ranging from 1 × 0.010 inch to 4 × 0.027 × 0.045 inch. Stem is made up of nylon, delrin, brass, and stainless steel.

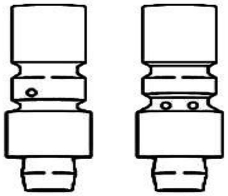


Figure 10.6: Valve Stem

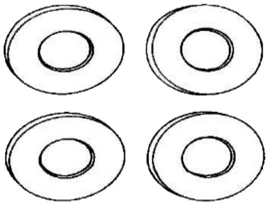


Figure 10.7: Stem Gasket

Stem Gasket

Stem gasket (**figure 10.7**) forms a covering around the stem orifice. It simply acts as an "on-off" switch. It is made up of buna-N, neoprene, butyl, or viton. Stem gasket should undergo some necessary tests because the rubber on coming in contact with different formulations may either shrink or swell. A suitable stem gasket should be selected to prevent the product loss due to leakage.

Spring

Spring (**figure 10.8**) closes the valve after the actuator has been released. It also holds the actuator in its place. The aerosol products mostly are equipped with stainless steel valves.

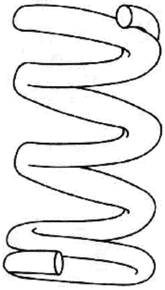


Figure 10.8: Spring

Housing

Housing (or **valve body**) made up of nylon or delrin, enfolds the stem, spring, and gasket (**figure 10.9**). It has an opening (ranging between 0.013-0.080 inches depending on the type of product to be dispensed) at the attachment point of the dip tube. It acts as a secondary metering orifice. This opening ejects a dry and warmer spray, thus the chilling effect of some products felt on skin, is reduced. An additional opening (called **vapour tap**) may also be present at the side or bottom of the housing. This opening permits the escape of vaporised propellant and the liquid product. The vapour tap also produces fine particles, prevents value clogging, allows the product to dispense in an inverted position, and reduces flame extension (in case of hydrocarbon propellants).

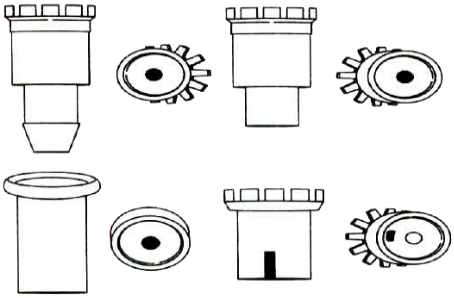


Figure 10.9: Different Types of Valve Housing

Dip Tube

Dip tube (**figure 10.10**) is meant for drawing up the product into the valve and help in delivering it. It is made up of polyethylene or polypropylene. The diameter of dip tube depends on the product viscosity and delivery rate. The usual **diameter** of dip tube ranges from:

1) **Standard:** 1/8" (0.122") inside diameter,
2) **Large:** 3/16" (0.190") inside diameter,
3) **Jumbo:** over 1/4" (0.260") inside diameter, and
4) **Capillary:** < 0.060" inside diameter.

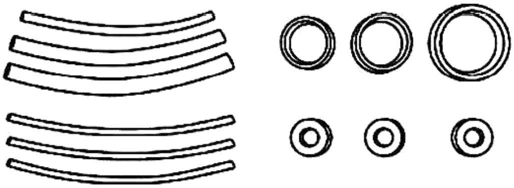


Figure 10.10: Dip Tubes

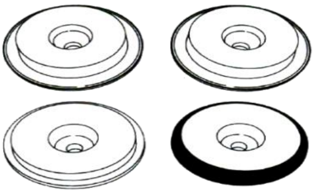


Figure 10.11: Mounting Cups

The dip tubes are notched at the bottom to prevent closing off at the bottom of the can.

Ferrule or Mounting Cup

Mounting cup (**figure 10.11**) is intended for holding the valve parts together and attaching the valve to the container. It is made up of tin-plated steel or aluminium. Its base should be applied with single or double coatings of epoxy or vinyl to provide protection against corrosion by the aerosol contents. Mounting cup is made up of softer metals (**e.g.,** aluminium or brass) with glass containers and small aluminium tubes. The cup is attached to the container either by clinching the metal under the lip or by rolling the end under the lip of the bottle.

10.1.5. Formulation of Aerosols

The formulation of an aerosol consists of the following two essential components:

1) Propellant, and
2) Product concentrate.

10.1.5.1. Propellant

A propellant develops pressure within the aerosol container, and forces out the product in the desired physical form (spray, mist, or foam) with the help of other components. Propellants are classified into:

1) Compressed gases, and
2) Liquefied gases.

The propellant type used for different pharmaceutical applications are listed in **table 10.1**:

Table 10.1: Types of Propellants for Different Applications

Applications	Types of Propellants
Oral and inhalation	Trichloromonofluoromethane (propellant 11), dichlorotetrafluoroethane (propellant 114), and dichlorodifluoromethane (propellant 12).
Topical	Propane, butane, isobutene, and compressed gases like nitrogen and carbon dioxide.

Compressed Gases

Compressed gases, **e.g.,** nitrogen, nitrous oxide, and carbon dioxide, are extensively used as propellants in pharmaceutical aerosols. The gas is compressed in the container and occupies the headspace above the liquid. On pressing the valve, the gas pressure (dependant on the propellant concentration) acts as a piston on the contents and pushes the liquid out of the container. The amount of gas in the headspace remains unchanged, but it expands to occupy more volume. Thus, the pressure drops throughout the life of container.

Compressed gases are used to dispense the product either in the form of a solid stream, wet spray, or foam. The form in which the product will be dispensed depends on the nature of formulation and the type of compressed gas used. A considerably high initial pressure of 90-100 psig at 70°F is required for **dispensing semisolids** so that most of the product is dispensed from the container. The product viscosity should be adjusted as per the desired dispensing characteristics. The product viscosity also regulates the amount of residual product in the container.

Soluble compressed gases, **e.g.,** nitrous oxide and carbon dioxide, are used for **dispensing the product as foams**. When the system is used, the gas dissolved in the product concentrate (emulsion form) evolves and whips the emulsion into foam. By shaking the container prior to use, some of the gas disperses throughout the product concentrate and facilitates foam formation.

Compressed gases and a mechanical breakup actuator are required for **dispensing the product as a wet spray**. Solutions of medicinal agents in aqueous solvents are generally dispensed in this form. Contact lens saline aerosols are formulated with compressed nitrogen gas as propellant and sterilised using γ-radiations.

Liquefied Gases

Liquefied gases are preferred as propellants for most of the aerosols. They exist in gaseous or vapour state at room temperature and atmospheric pressure. They can get liquefied easily by either lowering the temperature below its boiling point or by increasing the pressure. The boiling points of compounds selected as liquefied gases are usually below 70°F (21°C) and the exerted vapour pressure is between 14-85 psig at 70°F (21°C). Liquefied gases are inert and non-toxic.

Chlorofluorocarbons (CFCs) and **hydrofluorocarbons** are the two types of liquefied gases. Initially, pharmaceutical aerosols were prepared using CFCs -11, -12 and -114; but these propellants have an ozone depleting effect and the current global regulations demand the use of non-ozone depleting propellants in pharmaceutical aerosols. Therefore, they are not used in pharmaceutical aerosols, except in MDIs.

The alternatives to CFC propellants should be non-toxic and non-flammable. **Trichloromonofluoromethane** (propellant-11), **dichlorodifluoromethane** (propellant-12), and **dichlorotetrafluoroethane** (propellant-114) are the fluorocarbon propellants used in aerosols nowadays. The two or three digit number helps in identifying the propellant. The first digit is one less than the number of carbon atoms in the compound; the second digit is one more than the number of hydrogen atoms in the compound; and the third digit is the number of fluorine atoms in the compound. If the first digit is zero, it can be represented by only two digits. The remaining carbon valency is satisfied by chlorine atom; **for example,** Propellant 11 is $CFCl_3$, Propellant 12 is CF_2Cl_2, and Propellant 114 is $C_2F_4Cl_2$. The liquefied gas propellants are discussed below:

1) **Chlorofluorocarbons:** These propellants, **e.g.,** trichloromonofluoromethane (propellant-11), dichlorodifluoromethane (propellant-12), and dichlorotetrafluoromethane (propellant-114), are used for oral and inhalation.

   Advantages
   i) They are chemically inert.
   ii) They are non-toxic.
   iii) They are non-flammable.
   iv) They are non-explosive.

   Disadvantages
   i) They are expensive.
   ii) They are ozone-depleting by nature.

2) **Hydrocarbons:** These propellants, **e.g.,** propane (propellant A108), isobutane (propellant A-31), and butane (propellant A17), are used for water aerosols and topical use.

   Advantages
   i) They are inexpensive.
   ii) They are excellent solvents.
   iii) They are not ozone-depleting by nature.

   Disadvantages
   i) They are inflammable.
   ii) They are capable of producing unknown toxicity.

Mechanism of Aerosol Operation

Liquefied gases have been mostly used as propellants for aerosols. The liquefied gas in a sealed container (such as an aerosol can), exists in liquid and gas (or vapour) phases, thus behaving as a two-phase system. The molecules in the vapour phase exert pressure on the contents.

With increased number of molecules in the vapour phase, the vapour pressure of the propellant also increases. Pressure attained at equilibrium is the vapour pressure, which is unique for a particular propellant at a given time. This vapour pressure is equally exerted in all the directions and does not depend on the quantity present.

When valve is actuated, gas exerts a vapour pressure on the liquid phase, which further exerts pressure on the product and pushes it upward (liquid state) through the dip tube. If no dip tube is present (as in MDIs), the container is used in inverted position. With the opening of valve, the liquid phase is expelled with sudden volume of expansion and comes in contact with the atmospheric temperature. The propellant having boiling point much less than the room temperature immediately turns into vapour. The pressure drop within the container is restored as more of the liquid propellant vaporises into the headspace.

As compared to compressed gases, the advantage of these propellants is that the pressure drop within the container does not occur while using the product. The pressure exerted does not depend on the propellant concentration in the container. Due to its large volume expansion ratio, the spray performance is maintained constant throughout the shelf-life of the aerosol until the last dose of drug is left in it.

Aerosols with liquefied gas propellant and compressed gas propellant are shown in the **figure 10.12**:

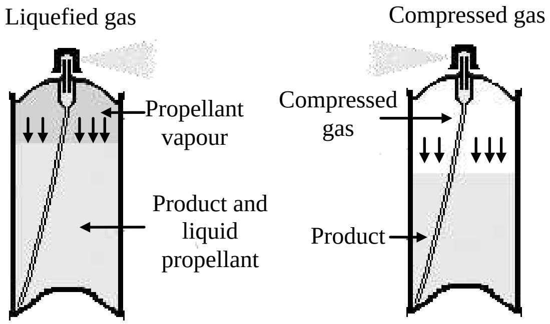


Figure 10.12: Aerosols with Liquefied Gas Propellant and Compressed Gas Propellant.

Selection of Propellants

Mixtures of various fluorocarbon propellants are capable of achieving the desired pressure, delivery, and spray characteristics, thus are used in pharmaceutical aerosols. The desired vapour pressure can be obtained by altering the proportion of each component.

The CFCs can deplete the ozone layer, thus allowing increased amount of UV radiations to reach the earth's surface, further resulting in greenhouse effect and global warming. Depletion of ozone layer may also increase the incidences of skin cancer. A **Montreal protocol** was signed in **1987** to phase out the use of ozone depleting substances (including CFCs). Thereafter, the pharmaceutical companies introduced some alternate substances that can be used as propellants in medicinal products.

Hydrocarbon propellants and their various mixtures are used in aerosol formulations. CFCs were replaced with hydrocarbon propellants, **e.g.,** butane, propane, and isobutene, in topical pharmaceutical aerosols as they have lower solubility and cost, but higher flammability. Their density is less than one and they are immiscible with water, thus are suitable for three-phase systems.

Their solubility characteristics are better than those of fluorinated hydrocarbons. They are chemically stable. Since they are not susceptible to hydrolysis, they are used for water-based formulations. Hydrochlorofluorocarbons (HCFCs) and hydrofluorocarbons (HFCs) can also replace the CFCs in appropriate formulations. Liquefied gases and compressed gases as propellants are differentiated in the **table 10.2**:

Table 10.2: Comparison of Liquefied Gases and Compressed Gases as Propellants

Liquefied Gases	Compressed Gases
Propellant is an integral part of the formulation.	Propellant forms a separate phase on product surface.
Spray consists of smaller and finer particles.	Spray consists of larger and wet particles.
Pressure is maintained throughout the product life.	A pressure drop occurs throughout the product life.
Large temperature changes affect the pressure inside the container.	Changes in temperature do not affect the pressure exerted by the gases in the container.
Pressure exerted does not depend on propellant concentration, hence no pressure drop is seen.	Pressure exerted depends on the propellant concentration, hence pressure drop is seen.
Cost varies with the nature of propellant and generally of higher cost.	Low cost.

10.1.5.2. Product Concentrate

Concentrate is either the **active ingredient** or is a **mixture of active ingredients** and other required agents (like solvents, antioxidants, and surfactants). Propellants and the active ingredients can be combined in many ways to obtain products having variable characteristics.

10.1.6. Types of Aerosol Systems

The aerosol systems are of the following types:

1) Solution system.
2) Water based system.
3) Suspension or dispersion system.
4) Foam systems:
    i) Aqueous stable foams,
    ii) Non-aqueous stable foams,
    iii) Quick breaking foams, and
    iv) Thermal foams.
5) Intranasal aerosols.

10.1.6.1. Solution System

Solution system is also referred to as the two-phase system, i.e., a liquid and a vapour phase. This system is easy to formulate and consists of either a solution of active ingredients in pure propellant or a mixture of propellant and solvents. In case the active ingredients are soluble in the propellant, no other solvent is required. The propellant used depends on the type of desirable spray. Propellant-12 or A-70, or a mixture of propellant-

12 and other propellants produces fine particles. Larger particles can be produced by reducing the pressure of the system; this is done by adding to the above mixture, the propellants having vapour pressure lower than that of propellant -12. Vapour pressure can be reduced by adding less volatile solvents (**e.g.,** ethyl alcohol, propylene glycol, ethyl acetate, glycerine, and acetone). These types of sprays produce wetness and are suitable for topical aerosols wherein a film of medicament forms on the surface. A **two-phase solution system** is shown in **figure 10.13**:

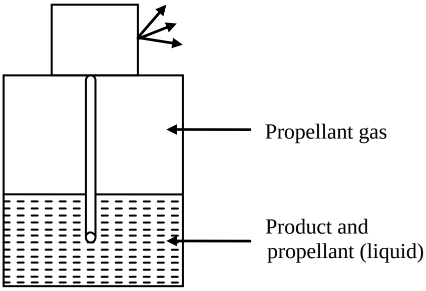


Figure 10.13: Diagrammatic Representation of a Two-Phase Solution System

The system can be exemplified by the following general formula:

Formula	Weight (%)
Active ingredients	10-15
Propellant 12/11 (50:50) q.s	100

The ratio of propellant -12 and -11 or propellant -12 with any other propellant (such as propellant-114) can be used for oral inhalation also. As the pressure increases, the choice of container also needs to be changed. Hydrocarbons in topical aerosol pharmaceutical preparations are used as follows:

Formula	Weight (%)
Active ingredients	10-15
Solvents such as ethanol or propylene glycol	10-15
Distilled water	10-15
Hydrocarbon propellant A-46	55-70

10.1.6.2. Water Based System

A water-based aerosol is dispensed as spray or foam depending on the formulation. This aerosol system consists of an emulsion of active ingredients and other solvents. When the product is dispensed, the propellant turns into vapour and disperses the active ingredients into minute particles, forming three phase, i.e., liquid propellant, product concentrate, and vapourise propellant. A **three-phase water-based system** is shown in **figure 10.14**:

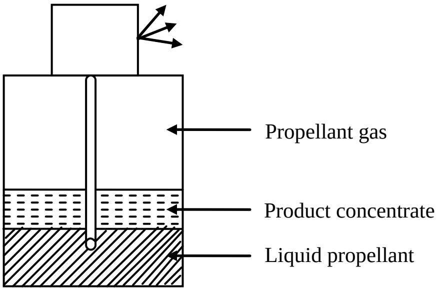


Figure 10.14: Diagrammatic Representation of a Three-Phase Water-Based System

Ethanol is used as a co-solvent in water-based system to solubilise some of the propellants in water. The **surfactants** (0.5-2.0%) that are highly soluble in non-aqueous solvents are used to produce a homogenous dispersion. The propellant should be used in 25-60% concentration; however, the content can be as low as 5% depending on the product nature. If a fine particle spray is desired, the propellant concentration should be low, the water content should be high, and a mechanical breakup actuator along with a vapour tap should be used.

The **aquasol system** is an **example** where the propellant content is less than that of water. The product from this system is dispensed as a fine mist or spray. Since the propellant is present in a small amount, it does not produce any chilling effect. The aquasol system is a three-phase system; however, unlike the other three-phase systems it uses large quantities of water in the formulation. Also, hydrocarbon propellant is used in low concentration. The resulting spray from aquasol system is non-flammable and the product is also economical.

10.1.6.3. Suspension or Dispersion System

In the suspension or dispersion system, the active ingredients are dispersed in a mixture of propellants. The suspending agents or surfactants are added to decrease the settling rate of dispersed particles. This system is used for oral inhalation aerosols. The stability problems of disperse systems (such as caking, agglomeration, and particle size growth) are also observed in this system. In some cases, the particles adhere to the container walls. Agglomeration of particles clogs the valve, and thus leads to inaccurate dosing.

These **problems can be overcome** by the following **steps**:

1) Lubricants, **e.g.,** isopropyl myristate and oleic acid, should be added as they provide slippage between the particles and also lubricate the valve components.
2) Surfactants should be added to disperse the particles.
3) Dispersing agents, **e.g.,** oleic acid and lecithin, should be added as they prevent the agglomeration of suspended particles.
4) The particle size for metered-dose inhalant should lie between 2-8µm, while that for topical aerosol should lie between 50-100µm to prevent the aerosol valves from getting blocked.
5) The moisture content of propellant and suspension should be below 300ppm because higher moisture levels cause particle agglomeration.
6) The initial particle size should be reduced to less than 5 µ to overcome the particle size growth during the product shelf-life.
7) The density of propellant and suspension should be equalised.
8) Vapour tap valves should be used to reduce valve clogging. The escaping of propellant as vapour helps in clearing the valve of solid particles.

An **example** of a formulation for steroid-containing oral inhalation is given below:

Steroid compound	8.4mg
Oleic acid	0.8mg
Propellant 11	4.7gm
Propellant 12	12.2gm

In the above formulation, oleic acid is added as a dispersing agent for the steroid. It reduces the growth and agglomeration of particles. It also acts as a valve lubricant and prevents the sticking of metered valves in the open position.

10.1.6.4. Foam System

In the foam system, the liquefied propellant is emulsified. This system comprises of aqueous or non-aqueous vehicles, propellants, and surfactants. Foam system is classified as:

1) **Aqueous Stable Foam:** This system consists of propellant in 3-4% concentration. The added propellant produces a dry spray. On increasing the concentration of propellant, more contents can be delivered in dried form. As the propellant is present in the internal phase, the concentration of propellant is less. This system is used in steroid antibiotics.
2) **Non-Aqueous Stable Foam:** This system consists of glycol as the emulsion base and is used as the emulsifying agent.
3) **Quick Breaking Foam:** This system consists of propellant (the external phase), and cationic, anionic or non-anionic surfactants. The product comes out in the form of foam which amalgamates to form liquid. This system is used topically and can be applied to small area or larger surface.
4) **Thermal Foam:** In this system, aerosol is delivered in the form of foam on the application of heat. This system is used in shaving creams.

10.1.6.5. Intranasal Aerosols

Intranasal aerosols deposit the medication into nasal passages to provide local and systemic effects.

Advantages

1) They deliver a measured dose of drug.
2) They require lower doses compared to other systemic products.
3) They provide an excellent depth of penetration into the nasal passage way.
4) They decrease the mucosal irritability.
5) They maintain sterility from dose to dose.
6) They provide greater flexibility in the product formulation.

10.1.7. Manufacture of Aerosols

Pharmaceutical aerosols are prepared and packaged successfully only with special knowledge, skills, and equipment. Aerosols should be manufactured under strict supervision and adherence to rigid quality controls. Since the propellant is added to the concentrate during the packaging operation, the quality control system should be modified to account for this difference.

Apart from the equipment used for compounding of liquids, suspensions, emulsions, creams, and ointments, some specialised equipment that can handle and package materials at relatively low temperatures (about –40°F) or under high pressure should be available. These equipments are used only for aerosol or pressurised packaging, and not for other pharmaceutical operations. The following apparatus are used for manufacturing aerosols:

1) Cold filling apparatus,
2) Pressure filling apparatus, and
3) Compressed gas filling apparatus.

10.1.7.1. Cold Filling Apparatus

Cold filling apparatus is a simple apparatus that comprises of an insulated box fitted with coiled copper tubing to increase the area exposed to cooling. This system can be used with both metered and non-metered valves. Hydrocarbon aerosols cannot be filled using this system since an excessive amount of propellant escapes and vaporises from it that may form an explosive mixture at the floor level. However, the fluorocarbon vapours are heavier than air and thus do not form explosive or flammable mixtures.

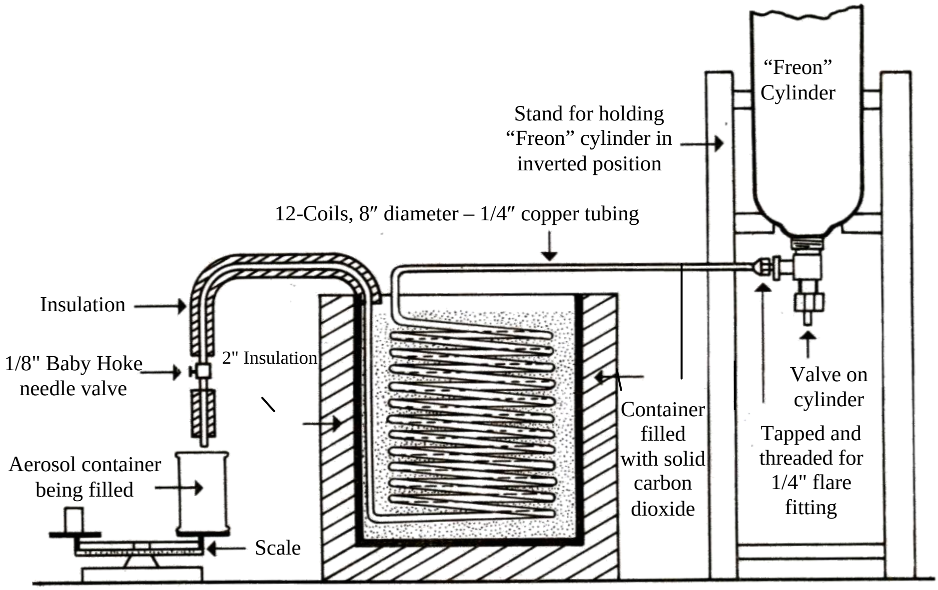


Figure 10.15: Apparatus for Cold Filling

Procedure

1) This method is used to fill non-aqueous products and products that can withstand low temperatures (–40°F).
2) The product concentrate is chilled to –40°F temperature and filled in already chilled container.
3) This chilled propellant is completely added in 1 or 2 stages depending on its amount.
4) In another method, the product concentrate and propellant are chilled in a separate pressure vessel to –40°F and then filled into a container.
5) The valve is placed and crimped over the container.
6) The leakage and strength of container can be tested by passing it into a heated water bath, where the container contents are heated at 130°F temperature.
7) Then the containers are dried, capped, and labelled.

Advantage

It is an easy process.

Disadvantage

Aqueous products, emulsions, and products that get adversely affected by cold temperature are not filled by this method.

10.1.7.2. Pressure Filling Apparatus

Pressure filling apparatus comprises of a pressure burette capable of metering small volumes of liquefied gas under pressure into an aerosol container. Propellant is added into the burette through the inlet valve located at its bottom or top. Trapped air is allowed to escape through the upper valve. The propellant under its own vapour pressure is allowed to flow in desired amount into the container through the aerosol valve.

When the pressure between the burette and the container equalises (this happens when low-pressure propellants are used), the propellant stops flowing. Additional propellant is added by attaching a hose leading to a cylinder of nitrogen or compressed air to the upper valve. This added nitrogen pressure causes the propellant to flow. In another pressure filling apparatus, a piston arrangement is used to maintain a positive pressure.

Procedure

1) This method is used to fill the concentrate into the container at room temperature.
2) The valve is placed in the container and crimped.
3) The propellant is added either through the valve opening or "under the cap".
4) The valve opening is smaller in size (0.018 -0.030 inches), thus the production is limited and the process is slow.
5) The production rate can be increased by using rotary filling machines and newer filling heads where the propellants are filled through valve stem.
6) The air entrapped in the container and the air in head space is removed before the propellant is filled to protect the products from getting affected.

Advantages

1) This method does not involve chilling, thus is used for filling solutions, emulsions, and suspensions.
2) Contamination due to moisture is less in this method.
3) High production speed can be achieved in this method.
4) This method involves less propellant loss.

Disadvantages

1) Certain types of metering valves cannot be handled by pressure filling method, but only by the cold filling method or by using an under the cap filler and valve crimper.
2) This method is slow.

10.1.7.3. Compressed Gas Filling Apparatus

Handling of compressed gases in the laboratory does not require any specialised equipment and is easy.

Aerosol containers are made up of aluminium, tin plated steel, stainless steel, uncoated or plastic coated glass and synthetic resins, or plastics. Valve mechanism is the most essential part of an aerosol as it regulates the package performance and the form in which the product will be dispensed. An aerosol valve comprises of actuator, valve stem, valve housing, sealing gasket, mounting cap, spring or toggle return action, and dip tube. The aerosol valve stem is fitted with an actuator. On pressing the actuator, the valve opens and directs the spray outside.

Metered valves dispense a measured quantity of spray at each actuation. These valves are used to dispense potent medicaments, and to minimise wastage and errors of overdosing. Time measurement of a dose in metered valves is also not a problem, which is however difficult to control in other valve systems.

Aerosols are packaged either by cold filling method in which the propellant and the product concentrate are filled at low temperatures (–30 to 40°F and below 0°, respectively) or pressure filling process method in which the aerosol products are filled under pressure.

Procedure

1) In this method, the product concentrate is filled in the container.
2) Valve is placed and crimped on the container.
3) Vacuum is applied to remove the air from the container.
4) Filling head is put in the valve opening and gas is allowed to flow into the container.
5) The valve is depressed and gas is allowed to flow into the container.
6) When the delivery pressure and the pressure within the container equalises, the gas stops flowing.
7) If more amount of gas is required, carbon dioxide and nitrous oxide is used.
8) By shaking the container either manually or with mechanical shakers, high solubility of the gas in the product can be achieved.

10.1.8. Evaluation of Aerosols

Pharmaceutical aerosols are evaluated for the following parameters:

1) Flammability and combustibility:
    i) Flame extension or projection test, and
    ii) Flash point test.
2) Physicochemical characteristics:
    i) Vapour pressure,
    ii) Density,
    iii) Moisture content, and
    iv) Qualitative and quantitative tests for propellants.
3) Performance characteristics:
    i) Aerosol valve discharge rate,
    ii) Spray pattern,
    iii) Dosage with metered valves,
    iv) Net contents,
    v) Foam stability,
    vi) Particle size determination, and
    vii) Leakage.
4) Biological testing:
    i) Therapeutic efficiency, and
    ii) Toxicity.

10.1.8.1. Evaluation of Aerosols for Flammability and Combustibility

The effect of an aerosol on extension of an open flame can be evaluated by the following two tests:

1) **Flame Extension Test:** In this test, the aerosol product is sprayed for 4 seconds into the flame. Depending on the formulation nature, the flame extends and its length is measured with ruler.

2) **Flash Point Test:** In this test, the aerosol product is chilled to −25°F temperature and transferred to a standard **tag open cap apparatus**. The temperature of test liquid is gradually increased, and the temperature at which the vapours ignite is considered as the flash point. The flammable component is calculated in case of topical hydrocarbons.

10.1.8.2. Physicochemical Characteristics

The following physicochemical characteristics of aerosols are tested as follows:

1) **Vapour Pressure:** A pressure gauge is used to determine the vapour pressure of aerosol product. Presence of air in the headspace is confirmed when excessive variations occur in the pressure from container to container. Pressure is accurately determined using can puncturing equipments available for metal as well as glass containers.

2) **Density:** A hydrometer or a pycnometer is modified and used to determine the density of aerosol product and the liquefied gas propellants.
3) **Moisture Content:** Karl Fischer apparatus or gas chromatography is used to determine the moisture content of aerosol product.
4) **Qualitative and Quantitative Tests for Propellants:** IR spectroscopy and gas chromatography are used for the qualitative and quantitative tests for propellants; these methods also indicate the proportion of each propellant in the blend.

10.1.8.3. Performance Characteristics

The container and valve design influences the dosing, performance, and clinical efficacy of aerosol products (especially a MDI). The following tests are performed to determine the efficiency and performance of the valve:

1) **Aerosol Valve Discharge Rate:** In this test, a standard apparatus is used to discharge the contents of an aerosol product of known weight for a given time period. After the specified time limit, the container is re-weighed and the change in weight per unit time dispensed is considered as the discharge rate (grams/second).
2) **Spray Patterns:** In this test, the spray patterns obtained from different batches of material or through the use of different valves are compared. The spray is impinged on a paper, treated with a mixture of dye and talc. An oil-soluble or water-soluble dye is used depending on the aerosol nature. The particles striking the paper cause the dye to move into the solution and to get absorbed on the paper, thus giving a pattern of the spray which is used for making comparison. The amount of material coming into contact with the paper can be controlled by attaching the paper to a rotating disk with an adjustable slit.
3) **Dose Uniformity Test:** This test determines that whether or not the patient receives the same dose of medicament each time the valve is depressed. The dose uniformity test is performed by the following **two ways**:
   i) One or two doses are dispensed into a solvent or onto a material that absorbs the active ingredient, and then the amount of active ingredient is dispersed in the solvent or sample.
   ii) A filled container is weighed. Several doses of the product dispensed in it and the container is re-weighed. The average dose is determined by dividing the difference in weight by the number of doses dispensed.
4) **Net Contents:** This test determines that whether or not sufficient product has been placed into each container. The tarred cans placed onto the filling line are re-weighed and the difference in weight is considered as the net content. In **destructive method**, a full container is weighed and then the contents are dispensed. The contents are then weighed, with provision made for the amount retained in the container.

   In other modifications, as much product as possible is removed from the container. These tests do not determine the actual net weight of each container as related to the amount that can be dispensed. The National Bureau of Standards has issued methods for determining the net contents of foam type, low-viscosity, high-viscosity, and food aerosols. These methods standardise the manner in which the containers are to be dispensed.
5) **Foam Stability:** The foams either break down rapidly or remain stable for an hour or more depending on the formulation. Foam stability can be determined by visual examination, by determining the time taken for a given mass to penetrate the foam, time taken for a given rod that has been inserted into the foam to fall, or by using rotational viscometers.

6) **Particle Size Determination:** The aerosol particle size can be determined using the following tests:
   i) **Microscopy:** In this test, the aerosol is actuated on a glass slide after priming the valve and washing the slide with carbon tetrachloride (avoiding loss of any particulate matter). The slide is dried and examined microscopically.
   ii) **Cascade Impaction:** A cascade impactor is used to measure particles of size ranging between 0.2 -20μm. The aerosol passes through a series of nozzles of decreasing diameter under vacuum. After each stage, a glass slide coated with viscous fluid is placed. The largest particle entraps in the first glass slide, the smaller one flows around the glass slide and passes through the second nozzle, and so on. The remaining particles pass through another nozzle. Then the size distribution of aerosol is determined.
   iii) **Light Scattering Methods:** These methods are used to measure the particles of size ranging between 0.1 -20μm using either white light or laser light. In these methods, the particles suspended in air cause a scattering of light that is monitored by a photodetector.
   iv) **Leakage:** This test determines that whether or not the valve crimping is free from any leakage. In this test, the dimensions of the crimp in metal containers are determined to make sure they fulfil the required standards. The aerosol -filled containers are carried by a magnetised chain and submerged into heated water baths. The containers travel in the water bath and by the time they are emerged out, the product temperature should reach 130 °F. The container should not show any signs of leakage or distortion.

10.1.8.4. Biological Testing

These tests are similar to those performed on non -aerosol preparations. The biological tests for aerosols involve determining the following parameters:

1) **Therapeutic Efficacy:** The inhalation aerosols or MDIs are tested for their dose uniformity and particle size distribution along with their pharmacokinetic and pharmacodynamic studies. Topical aerosols are applied to the test area and absorption of therapeutic ingredients is determined.
2) **Toxicity:** The topical as well as inhalation aerosol products are tested for toxicity. The topical aerosols can irritate the affected area and/or may produce a chilling effect. When an aerosol is sprayed on the skin for a given time period, the change in skin temperature is determined using thermistor probes attached to recording thermometers. The toxicity of inhalation aerosols is determined by exposing the test animals to the sprayed vapours.

10.1.9. Quality Control

Quality control of pharmaceutical aerosol includes the following tests:

1) **Propellant:** A sample of propellant is taken to determine its vapour pressure and density, which are compared to the specified standards. **Other tests** include:
   i) Identifying two or more blends of propellant by gas chromatography.
   ii) Checking the purity of propellant by determining moisture, halogen, and non -volatile residue.
2) **Valves, Actuators, and Dip Tubes:** These components are determined by physical and chemical examinations. They are sampled as per the standard procedures in “Military Standard Mil -STD-105D”. Aerosol Specifications Committee, Industrial Pharmaceutical Technology section, Academy of Pharmaceutical Sciences

developed a test method for metered dose pharmaceutical aerosols to determine the magnitude of valve delivery and degree of uniformity between individual valves. Composition of the test solution is given in **table 10.3**:

Table 10.3: Ingredients Used in the Preparation of Test Solutions

Ingredients % w/w	Test Solution A	Test Solution B	Test Solution C
Isopropyl myristate	0.1%	0.1%	0.1%
Dichlorodifluoromethane	49.95%	25%	50.25%
Dichlorotetrafluoroethane	49.95%	25%	24.75%
Trichloromonofluoromethane	–	–	24.95%
Alcohol USP	–	49.9%	–
Specific gravity at 25°C	1384	1.092	1.388

Testing Procedure

i) 25 valves are placed on suitable containers filled with specific test solutions.
ii) The valves are attached with button actuators with 0.02 inch orifice.
iii) The filled containers are placed in a suitable atmosphere at 25±1 °C temperature.
iv) When the products have attained this temperature, the filled containers are actuated to fullest extent for 2 seconds.
v) This procedure is repeated for a total of 2 deliveries from each 25 test units.

$$\text{The valve delivery per actuation in } \mu\text{l} = \frac{\text{Individual Delivery Weight in Mg}}{\text{Specific Gravity of Test Solution}}$$

The **limits** for acceptance out of 50 deliveries are as follows:

i) If 4 or more deliveries are outside limits, the valves are rejected.
ii) If 3 or more deliveries are outside limits, another 25 valves are tested.
iii) If more than 1 delivery is outside limits, the lot is rejected.
iv) If 2 deliveries from 1 valve are outside limits, another 25 valves are tested.
v) If more than 1 delivery is outside limits, the lot is rejected.

3) **Containers:** These are examined for defects in linings. Quality control aspects include conductivity degree of electric current as a measure of exposed metals. Glass containers are examined for flaws.

4) **Weight Checking:** It is done by adding empty tarred containers periodically into filling lines. After filling with the product concentrate the containers are removed and re-weighed. The same procedure is used for checking the propellant weight.

5) **Leak Test:** In this test, the crimp's valve dimension is measured and compared with the standard value. The final testing of valve enclosure involves passing the filled containers through water bath.

6) **Spray Testing:** In this test, the dip tube of pure propellant and concentrate is cleared and any defects in the valve and the spray pattern are checked.

10.1.10. Stability Studies

An entire aerosol package is made up of the product and the container. Therefore, the product effect on the container and *vice versa* should be studied while studying the stability aspects of aerosols.

Since various materials are used for making an aerosol valve and container, the effect of each material on the product should be studied separately as well as collectively. Several container coatings and valves with different sub-components should be studied to detect any reaction between the component and the product.

The pharmaceutical aerosols are tested for their stability based on the following components:

1) The product concentrates including the propellant,
2) The container, and
3) The valve assembly.

The **stability testing of product concentrate** involves determining the physicochemical parameters (such as vapour pressure, spray rate of the valve, pH, density or specific gravity, refractive index, viscosity, total weight, assay of active ingredients, chromatography curves, colour, and odour). Compatibility between the product and the container is determined by keeping the contents and the different container parts in close contact.

The **stability testing of container** involves chilling the container to 0 °F or less temperature and then examining the insides of container (after emptying them) for any signs of corrosion. The containers lacquered on the insides are examined for the softening of lacquer, and the plastic containers are checked for leaching or sorption.

The **stability testing of valve assembly** involves checking for any evidence of corrosion in the valve components, especially the mounting cup. The other valve components are checked for softening, cracking, elongation, or distortion. Since these problems lead to improper functioning of the valve, they should be overcome in the initial stage only.

10.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) An **aerosol** is a disperse phase system, consisting of very fine solid drug particles or liquid droplets dispersed in the continuous phase, i.e., the propellant (gas).
2) An **aerosol** can also be defined as a pressurised dosage form containing one or more therapeutic active ingredients which when actuated emit a fine dispersion of liquid and/or solid materials (smaller than 50µm in size) contained in a gaseous medium.
3) The flow of therapeutic agents and propellant from the containers is regulated by the **valves**.
4) **Actuators** are buttons specially designed for easy opening and closing of the valve.
5) **Spray Actuators** can dispense the product concentrate and propellant in a stream of small particles.
6) **Foam Actuators** consist of large orifices of size ranging from 0.070-0.125 inch and greater.
7) **Solid Stream Actuators** have an orifice which is large so that semi-solid products (like ointments) can be dispensed.
8) **Stem** is a part of the valve assembly meant for controlling the product flow.
9) **Dip tube** is meant for drawing up the product into the valve and help in delivering it.
10) **Mounting cup** is intended for holding the valve parts together and attaching the valve to the container.
11) A **propellant** develops pressure within the aerosol container, and forces out the product in the desired physical form (spray, mist, or foam) with the help of other components.

12) Concentrate is either the **active ingredient** or is a **mixture of active ingredients** and other required agents (like solvents, antioxidants, and surfactants).

13) Solution system is also referred to as the two-phase system, i.e., a liquid and a vapour phase.

14) A water-based aerosol is dispensed as spray or foam depending on the formulation.

15) In the suspension or dispersion system, the active ingredients are dispersed in a mixture of propellants.

16) In the foam system, the liquefied propellant is emulsified. This system comprises of aqueous or non-aqueous vehicles, propellants, and surfactants.

17) Intranasal aerosols deposit the medication into nasal passages to provide local and systemic effects.

18) Cold filling apparatus is a simple apparatus that comprises of an insulated box fitted with coiled copper tubing to increase the area exposed to cooling.

19) Pressure filling apparatus comprises of a pressure burette capable of metering small volumes of liquefied gas under pressure into an aerosol container.

20) The **stability testing of product concentrate** involves determining the physicochemical parameters.

21) The **stability testing of container** involves chilling the container to 0 °F or less temperature and then examining the insides of container (after emptying them) for any signs of corrosion.

22) The **stability testing of valve assembly** involves checking for any evidence of corrosion in the valve components, especially the mounting cup.

10.3. EXERCISE

10.3.1. True or False

1) The flow of therapeutic agents and propellant from the containers is regulated by the valves.
2) Dip tube is a part of the valve assembly meant for controlling the product flow.
3) The stability testing of product concentrate involves determining the physicochemical parameters.
4) Mounting cup is intended for holding the valve parts together and attaching the valve to the container.
5) Solution system is also referred to as a single phase system.

10.3.2. Fill in the Blanks

6) __________ is either the active ingredient or is a mixture of active ingredients and other required agents (like solvents, antioxidants, and surfactants).
7) _________ are buttons specially designed for easy opening and closing of the valve.
8) _____________ apparatus is a simple apparatus that comprises of an insulated box fitted with coiled copper tubing to increase the area exposed to cooling.
9) _____________ comprises of a pressure burette capable of metering small volumes of liquefied gas under pressure into an aerosol container.
10) ___________ is also referred to as the two-phase system, i.e., a liquid and a vapour phase.

Answers:

1) True
2) False
3) True
4) True
5) False
6) Concentrate
7) Actuators
8) Cold filling
9) Pressure filling apparatus
10) Solution system

10.3.3. Very Short Answer Type Questions

1) Define aerosols.
2) Give the advantages of aerosols.
3) Discuss foam system.
4) Name the types of aerosol systems.
5) Discuss intranasal aerosols.

10.3.4. Short Answer Type Questions

1) Discuss the containers used for aerosols.
2) Give the mechanism of aerosol operation.
3) Discuss quality control of pharmaceutical aerosols.
4) Write a short note on stability studies of aerosols.

10.3.5. Long Answer Type Questions

1) Give a detailed note on evaluation of aerosols.
2) Briefly explain the types of aerosol systems.
3) Discuss propellants and their criteria of selection.

CHAPTER 11

Packaging Materials Science

11.1. PACKAGING MATERIALS SCIENCE

11.1.1. Introduction

The packaging process is employed to maintain the therapeutic effectiveness of pharmaceuticals as the packed products retain their potency till their consumption. The art and science of preparing the articles for their transport, storage, display, and use is termed **packaging**. A preparation which has been formulated with proper care but its packaging has been done inappropriately, fails to fulfil the purpose. Different formulations are packed in containers of different materials and of various shapes and sizes.

A **package** comprises of the following **components**:

1) **Container:** It encloses the drug, thereby remains in direct contact with the drug. Such a container which is always in direct contact with the drug is an **immediate container**.
2) **Closure:** It seals the container to eliminate oxygen, carbon dioxide, moisture, and microorganisms. A closure prevents the loss of volatile substances, and also the loss of medicament during transport and handling. It is a component of container system, and has no direct contact with the drug.
3) **Carton:** It is made up of cardboard, moulded wood pulp, or expanded polystyrene, and provides secondary protection. It is an outer covering and protects against mechanical and other environmental hazards.
4) **Box:** It is made up of thick cardboard, wood, or any other suitable material, and carries multiples of a product. It provides primary protection against external hazards during transportation and handling.

The **characteristics** of **packaging materials** are:

1) They should provide protection to the materials against environmental conditions (**e.g.,** temperature, humidity, oxygen, and light).
2) They should neither react with the product nor with its ingredients.
3) They should not impart to the product any odour or taste (**e.g.,** certain plastics impart odour to the product).
4) They should bear no toxic property.
5) They should be Food and Drugs Administration approved.
6) They should be tamper-resistant so that the package integrity is protected, thus preventing adulteration, substitution, or any such negligence.
7) They should be useful for packaging equipments and machines.

11.1.2. Objectives of Packaging

The packaging and package labelling have the following objectives:

1) **Physical Protection :** The package provides protection to the product against mechanical shock, vibration, electrostatic discharge, compression, temperature, etc.

2) **Barrier Protection:** A barrier is required to protect the product from oxygen, water vapour, dust, etc. The critical factor in the designing of such package is permeation. To extend the product shelf-life, some packages contain desiccants or oxygen absorbers. In some food packages, atmosphere maintenance is done with respect to modified or controlled atmospheres. Major aim is to sustain the contents clean, fresh, sterile, and safe throughout the shelf-life.

3) **Containment or Agglomeration:** Small objects are kept collectively in a package to sustain efficiency. **For example**, 100 syrups packed in a single box need a less physical effort in handling than 100 single syrups. Liquids, powders, and granular materials require containment.

4) **Information Transmission:** Packages and labels provide information about the usage, transport, recycling, or disposing of the package or product. Pharmaceuticals, food, medical and chemical products need special information stated by the governments. Some packages and labels have track and trace purposes.

5) **Marketing:** Marketers use the packaging and labels of a particular product for convincing the buyers to purchase it. Package graphic designing and physical designing phenomenon are progressing since many years. Marketing communications and graphic design are placed on the package surface and many a times at the point of sale display.

6) **Security:** The security risks of shipment are minimised by packaging. Packages with improved tamper resistance prevent tampering. Such packages also bear tamper-evident features to indicate tampering. Packages are designed such that the risks of package pilferage are reduced. Some packages can resist pilferage and can bear seals indicating pilferage.

   Packages bear authentic seals and security printing indicating that the package contents are not fake. Some packages are fitted with anti-theft devices (**e.g.,** dye-packs, electronic article surveillance tags), which get activated and detected at the exit points. These devices can be deactivated only with specialised tools. This type of packaging minimises loss.

7) **Convenience:** Packages exhibit features aiding in distribution, handling, stacking, display, sale, opening, reclosing, use, dispensing, and reuse.

8) **Portion Control:** Single serving or single dosage packages carry precise quantity of contents to manage usage. Bulk possessions (like salt) are placed in packages of suitable size for individual households. It also supports the inventory control, **e.g.,** by selling one-litre sealed milk bottles, individuals can stop bringing their individual bottles to fill.

11.1.3. Materials Used for Packaging of Pharmaceutical Products

The packaging materials selected should have the following properties:

1) They should protect the preparation from environmental conditions.
2) They should not react with the products.
3) They should be non-toxic.
4) They should not impart any taste or odour to the product.
5) They should not be influenced by adverse manufacturing conditions.
6) They should protect the light-sensitive drugs.
7) They should be easily available, feasible, and economical.

The various types of materials used for packaging of pharmaceutical products are:

1) Glass,
2) Plastic,
3) Rubber,
4) Metals,
5) Fibrous materials, and
6) Foils, films and laminates.

11.1.3.1. Glass

Glass is economical, chemically inert, impermeable, strong, rigid, has FDA clearance, and possesses superior protective qualities; thus, is used for packaging pharmaceuticals. Glass containers are available in various sizes and shapes.

Glass does not get depreciated with time. If a proper closure system is provided, glass serves as an efficient barrier against every element; however, only amber-coloured glass can provide protection against light. The fragile nature and weight of glass are its major **limitations** when used for packaging.

Composition

Glass is composed of **sand**, **soda-ash**, **limestone**, and **cullet**. Sand is pure silica, soda-ash is sodium carbonate, limestone is calcium carbonate, and cullet is broken glass mixed with the batch and serves as a fusion agent for the entire mixture. Glass composition varies and needs to be adjusted specifically for different purposes. Silicon, aluminium, boron, sodium, potassium, calcium, magnesium, zinc, and barium are the cations commonly found in pharmaceutical glassware; while oxygen is the only anion.

Types, Properties, and Applications

Type I – Borosilicate Glass

Borosilicate glass is highly resistant, and a large part of the alkali and earth cations are replaced with boron and/or aluminium and zinc. This glass is more chemically inert in comparison to the soda-lime glass that contains either an insignificant amount or none of these cations. Since glass is a practically inert material, it is used for storing strong acids and alkalis, and all types of solvents. It undergoes a definite and measurable chemical reaction with some substances, especially water.

Type II – Treated Soda-Lime Glass

On storing the glassware in a damp atmosphere or under extreme temperature variations for a few months, the condensed moisture makes the glass surface wet and the salts dissolve out of the glass; this phenomenon is termed **blooming** or **weathering**. In the early stages of this process, fine crystals appear on the glass. The salts that dissolve out of the glass can be washed with water or acid.

Treated soda-lime glass has been de-alkalised or treated to remove their surface alkali and prevent the weathering of empty bottles; this de-alkalising process is termed **sulphur treatment**.

Type III – Regular Soda-Lime Glass

Regular soda-lime glass is untreated and exhibits average or better-than-average chemical resistance.

Type NP – General-Purpose Soda-Lime Glass

General-purpose soda-lime glass is used for non-parenteral products that are meant for oral or topical use.

Different types of glass, their constituents, properties, and uses are enlisted in **table 11.1**:

Table 11.1: Types of Glass, their Composition, Properties and Uses

Types of Glass	Main Constituents	Properties	Uses
Type-1: Borosilicate glass, **e.g.,** Pyrex, Borosil	SiO_2 (80%), B_2O_3 (12%), Al_2O_3 (2%), and Na_2O + CaO (6%)	High melting point to withstand high temperature; resistant to chemical substances; reduced leaching action.	For laboratory glass apparatus, injections, and water for injection.
Type-II: Treated soda-lime glass	Made up of soda lime glass whose surface is de-alkalised or treated with an acidic gas (SO_2) at 500°C and moisture.	Glass surface is resistant to water attack for a definite time period; sulphur treatment neutralises the alkaline oxides on the surface, thus the glass is chemically resistant.	For alkali sensitive products, infusion fluids, blood and plasma, and large volume containers.
Type-III: Regular soda-lime glass	SiO_2, Na_2O, and CaO	Contains high concentration of alkaline oxides and imparts alkalinity to aqueous substances; flakes separate easily; may crack due to sudden change of temperature.	For all solid dosage forms (**e.g.,** tablets, powders), and oily injections; not for aqueous injections and alkali-sensitive drugs.
Type NP: Non-parenteral glass or general purpose soda-lime glass.	–	–	For oral and topical purpose; not for ampoules.
Neutral Glass	SiO_2 (72-75%), B_2O_3 (7-10%), Al_2O_3 (6%), Na_2O (6-8%), K_2O (0.5-2%), and BaO (2-4%)	Softer and can be moulded; good resistance to autoclaving; resistant to alkali-preparations (with pH upto 8); lower cost than borosilicate.	For small vials (<25ml) and large transfusion bottles.
Neutral Tubing for Ampoules	SiO_2 (67%), B_2O_3 (7.5%), $A1_2O_3$ (8.5%), Na_2O (8.7%), K_2O (4%), CaO (4%), and MgO (0.3%)	Melting point is less; after filling the glass ampoules are sealed by fusion, therefore the glass is easy to melt.	Ampoules for injection.
Coloured Glass	Glass + iron oxide	Amber coloured glass; resist radiation from 290 to 400 to 450nm UV visible.	For photosensitive products.

Merits

1) It has superior protective qualities.
2) It is available in various colours (**e.g.,** amber, red, blue, emerald, green, and opal), and most of them are used for ornamental purposes.
3) Amber-coloured glass provides protection against light to those ingredients of a pharmaceutical product which gets chemically deteriorated by UV rays.
4) Red and yellow-green coloured glasses also provide protection to light-sensitive products.

5) Green-coloured glass provides protection against IR rays.
6) Transparent glass allows visual inspection of the products.
7) It does not deteriorate with age.
8) It is heat resistant, thus can undergo heat sterilisation.
9) It can be easily cleaned.
10) It is impermeable.
11) It provides clarity to products.
12) It enables identification of products.
13) It is economical.
14) Glass containers are available in various shapes and sizes.

Demerits

1) It is of fragile and brittle nature.
2) It is heavy in weight and occupies more volume.
3) Its tensile strength is 1/20th that of steel.
4) It cannot undergo operations involving pressure and vacuum.
5) Alkaline glasses impart alkalinity and flakes to the products.
6) Once broken, it cannot be joined back.

11.1.3.2. Plastic

Plastic used as a material for container is composed of thermoplastic polymer. This polymer forms the basic organic structural unit for each plastic type, and is commonly used in medical field. The plastic materials used in medical field are added with a less amount of ingredients; however plasticisers, fillers, antistatic agents, antioxidants, and other ingredients are added in large amounts to some plastic materials used for special purposes. Plastic containers are used because of their light weight, non-breakable nature, low toxicity, and low reactivity with the products (provided they contain fewer amounts of additives).

Materials

Nowadays, there are many plastic resins available to be used for packaging drug products. Some commonly used plastic materials are discussed below:

1) **Polyethylene:** This material, having **high density**, is used in pharmaceutical industries for making containers. Polyethylene serves as an efficient **barrier against moisture**; however, it provides **poor protection against oxygen** and other gases. It remains unaffected by most of the solvents, strong acids and alkalis. Polyethylene has the **drawbacks** of **lack of clarity** and **high permeation rate** of essential odours, flavours, and oxygen; thus its use as a material for container of pharmaceutical preparations is limited.

   Polyethylene's density ranging from 0.91-0.96, directly determines the following **physical characteristics of blow-moulded containers**:

   i) Stiffness,
   ii) Moisture-vapour transmission,
   iii) Stress cracking, and
   iv) Clarity or translucency.

   With increasing density, polyethylene becomes stiffer, less permeable to gases and vapours, less resistant to stress cracking, and has a higher distortion and melting temperature.

2) **Polypropylene:** This polymer material possesses many good properties of polyethylene, thus its use at the current time has increased. Only hot aromatic or halogenated solvents can soften polypropylene, otherwise it does not stress-crack

under any conditions. It is **resistant** to **strong acids**, **alkalis**, and most **organic materials**. It has a **high melting point**, thus can be used for boilable packages and for sterilisable products. It serves as an efficient **barrier against gas** and **vapour**. Polypropylene has a **drawback** of **lack of clarity**; however, this can be improved by making its walls comparatively thinner.

3) **Polyvinyl Chloride (PVC):** Natural PVC is **inexpensive**, **clear**, and **stiff**; however it can be made soft by adding plasticisers. Stabilisers, anti-oxidants, lubricants, and colourants can also be added. Pure form of PVC is used rarely. PVC can be **easily processed**. Containers of PVC have extreme **clarity**, are **rigid**, serve as an efficient **barrier against oxygen**, and thus overcome the drawbacks of polyethylene. The major **disadvantages** of PVC are that it has **poor impact resistance**; on overheating it starts degrading at 280°F, giving highly corrosive degradation products; and on exposure to heat or UV rays, it turns yellow, which can be prevented by adding a stabiliser.
4) **Polystyrene:** It is an **inexpensive**, **clear**, and **rigid** plastic material. Polystyrene containers are in use since many years by the pharmacists for dispensing solid dosage forms. It is **not suitable for dispensing liquid products**. Its water vapour transmission is higher than that of high-density polyethylene; its **oxygen permeability** is also **high**; and it is **resistant** to **acids** (except the strong oxidising acids) and **alkalis**. The **disadvantage** of polystyrene is that on exposure to certain chemicals, it gets **cracked**, thus is preferred only for packaging dry products.
5) **Polyethylene Terephthalate (PET):** It is a condensation polymer, formed when terephthalic acid or dimethyl terephthalate reacts with ethylene glycol in the presence of a catalyst. It has exceptional **impact strength**, and also serves as a **barrier against gas** and **aroma**; thus it is preferred for packaging cosmetics and mouth washes, and other products which consider strength, toughness, and barrier important.

Properties
1) It can be remoulded.
2) It has flexibility.
3) It provides transparency.
4) It provides elasticity.
5) It has permeability.

Applications
1) It is used as a lining for tanks and vessels and as coatings on stirrers and fans.
2) Plastic cements are used for spaces between acid-resistant tiles and bricks.
3) Transparent plastic guards are used for moving parts of machinery and asepsis screens.
4) Nylon and PVC fibres are woven into filter clothes.
5) Rigid or semi-rigid mouldings are used for tanks, pipes, ducts, and other similar items.
6) Unbreakable plastics are used for slightly flexible funnels, buckets, and jugs.

Merits
1) It has a low thermal and electrical resistance.
2) It is resistant to weak mineral acids.
3) It remains unaffected by inorganic salts.
4) It is resistant to slight pH changes.

Demerits
1) It has a low mechanical strength.
2) Its expansion rate is high.

11.1.3.3. Rubber

Rubber is either used as such or as lining materials for plant construction. Rubbers are categorised into:

1) **Natural Rubber:** This naturally occurring polymer is obtained from rubber trees in the form of latex. It is a common **example** of an **elastomer**, which is a substance that can be **easily stretched**, but quickly move to its original form on releasing.

   Natural rubber is further categorised into:

   i) **Soft Rubber:** It is also a naturally occurring polymer of monomeric isoprene (C_5H_8). Thus, rubber is a **polyisoprene** with molecular formula $(C_5H_8)_n$. Soft rubber when added with carbon black yields **hardened rubber**, which is used for making tyres, tubes, and conveyor belts. Soft rubber is also used as a lining material for plants as it gets easily bonded to the steel.

   ii) **Hard Rubber:** It is formed by the process of **vulcanisation**, in which soft rubber is mixed and warmed with sulphur, and set into a given shape. The sulphur then combines with the polymeric chains of rubber and cross-links between them, thus soft rubber attains the shape in which it was set. **Soft rubber with 25% or more sulphur** is termed hard rubber. Hard rubber due to its hardness and strength is used for making gloves, bands, tubes, and stoppers.

2) **Synthetic Rubber:** This rubber is **resistant** to **oxidation**, **solvents**, **oils**, and other chemicals. Due to these superior properties, synthetic rubber is more important than natural rubber. **Examples** of some synthetic rubbers, their properties, and applications are given in **table 11.2**:

Table 11.2: Types of Synthetic Rubber

Synthetic Rubber	Properties	Applications
Neoprene (polychloroprene)	Does not burn readily like natural rubber; is stable at high temperature.	Insulating material in electric cables, conveyor belts in coal mines, making hoses in the transportation of oils, rubber stoppers, cap-liners, dropper assemblies for eye drops, etc.
Nitrile rubber	Resistant to oil and solvents.	Non-latex gloves for healthcare industries, automotive transmission belts, hoses, O rings, gaskets, oil seals, V belts.
Butyl rubber	Resistant to mineral acids and alkalis, and concentrated acids (except nitric and sulphuric acids).	Closures of freeze-dried product containers because of their low water vapour permeability.
Silicon rubber (polysiloxanes)	Resistant to high and low temperatures, and also to the attack of aliphatic solvents, oils, and greases.	Tubing for dialysis and transfusion equipment, bellows for artificial respirators, and catheters.
Polyisoprene	Stable at high temperature; is translucent and flexible.	Preparation of stoppers and closures.

Applications

1) Rubber is used in pharmaceutical industries for making stoppers, cap liners, and bulbs for dropper assemblies.
2) Rubber stopper is used for multi-dose vials and disposable syringes. More commonly used rubber polymers are natural, neoprene, and butyl rubber.

Merit: Soft rubber provides resistance against dilute mineral acids, dilute alkalis, and salts.

Demerit: Soft rubber can be attacked by oxidising media, oils, and organic solvents.

11.1.3.4. Metals

Tin

It is a malleable, ductile, highly crystalline, silvery white coloured, and a non-reactive metal. Tin acts as a catalyst when oxygen is in solution.

Advantages

1) It is highly resistant to chemical attack.
2) It readily coats several metals, **e.g.,** tin-coated lead tubes combine the softness of lead with the inertness of tin and so it was earlier used for packaging fluoride toothpastes.

Disadvantages

It is the most expensive metal among lead, aluminium, and iron.

Uses

1) Tin containers are used for storing food materials, **e.g.,** tin-coated milk powder containers.
2) Pure tin ointment tubes are used for packaging some eye ointments.

Aluminium

Advantages

1) It is a light metal, thus its shipment cost is less.
2) It provides attractiveness of tin at a lower cost.
3) Its surface reacts with atmospheric oxygen to form a thin, tough, coherent, and transparent coating of oxide to prevent the oxidation of metal.

Disadvantages

If any substance reacts with this oxide coating, corrosion occurs, **e.g.,** products of high or low pH and some complexing agents can cause corrosion by reacting with the oxide coating. This corrosion process leads to evolution of hydrogen.

Uses

1) It is used for making ointment tubes and screw caps.
2) Aluminium strips are used for strip-packaging of tablets, capsules, etc.
3) Aluminium containers are lacquered from inside to prevent its reaction with the contents.

Iron

Advantages

Iron as such is not used for pharmaceutical packaging, but large qualities of tin-coated steel called ‘tin’, combines the strength of steel with the corrosion resistance of tin.

Disadvantages

If an aqueous liquid penetrates a pinhole or other fault in the tin layer, a short-circuited galvanic cell is set-up; and the resultant intense chemical reaction causes rapid corrosion of underlying steel. Thus, the tin surface is lacquered.

Uses

Iron is used for fabrication of milk containers, screw caps, and aerosol cans.

Lead

Advantages

1) It is of lowest cost of all the metals used in pharmaceutical containers.
2) It is a soft metal.

Disadvantages

If taken internally, lead poisoning may occur; thus, the lead containers and tubes should have an internal lining of inert metal or polymer.

Uses

The lining lead tubes are used for fluoride toothpastes.

11.1.3.5. Fibrous Materials

Paper and cardboard are materials of cellulose fibres. They are used in primary as well as secondary packaging of pharmaceutical products. **Cardboard cartons** are used to provide protection to the primary pack and also a suitable area for decorative design and mentioning the information required by regulatory authorities. **Cartons** are convenient for stacking and can bear information leaflets. **Cards** can also be used as dividers or trays inside secondary packs. Thicker, **corrugated cardboard** and **fibreboard** are used for shipping cartons as they are subjected to greater mechanical stresses than the ordinary cartons.

Paper is used in most of the packs as the label on the container and as the patient information leaflet. The paper is usually printed and coated as a part of a laminate or adhesive backed. In sterile sachets for syringes and dressings, paper is a constituent of the primary pack. **Sacks** made from thick paper and lined with polyethylene are used as the primary pack for some bulk powders.

11.1.3.6. Foils, Films, and Laminates

Foils, films, and laminates are the major types of thin and flexible packaging. **Foils** are thin metal sheets of less than 100 μm thickness; **films** are non-fibrous and non-metallic sheets of less than 250 μm thickness; and **laminates** are formed by bonding two or more film or foil webs together.

These are described as follows:

1) **Foils: Aluminium** is more commonly used as foils. Foils have excellent barrier properties. With the help of modern technology, they are produced to 10μm thickness; however, pinholes may form and deteriorate the barrier properties of foils, if their thickness is below 25 μm. Foils are either used alone or in combination with other materials in laminates to provide an attractive and reflective surface. Thicker aluminium sheets are used in rigid packaging, such as the trays of blister packs (where they are formed by cold-moulding) that are becoming an alternative to plastic trays.

   Another development, in which aluminium is used as part of a thin film, is **vacuum dis-positioning** wherein a thin aluminium film is sprayed on a polymer substrate (like polyester). This imparts some barrier properties on the polymer, although not as good as a proper aluminium foil. This film has a shiny aluminium coating on one side and can be printed on the other.

2) **Films:** The packaging films used before were of regenerated cellulose and are now called **cellophane**, which is an attractive, transparent film that can be coloured and printed, and is used as an outer wrap. Cellophane provides an efficient barrier against vapours, but not against moisture, so the cellophane is coated with various substances. This coated cellophane is used for heat-sealing purposes. The coated and non-coated cellophane are widely used in pharmaceutical, food, and other types of packaging.

   At the present time, many other plastics (**e.g.,** PVC, LDPE, polypropylene, and polyester) are used to make films that can be used as outer wraps for other packs. Plastics like **thicker grades of PVC** are suitable for thermo-moulding into trays which can be used as part of a blister pack or to hold primary packs within a secondary pack (**e.g.,** a tray holding several glass ampoules inside a cardboard carton). Plastic films have limited beneficial properties, thus their use as the sole packaging material is still restricted. Films with desired properties can be selected and combined in a laminate to provide multiple functions.

3) **Laminates:** They are made by bonding the layers with adhesive; but if the product is a liquid or semi-solid and is in close contact with the laminated walls of a sachet, the adhesive can migrate into the product through the inner layers of the laminate. Laminates are used to combine the properties of individual foils and films. To fulfil all the pack requirements, a laminate may have many layers, thus a sachet for a tablet may also have multiple layers (from the outside in), i.e., a layer for decoration and information, a layer for mechanical protection, a layer for light and moisture barrier, and a heat sealer layer. Laminates are widely used in blister packs, bubble packs, strip packs, pouches, sachets, and other types of flexible packs.

11.1.4. Types of Packaging

Packaging comes in many different types. **For example,** a **transport package** or **distribution package** are the shipping containers used for transporting, storing, and handling product or inner packages. A **consumer package** is the one that reaches a consumer or household directly. Packaging depends on the type of product being packaged (medical device packaging, bulk chemical packaging, over-the-counter drug packaging, retail food packaging, military material packaging, pharmaceutical packaging, etc.). Packages are categorised as follows by layer or function:

1) Primary packaging,
2) Secondary packaging, and
3) Tertiary packaging.

A product requires all the three packaging types as per the intended purpose.

11.1.4.1. Primary Packaging

The material used in primary packaging is the first to surround the product and hold it. This type of packaging is the smallest unit of distribution or use. It is always in direct contact with the product.

Materials Used in Primary Packaging

Glass is the major primary packaging material. The different types of materials used for primary packaging are discussed below:

1) **Type-I Glass:** It is employed as glass ampoules and vials for fluids for injection:
   i) **Ampoules**
      a) One point cut ampoules,

b) Flat based and constricted neck ampoules,
c) Flame cut ampoules,
d) Closed ampoules, and
e) Ampoules with colour break band and identification bands.

ii) **Tubular Vials:** These are clear or amber-coloured, neutral, type I glass vials.

Types of Glass Containers

i) **Bottles:** Amber metric medical bottles or ribbed (fluted) oval bottles are used in the dispensaries. Their size ranges from 50-500ml. Various oral medications are packed in amber metric medical bottles; while liniments, lotions, inhalations, and antiseptic solutions are packed in ribbed oval bottles.

ii) **Dropper Bottles:** These bottles used for packaging ear, nasal, and eye drops are hexagonal-shaped, amber-coloured, and fluted on three sides. These are additionally fitted with a closure kit comprising of a cap, rubber teat, and a dropper. Dropper bottles are available in capacity of 10-20ml.

iii) **Jars:** These are used for packaging powders and semi-solid preparations (like ointments and pastes). Jars are cylindrical-shaped, have a wide mouth, and are made up of clear or amber-coloured glass. The size of jars ranges from 15-500ml.

2) **Plastics:** These materials are preferred for product container and also as a secondary packaging. These are classified into **thermosets** and **thermoplastics**. Plastics can be used for making several types of pack like rigid bottles for tablets and capsules, squeezable bottles for eye drops and nasal sprays, jars, flexible tubes, and strip and blister packs.

Merits

i) They are flexible and hard to break.
ii) They have a low density and are light weighted.
iii) They are inexpensive.

Demerits

i) They are chemically less inert than type-I glass.
ii) They are less impermeable to gas and vapour than glass.
iii) They carry electrostatic charge which attracts particles.

Examples

i) **Polyethylene:** It is available as high and low density polyethylene. Low Density Poly Ethylene (LDPE) is used for making squeeze bottles, while High Density Poly Ethylene (HDPE) is used for making bottles for solid dosage forms. HDPE shows less permeability to gases and greater resistant to oils, chemicals, and solvents.

ii) **Polyvinylchloride (PVC):** It is a rigid packaging material that forms the major component of intravenous bags.

iii) **Polypropylene:** It does not crack when flexed. It is used for making closures, tablet containers, and intravenous bottles.

iv) **Polystyrene:** It is used for making jars to pack ointments and creams having low water content.

3) **Metals:** Various metals, **e.g.,** tin-plated steel, mild steel, stainless steel, tin-free steel, and aluminium and its various alloys are used as packaging material. Metal has properties of being strong, opaque, impermeable to moisture, gases, odours, light, bacteria, etc., and resistant to high and low temperatures. The metals used for packaging purpose are as follows:
   i) **Tin:** It has the most chemically inert nature. Tin as a packaging material for many products is reliable, compatible, and provides a good appearance to the product.
   ii) **Tinplate:** It is a steel structure on one or both sides of which a thin layer of tin is deposited. This layer prevents the product from getting corroded.
   iii) **Aluminium:** It is a light-weighed metal, which can be easily casted in any shape. The thick, rigid closures are used for making cans or aerosol containers, whereas the thin flexible material is used for making closure of bottles or thermoforms. Blister packaging is done using a hard tamper (where tablet is pushed through the material). Tubes are internally lacquered, wax coated, and latex lined.

4) **Plastic Tubes:** The size of flexible plastic tubes ranges between 19-50mm in diameter, up to 300ml in volume, 2-8mm orifice (3mm is considered standard), and around 400-500µ of tube wall thickness.

5) **Laminated Tubes:** These tubes have multiple layers of aluminium foil or nylon or polyester which provides protection against oxygen and moisture, prevents loss of odour, and makes the surface glossy that improves printing quality. These are transparent and stretched polypropylene. PET tubes with dispenser caps are available. Caps are available in variety of designs (like conical or flip-top) for an appealing look.

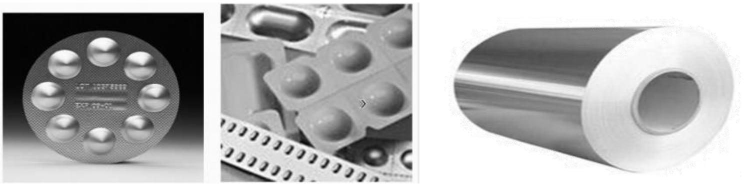
6) **Bulk Containers:** These hold the bulk drug and active pharmaceutical ingredients. They are available as packages, bags, and drum liners manufactured by following cGMP (Current Good Manufacturing Practices). cGMP compliance in terms of quality systems, complete traceability, change control, SOPs, and pharmaceutical grade housekeeping are recorded in the drug master file. LDPE, foil laminate bags, and drum liners come in many sizes and designs.


Bulk Container

7) **Blister Packs:** These are unit dose packs for pharmaceutical tablets, capsules, or lozenges. The two principal **components** of blister packs are:
   i) A base-like web that creates a cavity to fit the product inside, and
   ii) The lidding foil that dispenses the product out of the pack.


Types of cavity forming into a base web sheet are:

i) **Thermoforming:** In this type, a plastic film or sheet from the reel is unwound, and directed towards the blister line by passing through the pre-heating station. These pre-heating upper and lower plates have a temperature sufficient enough to soften the plastic and make it mouldable.



ii) **Cold Forming:** In this type, an aluminium-based laminate film is pressed through a mould using a stamp. Thus, the aluminium film gets stretched and takes the desired shape. The cold form foil blisters have the **advantage** that aluminium provides almost complete protection against water and oxygen, thus prolonging the product expiry date. The cold form foil blisters have the **disadvantages** that their production speed is slower than thermoforming, the package is non-transparent, and the blister card is larger in size.

Examples

a) Aluminium foils for blister packing.
b) Aluminium foils used for blister packing of pharmaceutical products like tablet, capsules, etc.

8) **Strip Package:** It is used for packing tablets and capsules. It is made up of cellophane, polyester, polyethylene, polypropylene, and polyvinyl chloride. A strip package is produced by feeding two webs of films (which are flexible and heat sealable) through a heated crimping roller. The product is allowed to reach the pocket formed prior to the formation of the final set of seals. The obtained continuous strips of packets are cut into desired number and length.

2×5 Pill Pack

9) **Closures:** These are used for facilitating the opening and closing of containers. Container should be closed properly to prevent:

i) Spilling or volatilisation of components,
ii) Product contamination from dirt, microbes, or insects, and
iii) Product deterioration by the environmental factors like moisture, oxygen, or carbon dioxide.

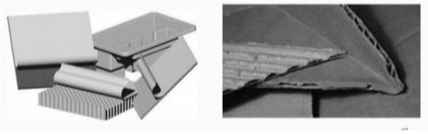
Materials Used for Making Closures: Cork, glass, plastic, metal, and rubber are used to make closures of containers used to pack pharmaceutical products.

11.1.4.2. Secondary Packaging

The materials employed in secondary packaging covers the primary package. This type of packaging forms an outer wrapping to store, transport, inform, display, and protect the product. An **example** of a secondary package is decorated cartons.

Materials Used

1) **Paper:** This is used as a flexible wrap for products and sometimes as a closure material for jars. Generally, the paper materials are applied with a liner either as a laminate or coating.



2) **Pharmaceutical Corrugated Fibreboard:** This paper-based material having fluted corrugated sheet and one or two flat linerboards is used for manufacturing corrugated boxes.
3) **Carton:** This is used for packing food, pharmaceuticals, hardware, and other products. Folding cartons are combined into a tube at the manufacturer and shipped flat (knocked down) to the packager.

Symbols on Packages and Labels

Several symbols used nationally and internationally for package labelling have been standardised for product certifications, trademarks, proof of purchase, etc., identification code.

Fragile

This way-up

Keep away from Sunlight

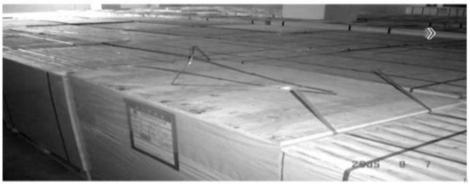
Keep away from Water

Do not use Hand Hooks

Do not clamp as indicated

11.1.4.3. Tertiary Packaging

Tertiary packaging is suitable for bulk product handling, warehouse storage, and transport shipping. These are commonly available as palletised unit load for tightly packing into containers.



11.1.5. Factors Influencing Choice of Containers

The choice of containers is affected by the following factors:

1) **Compatibility and Safety Concerns:** The administration route of drug product and the dosage form nature (**e.g.,** solid, semi-solid or liquid based) influences the compatibility and safety of packaging materials.

The drug samples selected for stability studies should be packaged in the same manner as they will be for marketing and distribution.

i) **Compatibility of the Packaging Material with the Formulation:** The packaging material should not produce any adverse effect on the formulation by undergoing chemical reactions, by leaching of packaging materials, by absorption or adsorption.

ii) **Compatibility of the Formulation with the Packaging Material:** The formulation should not affect the properties and/or the protective functions of the packaging materials.

2) **Degree of Protection Required:** Since the stability of active pharmaceutical ingredients is lowered when they are formulated into dosage forms, they may decompose under the influence of excipients, moisture, oxygen, light, temperature, the formulation process, etc. The degree of protection required depends on the formulation; **for example**, the packaging materials used for photosensitive products should provide protection against light. The same is also applicable to hygroscopic, easily oxidised drug products and so on.

3) **Cost:** To make the drugs affordable, cost effectiveness of the packaging materials should be considered. However, the manufactures should not compromise with the formulation integrity while reducing its cost. Instead, they should find a better way to reduce cost which can also reduce the wastage of packaging materials.

4) **Convenience:** The packaging materials for a dosage form should be selected by considering its size, weight, method of opening or reclosing during administration for patient convenience.

5) **Legibility:** The legibility of printing should be considered while choosing and designing a package as it serves as a source of information and identification of the formulation.

11.1.6. Legal & Other Official Requirements for Containers

Different specifications are required for parenteral, non-parenteral, pressurised and bulk containers and for those made of glass, plastic, and metal. In each case, the package and closure system should be effective for the particular product for which it is intended. The packaging materials should neither physically nor chemically interact with the finished product to alter its strength, quality, or purity beyond the specified standards. Specifications and test methods for light resistant, tightly closed, and four types of glass containers are provided in the compendium. These specifications and test methods are designed for containers based on the tests performed on the product in the container. The **following features** should be considered while developing container specifications:

1) The properties of container tightness,
2) Moisture and vapour tightness regardless of container construction,
3) Toxicity and chemical/physical characteristics of materials to be used in container construction,
4) Physical or chemical changes of container when kept in prolonged contact with the product, and
5) Compatibility between the container and product.

As per the Good Manufacturing Practices, stability data should be submitted for the finished dosage forms in the container closure system in which it is to be marketed.

Label Control

The production control issues a packaging form bearing the product name, item number, lot number, number of labels, inserts, packaging materials to be used, operations to be performed, and the quantity to be packaged. The supervisor of label control receives a copy of this form, and counts out the required number of labels. The labels during the packaging operation may get damaged, thus they are issued in numbers more than actually required; however, all the labels should be accounted for at the end of the operation, and unused labels should be accounted for before their destruction.

11.1.7. Closures

A container's most vulnerable and critical component is the closure with respect to the stability and compatibility with the product. A closure should effectively prevent the contents from escaping and the access of substances into the container. A simplest closure system should retain or contain the contents.

Safety and security concerns should be considered to prevent hazards due to leakage, seepage, spillage, pilferage, exposure to wrong persons (**e.g.,** children), or loss of quality, purity, etc., by some source of contamination, impurity, etc.

Closures form a part of the overall design of the package, enhance the product appearance, act in a functional role during use (**e.g.,** reclosables), or assist in the product administration (**e.g.,** aerosol valve). They also play a protective/preventive role by controlling ingress (odours, taints, moisture, oxygen, carbon dioxide, mould, bacteria, etc.) and egress (loss by evaporation, loss of moisture, perfume, flavourings, volatiles, etc.).

Closures should be clean and inert so that they do not affect the product by absorption/adsorption, prevent the interaction or migration of substances into the product, and provide protection against any hazard during the product shelf-life, **e.g.,** climatic, chemical, biological, and mechanical hazards. Not only the closures cover the primary or immediate pack, they are also important to the secondary pack.

For example, a fully taped (H-seal) and glued case is more robust than a partially taped case, thus a better closuring system makes a more rigid unit that more effectively withstands transit and stacking.

Basis of Closure Systems

Closures may be achieved by the following basic means either alone or by the combination of two or more:

1) **Pressure**
    i) **Mechanical Pressure: For example,** the top and side internal pressure on a container finishes ideally involving a seal between a fairly rigid and a more resilient material. It includes screw closures, plug seals, lever lids, etc., to create an interference fit between the two materials.
    ii) **Atmospheric Pressure (Pressure and Vacuum):** A similar mechanical seal occurs, but this is initially achieved by a differential pressure (**e.g.,** vacuum sealed tin).
2) **Temperature**
    i) **Welding/Heat Sealing:** It involves direct and indirect application of heat, under pressure, for a given time (dwell) followed by a cooling period, so that two materials bound together.
    ii) **Electrical: For example,** ultrasonic, high-frequency/radio frequency, impulse, and induction sealing; basically a modification of the heat seal process.
3) **Adhesion:** This is achieved by aqueous solvent, hot melt, etc., adhesives or self-adhesives, cold seal materials.

Closure Designs

1) **Threaded Screw Cap:** It is made up of metal (tinplate or aluminium) or plastics (both thermoplastic and thermosetting materials). The threads of the screw cap (when applied on the bottle) engage with the corresponding threads moulded on the bottle neck. When the screw cap is applied, it overcomes the sealing surface irregularities and provides physical and chemical protection to the contents.

Figure 11.1: Threaded Screw Cap

Figure 11.2: Threaded Screw Cap Bottle

2) **Lug Cap:** It is used for both normal atmospheric-pressure and vacuum-pressure closing. Lug cap is similar to the threaded screw cap and operates on the same principle. It is an interrupted thread (and not a continuous thread) on the glass finish. A lug on the cap sidewall is engaged and the cap is drawn down to the sealing surface of the container. Unlike the threaded closure, it requires only a quarter turn.

Figure 11.3: Lug Cap

Figure 11.4: Crown Caps

2) **Crimp-on/Crown Cap:** This cap is used as a crimped closure for beverage bottles and has remained unchanged for more than 50 years.

3) **Roll-on Cap:** It can be sealed securely, opened easily, and resealed effectively. The roll-on closure requires an easy-to-form material, such as aluminium or other light-gauge metal. Re-sealable, non-re-sealable, and pilfer proof types of the roll-on closure are available for use in glass or plastic bottles and jars.

Figure 11.5: Roll-On Closures

Figure 11.6: Pilfer Proof Closures

4) **Pilfer-Proof Screw Cap:** It is similar to the standard roll-on closure except that it has a greater skirt length that extends below the threaded portion to form a bank fastened to the basic cap by a series of narrow metal bridges. On removing the pilfer-proof closure, the bridges break and the bank remains in place on the container neck. The closure can be easily re-sealed. The detached band indicates that the package has been opened. The torque is necessary to remove the cap.

5) **Rubber Stopper:** Rubber polymers (like natural, neoprene, and butyl rubber) are used for making stoppers, cap liners, and bulbs for droppers. Rubber stopper is used for multiple-dose vials and disposable syringes.

6) **Other Metal Closures for Glass and/or Plastics:** The foremost metal closure in this category is the **crown closure** (beer bottle), the **foil heat seal** (for yoghurt pots), or the **induction sealed diaphragm**. The **crown cork closure** is a tinplate shell containing a wad/facing. This may be conventional, polythene or a flowed-in compound. Its application works on the principle that top pressure is applied first, followed by the application of crimping action. Some other types of metal closures are:
   i) **Metal Lever Cap (Narrow Neck Mineral Bottle):** It can be resealed but is being replaced with flavour-lock type closures.
   ii) **Centre Pressure Cap:** It has a press cap centre for cap removal and press cap sides for retention. It is used on glass jars but is mainly used on metal drums.
   iii) **Metal Vacuum Seal:** It is top sealing disc plus rubber or plastic seal that is held on by a safety band ring (as used on jars of paste). The cap is crimped under the neck ring (as in jam, pickles, etc.). Omnia (continuous beading) and Gerda (perforated beading) are more rigid tinplate closures applied by a side seal on the neck by a rubber ring or flowed-in compound.

11.1.8. Stability Aspects of Packaging Materials

Medicinal products are provided protection against moisture, oxygen, light, and chemicals. The International Conference on Harmonisation (ICH) implemented guidelines in 1999, which are now strictly followed during the stability testing of new drug substances. The actual conditions used for the ICH guidelines were based on years of development work using forced degradation studies or stress testing. These guidelines have standardised stability testing and package determination. However, there are still some limitations to the current ICH testing. These guidelines were developed for climatic zones I and II, thus they do not meet the requirements of other climatic zones.

Pharmaceutical customers select the appropriate packaging based on the ICH stability studies of the packed product. Some, however, fail to select optimum packaging as the stability becomes only a confirmatory test for the selected packaging material.

The stability studies do not give a quantitative understanding of the cause and conditions of tablet failure. Moreover, there are little chances that the parameters interact among themselves.

Forced Degradation and Stress Testing

No regulatory practical and scientific guidelines are available that describe the method of stress testing as a guide for the pharmaceutical scientists. Stress testing and accelerated testing, although different, are often used synonymously.

The ICH has defined **accelerated testing** as the "studies designed to increase the rate of chemical degradation or physical change of an active substance or drug product using exaggerated storage conditions as part of the formal, definitive storage program".

These data are used in long-term stability studies, to assess long-term chemical effects at non-accelerated conditions, and to evaluate the impact of short-term excursions outside label-storage conditions that might occur during shipping.

The ICH has defined **stress testing** as the "studies being carried out to elucidate the intrinsic stability of the drug substance". Such testing is a part of the development strategy and is carried out under more severe conditions than those used for accelerated testing. From regulatory viewpoint, stress testing or forced degradation study is a scientific tool to understand stability issues, and is characteristically predictive in nature; while, the accelerated testing aims to maintain stability at a pre-set condition, identify the conditions under which the product becomes unstable, and identify the moisture-, gas-, and light-barrier properties in the protective packaging.

The actual dosage form is evaluated in an open-dish environment, instead of the solid oral dose as part of a set of packaging materials. The dosage form is tested under different conditions to determine the critical characteristics, which further determine the product shelf-life. An evaluation of the test data along with a blister cavity model, results a recommendation for the best material specific to that dosage form.

Three batches of dosage forms are studied under different environmental conditions to obtain a more precise understanding of the following:
1) Hygroscopic tendency,
2) Dehydration tendency (if needed),
3) Degradation tendency (physical and chemical),
4) Effect on drug release properties,
5) Effect on hardness,
6) Photosensitivity as a function of RH and temperature,
7) Gas liberation tendency, and
8) Dimensional aspects.

When these properties have been evaluated, an exact determination is made to decide the oral dose characteristic that was highly sensitive to the varying environmental conditions. Based on this determination, the blister configuration for the solid oral dose is moulded, and the maximum amount of moisture transmission is determined to make appropriate material selection. All the polymers become thin on thermoforming, thus a critical understanding of the thinning characteristics of various polymers in relation to the cavity design through a software package using cavity-forming parameters is critical to optimise the barrier properties of the blister structure for the specific application.

Based upon the test data and the blister cavity design work, a recommendation is made regarding the appropriate Moisture-Vapour Transmission Rate (MVTR) and the packaging material.

11.1.9. Quality Control Tests

The evaluation of package helps in determining the physicochemical interactions that might occur between the product and the package. The evaluation parameters identify, characterise, and monitor these interactions to achieve a safe, unadulterated, stable, and efficacious product. An ideal package should be inert and should have a maximum shelf-life. Any defects in packaging material lead to contamination of the drug products and also reduce their therapeutic efficacy.

The various quality control tests performed for different packaging material are discussed below:
1) **Glass Containers:** The following tests are performed for glass containers:
    i) **Powdered Glass Test:** The selected glass containers are washed, dried, crushed, sieved, again crushed, and finally sieved through a nest of sieves. The amount

retained on the sieve is transferred to a closed container and stored in desiccators. After removing iron particles, the glass sample is washed with acetone and dried. 10gm of this dried sample is mixed with distilled water in a conical flask and autoclaved for 30 minutes at 121°C temperature. Water is decanted into another container and the washings of the sample made using distilled water are added to the residual powdered glass. The pooled sample is titrated against 0.02N sulphuric acid using methyl red indicator.

ii) **Water Attack Test:** Intact glass containers are filled with distilled water (up to 90% of its volume) and autoclaved for 30 minutes at 121°C temperature. Within 60 minutes of autoclaving, the contents are titrated against 0.02N sulphuric acid under warm conditions using methyl red indicator. Blank titration is performed in the similar manner but without autoclaving. The actual volume consumed (sample-blank) should not exceed the indicated value mentioned in **table 11.3** for the glass concerned.

Table 11.3: Glass Types and Their Test Limits

Types of Glass	General Description	Type of Test	Limit Size (ml)	Limit (ml of 0.20 N)
I	Highly resistant borosilicate glass	Powdered glass	All	1.0
II	Treated soda lime glass	Water attack	100 or less, Over 100	0.7, 0.2
III	Soda lime glass	Powdered glass	All	8.5
IV	General purpose soda lime glass	Powdered glass	All	15.0

iii) **Arsenic Test:** This test is performed on glass containers used for aqueous parenteral products. The inner and outer surface of the containers is washed with fresh distilled water for 5 minutes. 50ml sample is pipetted out into the flask of 10ml solution from the combined contents of all ampoules. 10ml HNO_3 is added to dryness on the water bath. The residue is dried in an oven for 30 minutes at 130°C temperature. On cooling, 10ml hydrogen molybdate reagent is added, swirled to dissolve, bath under water bath, and refluxed for 25 minutes. The contents are cooled to room temperature and the absorbance is determined at 840nm. The same procedure is repeated using 10ml hydrogen molybdate. The test solution absorbance should not exceed the absorbance obtained by repeating the determination using 0.1ml of arsenic standard solution (10ppm) in place of test solution.

iv) **Thermal Shock Test:** The samples are placed in upright position in a tray, which is immersed in hot water for a specified time and then transferred to cold water bath. The temperature difference between hot and cold water is typically 45°C. Any cracks or breaks before and after the test are examined carefully. The amount of thermal shock a bottle can withstand depends on its size, design, and glass distribution. Small bottles can withstand a temperature difference of 60-80°C and 1 pint bottle can withstand 30-40°C temperature difference.

v) **Internal Bursting Pressure Test:** American glass research increment pressure tester is used. The test bottle is filled with water and placed inside the apparatus chamber. A scaling head is applied and the internal pressure is automatically raised by a series of increments each held for a definite time. The bottle can be checked to a pre-selected pressure level and the test is continued till the container bursts.

- vi) **Leakage Test:** Drug filled container is placed in a container filled with dye coloured solution which is at high pressure than the pressure inside the glass container; thus, the coloured solution enters the container through any crack or breakage that might be present.
- vii) **Annealing Test:** The sample is examined using polarised light either in a polariscope or strain viewer. The strain pattern is compared against standard discs or limit samples.
- viii) **Vertical Load Test:** The container is placed between a fixed platform and a hydraulic ramp platform that is gradually raised so that a vertical load is applied. The load is registered on pressure gauge.

2) **Plastic Containers:** The following tests are performed for plastic containers:
   - i) **Leakage Test:** 10 randomly selected containers are filled with distilled water, sealed, and kept inverted for 24 hours at room temperature. The containers are considered to pass the test if no sign of leakage from any of the containers is noticed.
   - ii) **Collapsibility Test:** This test is performed on containers which are squeezed to remove the contents. A container when collapsed inwards during use should yield at least 90% of its nominal contents at the required flow rate at ambient temperature.
   - iii) **Transparency Test:** The prepared 16-fold dilution of a standard suspension should give an absorbance value of 0.37-0.43 at 640nm. Five empty containers are filled to their nominal capacity with suspension and viewed. The view through the containers should be the same as compared with the container filled with water.
   - iv) **Water Vapour Permeability Test:** Five containers are filled with nominal volume of water and heat sealed with aluminium foil-polyethylene laminate or other suitable seal. Each container is accurately weighed and left undisturbed for 2 weeks at a relative humidity of 60 ± 5% and a temperature between 20-25°C. After 2 weeks the containers are re-weighed, and the loss in weight in each container should not be more than 0.2%.
   - v) **Physicochemical Tests:** These tests determine the physical and chemical properties of plastics and their extracts. The following tests are performed after the extraction process:
     - a) **Non-Volatile Residue:** This test measures the solubilised organic/inorganic residue (should not be more than 15mg) in extraction media.
     - b) **Heavy Metals:** This test measures the presence of metals such as lead, tin, and zinc.
     - c) **Residue on Ignition:** This test is performed when the non-volatile residue is more than 5mg.
     - d) **Buffering Capacity:** This test measures the acidity or alkalinity of the product.
   - vi) **Compatibility Test:** The packaging material and its components should be compatible with the dosage form to prevent leaching. This is tested with mass spectrometry, liquid chromatography, LC/MS, and GC/MS.
   - vii) **Protection Test:** Light-resistant containers are evaluated by the light transmission test and the moisture-resistant containers are evaluated by the water vapour permeation test.

viii) **Clarity of Aqueous Extract:** Unlabelled, unmarked, and non-laminated portions from suitable containers are randomly selected. These portions are cut into strips (having total surface area of $20cm^2$), and washed with distilled water for about 30 seconds to remove extraneous matter. In each case, the water is thoroughly drained off. The processed sample is taken in a flask that was cleaned with chromic acid mixtures and washed with several portions of distilled water. 250ml of distilled water is also added to the flask, which is then covered and autoclaved for 30 minutes at 121°C temperature. Blank determination is performed using 250ml distilled water. The contents are cooled after autoclaving and the extract is examined. It should be colourless and free from turbidity.

ix) **Transparency Test**

a) **Standard Suspension Preparation:** 1gm hydrazine sulphate is dissolved in 100ml water and set aside for 6 hours. 25ml of this solution is added with 25ml of 10%w/v hexamine and set aside for 24 hours.

b) **Test Solution Preparation:** Sample is prepared by 16-fold dilution of the standard suspension. Five empty containers are filled to their nominal capacity with suspension and viewed. The view through the containers should be the same as compared with the container filled with water. The absorbance value measured at 640nm should range within 0.37 and 0.43.

3) **Other Tests:** The other evaluation tests performed on packaging components are:

i) Tests for barium, heavy metals, tin, zinc, etc.

ii) **Test on Extracts:** The specified volume of extracting medium is taken in it. Plastic of specified surface area is cut and extracted. The extract is checked for its appearance (should be colourless), light absorption capacity, and presence of oxidisable substances.

iii) **Bacteriological Tests:** These tests determine the biological response of animals to plastics and other polymeric materials by the instillation of specific extracts from the material under test.

11.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) The art and science of preparing the articles for their transport, storage, display, and use is termed **packaging**.
2) A **Container** encloses the drug, thereby remains in direct contact with the drug. Such a container which is always in direct contact with the drug is an **immediate container**.
3) A **Closure** seals the container to eliminate oxygen, carbon dioxide, moisture, and microorganisms.
4) **Carton** is made up of cardboard, moulded wood pulp, or expanded polystyrene, and provides secondary protection.
5) **Box** is made up of thick cardboard, wood, or any other suitable material, and carries multiples of a product.
6) Glass is economical, chemically inert, impermeable, strong, rigid, has FDA clearance, and possesses superior protective qualities; thus, is used for packaging pharmaceuticals.
7) Plastic used as a material for container is composed of thermoplastic polymer. This polymer forms the basic organic structural unit for each plastic type, and is commonly used in medical field.

8) Plastic containers are used because of their light weight, non-breakable nature, low toxicity, and low reactivity with the products (provided they contain fewer amounts of additives).
9) Rubber is either used as such or as lining materials for plant construction.
10) **Cardboard cartons** are used to provide protection to the primary pack and also a suitable area for decorative design and mentioning the information required by regulatory authorities.
11) **Cartons** are convenient for stacking and can bear information leaflets. **Cards** can also be used as dividers or trays inside secondary packs.
12) **Foils** are thin metal sheets of less than 100 µm thickness; **films** are non-fibrous and non-metallic sheets of less than 250 µm thickness; and **laminates** are formed by bonding two or more film or foil webs together.
13) A **transport package** or **distribution package** is the shipping containers used for transporting, storing, and handling product or inner packages.
14) A **consumer package** is the one that reaches a consumer or household directly.
15) Primary packaging is the smallest unit of distribution or use. It is always in direct contact with the product.
16) Secondary packaging forms an outer wrapping to store, transport, inform, display, and protect the product.
17) Tertiary packaging is suitable for bulk product handling, warehouse storage, and transport shipping.
18) A container's most vulnerable and critical component is the closure with respect to the stability and compatibility with the product.
19) **Lug Cap** is used for both normal atmospheric-pressure and vacuum-pressure closing.
20) The ICH has defined **accelerated testing** as the "studies designed to increase the rate of chemical degradation or physical change of an active substance or drug product using exaggerated storage conditions as part of the formal, definitive storage program".
21) The ICH has defined **stress testing** as the "studies being carried out to elucidate the intrinsic stability of the drug substance".

11.3. EXERCISE

11.3.1. True or False

1) Rubber is either used as such or as lining materials for plant construction.
2) The art and science of preparing the articles for their transport, storage, display, and use is termed packaging.
3) A transport package is the one that reaches a consumer or household directly.
4) Cartons are convenient for stacking and can bear information leaflets.
5) Box is made up of thick cardboard, wood, or any other suitable material, and carries multiples of a product.

11.3.2. Fill in the Blanks

6) ________ is used for both normal atmospheric-pressure and vacuum-pressure closing.
7) _____________ forms an outer wrapping to store, transport, inform, display, and protect the product.

8) A ______________ is the one that reaches a consumer or household directly.
9) _______ are thin metal sheets of less than 100 μm thickness.
10) A _________ seals the container to eliminate oxygen, carbon dioxide, moisture, and microorganisms.

Answers

1) True
2) True
3) False
4) True
5) True
6) Lug Cap
7) Secondary packaging
8) Consumer package
9) Foils
10) Closure

11.3.3. Very Short Answer Type Questions

1) Discuss packaging process.
2) Discuss the components of a package.
3) Give the characteristics of packaging materials.
4) Give the selection criteria for packaging material.
5) Write a short note on closures.
6) Write a short note on fibrous materials.

11.3.4. Short Answer Type Questions

1) Discuss rubber as a packaging material.
2) Write a note on forced degradation and stress testing.
3) Briefly discuss secondary and tertiary packaging.
4) Discuss legal and other official requirements for containers.

11.3.5. Long Answer Type Questions

1) Give a detailed explanation on glass and plastic as a packaging material.
2) Discuss primary packaging in detail.
3) Write about the quality control tests of packaging materials.

Index

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About the Book

This textbook introduces details of Industrial Pharmacy in a systematic way with exercises at the end of each chapter. Chapter 1 introduces preformulation considerations. Chapter 2 and 3 details on tablets and liquid orals. Chapter 4, 5, and 6 details on capsules and pellets. Chapter 7 and 8 illustrates parenteral and ophthalmic preparations. Chapter 9 and 10 describes cosmetics and aerosols. Chapter 11 details on packaging materials.

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