AS PER PCI REGULATIONS
THIRD YEAR B. PHARM

SEMESTER-V

INDUSTRIAL PHARMACY-I

(FORMULATIVE PHARMACY)

Dr. B. PRAKASH RAO
S. RAJARAJAN
Dr. BENY BABY

NIRALI PRAKASHAN
ADVANCEMENT OF KNOWLEDGE

A Text Book of

INDUSTRIAL PHARMACY - I

[FORMULATIVE PHARMACY]

As Per PCI Regulations

Third Year B. Pharm.

Semester – V

Dr. B. Prakash Rao
M.Pharm., Ph.D.
Professor in Pharmaceutics,
Acharya and B.M. Reddy College of Pharmacy
Bengaluru

S. Rajarajan
M.Pharm.
Assistant Professor,
Department of Pharmaceutics
Karnataka College of Pharmacy
Bengaluru.

.

Dr. Beny Baby
M.Pharm., Ph.D.
Associate Professor & H.O.D.
Department of Pharmaceutics
Karnataka College of Pharmacy
Bengaluru.

NIRALI PRAKASHAN
ADVANCEMENT OF KNOWLEDGE

N3997

Industrial Pharmacy-I **ISBN 978-93-89533-32-3**

First Edition : September 2019

Published By : **Polyplate**

NIRALI PRAKASHAN

Abhyudaya Pragati, 1312, Shivaji Nagar,
Off J.M. Road, PUNE – 411005
Tel - (020) 25512336/37/39, Fax - (020) 25511379
Email : niralipune@pragationline.com

➢ DISTRIBUTION CENTRES

PUNE

Nirali Prakashan (For orders within Pune) **:** 119, Budhwar Peth, Jogeshwari Mandir Lane, Pune 411002, Maharashtra
Tel : (020) 2445 2044; Mobile : 9657703145
Email : niralilocal@pragationline.com

Nirali Prakashan (For orders outside Pune) **:** S. No. 28/27, Dhayari, Near Asian College Pune 411041
Tel : (020) 24690204; Mobile : 9657703143
Email : bookorder@pragationline.com

MUMBAI

Nirali Prakashan **:** 385, S.V.P. Road, Rasdhara Co-op. Hsg. Society Ltd.,
Girgaum, Mumbai 400004, Maharashtra; Mobile : 9320129587
Tel : (022) 2385 6339 / 2386 9976, Fax : (022) 2386 9976
Email : niralimumbai@pragationline.com

➢ DISTRIBUTION BRANCHES

JALGAON

Nirali Prakashan **:** 34, V. V. Golani Market, Navi Peth, Jalgaon 425001, Maharashtra,
Tel : (0257) 222 0395, Mob : 94234 91860; Email : niralijalgaon@pragationline.com

KOLHAPUR

Nirali Prakashan **:** New Mahadvar Road, Kedar Plaza, 1st Floor Opp. IDBI Bank, Kolhapur 416 012
Maharashtra. Mob : 9850046155; Email : niralikolhapur@pragationline.com

NAGPUR

Nirali Prakashan **:** Above Maratha Mandir, Shop No. 3, First Floor,
Rani Jhanshi Square, Sitabuldi, Nagpur 440012, Maharashtra
Tel : (0712) 254 7129; Email : niralinagpur@pragationline.com

DELHI

Nirali Prakashan **:** 4593/15, Basement, Agarwal Lane, Ansari Road, Daryaganj
Near Times of India Building, New Delhi 110002 Mob : 08505972553
Email : niralidelhi@pragationline.com

BENGALURU

Nirali Prakashan **:** Maitri Ground Floor, Jaya Apartments, No. 99, 6th Cross, 6th Main,
Malleswaram, Bengaluru 560003, Karnataka; Mob : 9449043034
Email: niralibangalore@pragationline.com

Other Branches : Hyderabad, Chennai

Preface ...

It is our immense pleasure to bring out the "**First Edition**" of this book which is dedicated to the students and faculty of B. Pharma institutes of this country. This book is designed and edited in accordance to the syllabus requirement of "**Industrial Pharmacy-I**" **[Formulative Pharmacy]** for third year (5^{th} semester) B. Pharm course in pharmacy prescribed in "**Bachelor of Pharmacy (B. Pharm) course regulations 2014**" by Pharmacy council of India.

Sincere efforts have been made to present theoretical aspects in details along with flowcharts/ pictorial for easy understanding the mechanism of actions of drugs and their pharmacological aspects. Most aspects are described stating examples with an intention to scaffold theoretical concepts and easy attempted during study. The major objective of this book is to provide students, collective information about subject in simple and lucid language. We have kept in mind the difficulties which the students generally face.

We hope that this book shall be found useful by the students and quick lessons for teaching faculty.

We are thankful to the Publisher Mr. Dineshbhai Furia, Mr. Jignesh Furia and the Staff of Nirali Prakashan, Pune for bringing out nicely printed book.

Suggestions and comments are always welcome and they shall be gratefully acknowledged.

Dr. B. Prakash Rao

S. Rajarajan

Dr. Beny Baby

Syllabus ...

UNIT-I **(07 Hours)**

Preformulation Studies: Introduction to preformulation, goals and objectives, study of physicochemical characteristics of drug substances.

(a) Physical properties: Physical form (crystal & amorphous), particle size, shape, flow properties, solubility profile (pKa, pH, partition coefficient), polymorphism.

(b) Chemical Properties: Hydrolysis, oxidation, reduction, racemisation, polymerization, BCS classification of drugs & its significant.

Application of preformulation considerations in the development of solid, liquid oral and parenteral dosage forms and its impact on stability of dosage forms.

UNIT-II (10 Hours)

Tablets:

(a) Introduction, ideal characteristics of tablets, classification of tablets. Excipients, Formulation of tablets, granulation methods, compression and processing problems. Equipments and tablet tooling.

(b) Tablet coating: Types of coating, coating materials, formulation of coating composition, methods of coating, equipment employed and defects in coating.

(c) 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.

UNIT-III **(08 Hours)**

Capsules:

(a) 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.

(b) 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.

UNIT-IV **(10 Hours)**

Parenteral Products:

(a) Definition, types, advantages and limitations. Preformulation factors and essential requirements, vehicles, additives, importance of isotonicity.

(b) Production procedure, production facilities and controls, aseptic processing.

(c) Formulation of injections, sterile powders, large volume parenterals and lyophilized products.

(d) 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.

UNIT-V (10 Hours)

Cosmetics: Formulation and preparation of the following cosmetic preparations: lipsticks, shampoos, cold cream and vanishing cream, tooth pastes, 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.

Contents ...

Chapter 1 ...

PREFORMULATION STUDIES

Upon completion of the chapter, students will be able to understand:

- *Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could be affect the drug performance and development of a dosage form.*
- *Preformulation study is to develop the elegant, stable, effective and safe dosage form.*
- *To establishing kinetic rate profile, compatibility with other ingredients and establish physicochemical parameter of new drug.*
- *To generate useful data needed in developing stable and safe dosage forms that can be manufactured on a commercial scale.*
- *To provide on a depth knowledge and physical characters of drug molecule prior to dosage form development.*
- *To generate useful information on how to design a drug delivery system with good bioavailability.*

1.1 INTRODUCTION

Before developing a formulation like tablets, capsules, liquid orals we study the suitability of new drug or drug and excipients for the chosen formulation which is called preformulation.

1.1.1 Definition

Preformulation may be defined as a stage of the research and development process where the preformulation scientist characterizes the physical, chemical, biopharmaceutical and mechanical properties of a new drug substance, in order to develop stable, safe and effective dosage form.

1.1.2 Objectives

To generate useful information to the formulator to design an optimum drug delivery system. The preformulation investigations confirm that there are no significant barriers to the compound's development as a marketed drug. The formulation scientist uses this information to develop dosage forms.

Preformulation is a multidisciplinary development of a drug candidate. Preformulation is branch of Pharmaceutical science that uses biopharmaceutical principles in the determination of physicochemical properties of the drug substance. Prior to the development of any dosage for a new drug, it is vital that certain fundamental physical and chemical properties of drug powder are found out. This information may dictate many of subsequent event and approaches in formulation development. Investigation of physico-chemical properties of the new drug compound is essential because that could affect drug

performance and development of an effective dosage form. Preformulation starts when a newly synthesized drug shows a sufficient pharmacologic promise in animal model to warrant evaluation in man. The preformulation is the first step in the rational development of a dosage form of a drug substance alone and when combined with excipients.

1.1.3 Goals of Preformulation

- To find the necessary physicochemical properties like solubility, crystal form of new drug substances.
- To determine kinetic release of drug from dosage form.
- To establish physical characteristics.
- To establish compatibility (no interaction) with common excipients.

1.1.4 Preformulation Factors

It is study about physical and chemical properties of drug substance prior formulation is called as preformulation.

They are:

- pH /pka
- Solubility
- Thermal/heat effect
- Dissociation constant
- Compatabilty studies - FTIR / DSC
- Oxidation and reduction
- Particle size

1.2 PHYSICAL PROPERTIES

It is vital to understand the physical description of a drug substance (whether it is solid, semisolid or liquid) prior to dosage form development. Most drugs in use nowadays are solid materials and less number are liquid in nature. Flowability of powder and chemical stability depends on the habit and internal structure of a drug.

Principal Areas of Preformulation :

(I) Nature of Solid Drug:

1. Crystallinity and polymorphism
2. Hygroscopicity
3. Fine particle characterization
4. Powder flow

(II) Solubility Data:

1. Ionization constant – pKa v (- log Ka)
2. pH solubility profile
3. Common ion effect – KSP.
4. Thermal effects
5. Solubilization
6. Partition coefficient
7. Dissolution

(III) Stability Analysis:

1. Stability in toxicology formulation
2. Solution stability
   (a) pH stability profile
3. Solid state stability
   (a) Bulk stability
   (b) Compatibility

1.2.1 Nature of Solid Drug

When a drug molecule is invented, all the solid-forms are hardly identified. So, during bulk characterization the following characteristics are studied.

1. Crystallinity and Polymorphism:

Crystal habit (external shape of crystal) is the description of the outer appearance of a crystal. A single internal-structure for a compound can have many different habits, depending on the environment for growing crystals. Different habits of crystals are given below. Internal Structure of drug may be crystalline and amorphous forms.

(i) Crystalline state: In this state of matter atoms or molecules are arranged in highly well-ordered form and is associated with three-dimensional periodicity to organize themselves into their most favourable thermodynamic state, which under certain conditions results in their appearance as crystals. The repeating three-dimensional patterns are called crystal lattices. The crystal lattice can be analyzed from its X-ray diffraction pattern.

Crystal Habit: Platy, Needle, or Acicular, Tabular, Equant or Massive, Bladed, Prismatic

Amorphous forms: In this form the solids do not have any definite internal structure. They have atoms or molecules disorderly placed as in a liquid.

e.g. Amorphous Itraconazole, Amorphous Novobiocin

General Preparation: Amorphous forms are prepared by rapid precipitation, lyophillization or rapid cooling of molten liquids e.g. glass.

Difference between Crystalline and Amorphous Form:

Crystalline form	Amorphous forms
(i) Structure: Crystalline forms have definite ordered internal structure.	**(i) Structure:** Amorphous forms do not have any fixed or no shape internal (crystal) structure.
(ii) Stability: Stability of crystalline forms is more stable than its amorphous forms as it is having less internal energy.	**(ii) Stability:** Amorphous form has higher thermodynamic energy than its crystalline form hence lesser stable than crystalline forms.

Contd...

(iii) Solubility: Crystalline form has lesser solubility than its amorphous form.	**(iii) Solubility:** Amorphous forms have greater solubility than its crystalline forms.
(iv) Change to other form: Crystalline form has lesser inclination to change its form during storage.	**(iv) Change to other form:** Amorphous be likely to revert to more stable forms during storage.

(ii) Polymorphs: When a substance is in more than one crystalline form, the various forms are called polymorphs and the phenomenon as polymorphism.

e.g. Chloramphenicol palmitate has three polymorphs: A, B and C. Spironolactone exhibits 6 polymorphs.

Various polymorphs can be prepared by crystallizing the drug from different drugs under various conditions. Depending on their relative stability, one of the different polymorphic forms will be physically more stable than the others. Such a stable polymorph represents the lowest thermodynamic energy state, has highest melting point and least solubility. The representing polymorphs are called metastable forms which represent higher thermodynamic energy state; the metastable forms have a thermodynamic tendency to convert to the stable form. A metastable form cannot be called unstable because if it is kept dry, it will remain stable for years.

Molecular Adducts:

During the process of crystallization, some compounds have a tendency to trap the solvent molecules.

(a) Non-Stoichiometric Inclusion Compounds (or Adducts):

In these crystals solvent molecules are entrapped within the crystal lattice and the number of solvent molecules is not included in stoichiometric number. Depending on the shape they are of three types:

(i) Channel: At a point when the crystal contains continuous channels in which the solvent molecule can be incorporated. e.g. Urea and Thiourea forms channel.

(ii) Layers: Here solvent molecules are ensnared in between layers of crystals. Some compounds, such as clay Montmorillonite, the principle constituents of bentonite, can entrap hydrocarbons, alcohols and glycols between the layers of their lattices.

(iii) Clathrates (Cage): Solvent molecules are entrapped within the cavity of the crystal from all sides.eg Hydroquinone

(b) Stoichiometric Inclusion Compounds (or Stoichiometric Adducts):

This molecular complex has consolidated the crystallizing solvent molecules into specific sites within the crystal lattice and has stoichiometric number of solvent molecules complexed.

At the point when the merged solvent is water, the complex is called hydrates and when the solvent is other than water, the complex is called solvates. Depending on the ratio of water molecules within a complex the following nomenclature is followed.

(i) **Anhydrous:** 1 mole compound + 0 mole water e.g. Ampicillin
(ii) **Hemihydrate:** 1 mole compound + ½ mole water
(iii) **Monohydrate**: 1 mole compound + 1 mole water
(iv) **Dihydrate:** 1 mole compound + 2 moles water
(v) **Trihydrate:** 1 mole compound + 3 moles water e.g. Ampicillin Trihydrate

Properties of Solvates/Hydrates:

(i) Generally, the anhydrous form of a drug has more prominent fluid solvency than its hydrates. This is on the basis that the hydrates are already in equilibrium with water and therefore have less demand for water. e.g. anhydrous forms of theophylline and ampicillin have higher aqueous solubility than the hydrates.
(ii) Non aqueous solvates have greater aqueous solubility than the non-solvates. E.g. chloroform solvates of griseofulvin are more water soluble than their nonsolvate forms.

Analytical Methods for Characterization of Solid Forms:

Methods of studying solid forms are listed as below (amount of drug required for study):

(a) Microscopy (1 mg)
(b) Hot stage microscopy (1 mg)
(c) Differential Scanning Calorimetry (DSC) (2 - 5 mg)
(d) Differential Thermal Analysis (DTA) (2 - 5 mg)
(e) Thermogravimetric Analysis (10 mg)
(f) Infrared Spectroscopy (2 - 20 mg)
(g) X-ray Powder Diffraction (500 mg)
(h) Scanning Electron Microscopy (2 mg)
(i) Dissolution / Solubility Analysis (mg - g)

Liquids:

Liquid drugs have two problems in the design of a dosage form which are:

(i) The volatility: They must be physically sealed from the atmosphere to avoid evaporation.
(ii) They cannot generally be formulated into tablet (the most popular form of oral medication).

To solve these problems, two easy methods are used to formulate liquid drugs into solid dosage forms.

(i) By soft gelatin capsule, e.g. Vitamin A.
(ii) By converting of the liquid drug into solid derivatives such as salt or ester. For instance, scopolamine is liquid but its hydrobromide salt is solid.

(a) Microscopy:

Amorphous substances (e.g. super-cooled glass and non-crystalline organic compounds or substances with cubic crystal lattices e.g. NaCl) have single refractive index. Through this type of microscope, the amorphous substances do not transmit light, and they appear black. They are called isotropic substances.

(b) Hot-stage Microscopy:

In this case, the polarizing microscope is fitted with a hot plate to investigate polymorphism, melting points, transition temperatures and rates of transition at controlled rates. It facilitates in explaining the thermal behavior of a substance from the DSC and TGA curves.

Problem: A problem often encountered during thermal microscopy is that organic molecules can degrade during the melting process, and recrystallization of the melt may not occur, because of the presence of contaminant degradation products.

Thermal Analysis:

(a) Differential Scanning Calorimetry (DSC):

- In DSC method the difference in energy exothermic and endothermic (ΔH) into a sample and reference material is measured as a function of temperature as the specimens are subjected to an identically steady rise in temperature.

(b) Differential Thermal Analysis (DTA):

- In DTA instrument a record is formed where temperature difference (ΔT) (between the sample and reference material) is plotted against temperature (T) when two specimens are subjected to an identically steady rise in temperature.
  The reference material is alumina, kieselguhr.

Samples that may be studied by DSC or DTA are:

(i) Powders
(ii) Fibres
(iii) single crystals
(iv) polymer films
(v) Semi-solids or liquids.

Applications of DTA/DSC in preformulation studies:

(i) To find out the purity of a sample
(ii) To find out the number of polymorphs and to determine the ratio of each polymorph.
(iii) To determine the heat of solvation
(iv) To find out the thermal degradation of a drug or excipients.
(v) To determine the glass-transition temperature (tg) of a polymer.

(e) Thermogravimetric Analysis (TGA):

TGA measures the changes in sample weight as a function of time (isothermal changes) or temperature.

Applications of TGA in Preformulation Study:

(i) Desolvation and decomposition processes are monitored.

(ii) Comparing TGA and DSC data recorded under identical conditions can greatly aid in the interpretation of thermal processes.

(f) X-Ray Powder Diffraction:

When an X-ray beam falls on a powder the beam is diffracted and peaks are observed. Interpretation of x – ray diffraction: The peaks or finger prints are observed which indicates crystalline powder. No peaks are observed which indicate amorphous forms.

Applications of X-ray Powder Diffraction:

(i) Each diffraction pattern is characteristic of a specific crystalline lattice for a given compound. So in admixture different crystalline forms can be analyzed using normalized intensities at exact angles.

(ii) Identification of crystalline materials by using their diffraction pattern as a 'finger print'. First, the powder diffraction photograph or diffractometer trace is taken and matched with a standard photograph. All the lines and peaks must match in position and relative intensity.

2. Hygroscopicity:

Definition: Many pharmaceutical materials have a tendency to adsorb atmospheric moisture (especially water-soluble salt forms). They are called hygroscopic materials and this phenomenon is known as hygroscopicity.

Equilibrium moisture content depends upon:

(i) The atmospheric humidity

(ii) Temperature

Deliquescent materials:

(i) Surface area

(ii) Exposure time

(iii) Mechanism of moisture uptake.

They absorb sufficient amount of moisture and dissolve completely in it. (e.g. anhydrous calcium chloride.

Tests of Hygroscopicity:

Procedure: Bulk drug samples are placed in open containers with thin powder bed to assure maximum atmospheric exposure. These samples are then exposed to a range of controlled relative humidity (Relative Humidity) environments prepared with saturated aqueous salt solutions.

The amount of moisture adsorbed can be determined by the following methods:

(i) Gravimetry

(ii) Thermogravimetric analysis (TGA)

(iii) Karl-Fischer titration (KF-titration)

(iv) Gas chromatography (GC)

Time of monitoring depends on the purpose:

(i) For the purpose of 'handling' data points from 0 to 24 hours are taken

(ii) For the purpose of 'storage' data points from 0 to 12 weeks are taken.

Significance of Hygroscopicity Test:

(a) To decide

(i) The storage condition i.e. at low humidity environment.

(ii) Special packaging – e.g. with desiccant.

(b) Moisture level in a powder sample may affect the flowability and compatibility which, are important factors during tableting and capsule filling.

(c) After adsorption of moisture, if hydrates are formed then solubility of that powder may change affecting the dissolution characteristics of the material.

(d) Moisture may degrade some materials. So, humidity of a material must be controlled.

3. Characterization of Fine Particle:

Parameters those are measured:

(i) Particle size and size-distribution

(ii) Shape of the particle

(iii) Surface morphology of the particles

(iii) Zeta potential

Instrumental Methods of Particle Size Characterization:

(i) Light Microscope:

- First a standard graticule (BS 3625) is standardized with a stage micrometer. Then small number of particles are spread over a glass slide and placed on the stage of the microscope. Particles are focussed and the particle diameters are measured. Several hundred particles are measured and reported as a histogram.
- Disadvantage: The procedure is tedious (means it takes slow and monotonous long time.)

(ii) Stream counting devices:

Examples:

(a) Coulter counter – electrical sensing zone method

(b) HIAC – counter – optical sensing zone

(c) Malvern particle and droplet sizer – Laser diffraction method.

Procedure: Vacuum Amplifier and Counter Stirrer Electrodes Orifice:

- Samples prepared for analysis are dispersed in a conducting medium (e.g. saline) with the help of ultrasound and a few drops of surfactant (to disperse the particles uniformly). A known volume (0.5 to 2 mL) of this suspension is then drawn into a tube through a small aperture (0.4 to 800 μm diameter) across which a voltage is applied.
- As each particle passes through the hole, it is counted and sized according to the resistance generated by displacing that particle's volume of conducting medium.
- Size distribution is reported as histogram.

(iii) Sieve analysis:

- A powder sample is passed through a standard sieve set. The particle size is plotted against % weight retained on each sieve.
- **Use:** This method is used generally for large samples.

Instrumental Method for Determination of Specific Surface Area:

Brunauer, Emmett and Teller (BET) Nitrogen Adsorption Method:

- A layer of nitrogen molecules is adsorbed to the sample surface at –1960°C. Once the surface is drenched, the sample is heated to room temperature, the nitrogen gas is desorbed, and its volume is measured and converted to the number of adsorbed molecules via the gas law. Since each N_2 molecule occupies an area of 16 A_2, one may readily compute the surface area per gram of each pre-weighed sample.

Instrumental method for characterization of surface morphology:

- The scanning electron microscope creates the magnified images by using electrons instead of light waves. The images are black and white.

Procedure:

Biological materials are dried in a special way that prevents them from shrinking.

- Since SEM illuminates them with electrons, they are made conductive by coating with a very thin layer of gold by a machine called sputter-coater.
- The sample is placed inside the microscope's vacuum column through an airtight door.
- After the air is pumped out of the column, an electron gun emits a beam of high-energy electrons. This beam travels downward through a series of magnetic lenses designed to focus the electrons to a very fine spot.
- Near the bottom, a set of scanning coils moves the focussed beam back and forth across the specimen, row by row.
- As the electron beam hits each spot on the sample, secondary electrons are knocked loose from its surface. A detector counts these electrons and sends the signals to an amplifier.
- The final image is built up from the number of electrons emitted from each spot on the sample.

Bulk Density:

Apparent bulk density (g/cm^3): Bulk drug powder is sieved through 40 mesh screen. Weight is taken and poured into a graduated cylinder via a large funnel. The volume is called bulk volume.

$$\text{Apparent bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume}}$$

Tapped density (g/cm^3): Bulk powder is sieved through 40 mesh screen. Weight is taken and poured into a graduated cylinder. The cylinder is tapped 1000 times on a mechanical tapper apparatus. The volume reaches a minimum – called tapped volume.

$$\text{Tapped density} = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

True density (g/cm^3): Solvents of varying densities are selected in which the powder sample is insoluble. Small quantity of surfactant may be mixed with the solvent mixture to enhance wetting and pore penetration. After vigorous agitation, the samples are centrifuged briefly and then left to stand undisturbed until floatation or settling has reached equilibrium.

The samples that remains suspended (i.e. neither suspended not floated) is taken. So the true density of the powder is equal. So the true density of the powder is the density of that solvent. The density of that solvent is determined accurately with a pycnometer.

Source of Variation of Bulk Density:

Method of crystallization, milling, formulation

Methods of correction:

By milling, slugging or formulation

Significance:

Bulk density: Bulk density is required during the selection of capsule size for a high dose drug.

- In case of low dose drug mixing with excipients is a problem if the bulk densities of the drug and excipients have large difference.
- Near the bottom, a set of scanning coils moves the focussed beam back and forth across the specimen, row by row.
- As the electron beam hits each spot on the sample, secondary electrons are knocked loose from its surface. A detector counts these electrons and sends the signals to an amplifier.
- The final image is built up from the number of electrons emitted from each spot on the sample.

4. Powder flow properties:

Powder flow properties depend on

(i) particle size
(ii) density
(iii) shape
(iv) electrostatic charge and adsorbed moisture

that may arise from processing or formulation.

A free-flowing powder may become cohesive during development. This problem may be solved by any of the following ways:

(i) by granulation
(ii) by densification via slugging
(iii) by filling special auger feed equipment (in case of powder)
(iv) by changing the formulation.

Procedure:

For free flowing powder: A simple flow rate apparatus consists of a grounded metal tube from which drug flows through an orifice onto an electronic balance, which is connected to a strip chart recorder. Several flow rate (g/sec) determinations at various orifice sizes (1/8 to ½ inch) should be carried out.

The greater the standard deviation between multiple flow rate measurements, the greater will be the weight variation of the product (tablets or capsules).

Compressibility:

$$\text{Compressibility} = \frac{\rho_t - \rho_0}{\rho_t} \times 100$$

where ρ_t = Tapped bulk density

ρ = Initial bulk density

1.2.2 Solubility Data

Determination of equilibrium solubility of a drug:

The drug is dispersed in a solvent. The suspension is agitated at a steady temperature. Samples of the suspension are withdrawn as a function of time, clarified by centrifugation, and assayed to establish a plateau concentration.

Solvents taken:

(i) 0.9% NaCl at room temperature
(ii) 0.01 M HCl at RT
(iii) 0.1 M HCl at RT
(iv) 0.1 M NaOH at RT
(v) At pH 7.4 buffer at 37^{o}C

Drug concentration is determined by the following analytical methods:

(i) HPLC
(ii) UV –Spectroscopy
(iii) Fluorescence Spectroscopy
(iv) Gas Chromatography

Solubility depends on

(i) pH
(ii) Temperature
(iii) Ionic strength
(iv) Buffer concentration

Significance:

(i) A drug for oral administrative should be examined for solubility in an isotonic saline solution and acidic pH. This solubility data may provide the dissolution profile invivo.
(ii) Solubility in various mediums is useful in developing suspension or solution toxicologic and pharmacologic studies.
(iii) Solubility studies identify those drugs with a potential for bioavailability problems. E.g. Drug having limited solubility (7 %) in the fluids of GIT often exhibit poor or erratic absorption unless dosage forms are tailored for the drug.

pKa Determination:

- When a weakly acidic or basic drug partially ionizes in GI fluid, generally, the unionized molecules are absorbed quickly.
- Handerson-Hasselbach equation provides an estimate of the ionized and unionized drug concentration at a particular pH.
- For acidic drugs: e.g.

$$HA + H_2O \leftrightarrow H_3O^+ + A^-$$

Weak acid Strong base

$$pH = pK_a + \log \frac{[ionized]}{[unionized]} = pK_a + \log \frac{[A^-]}{[HA]}$$

For basic drugs:

$$B + H_3O^+ \leftrightarrow BH^+ + H_2O$$

Weak base Strong acid

$$pH = pK_a + \log \frac{[unionized]}{[ionized]} = pK_a + \log \frac{[B^+]}{[BH]}$$

Methods of Determination of pKa of a Drug:

(i) Detection of spectral change by UV or visible spectroscopy at a range of pH:

Advantage: Dilute aqueous solutions can be analyzed by this method.

(ii) Potentiometric titration:

Advantage: Maximum sensitivity for compounds with pKa in the range of 3 to 10.

Disadvantage: This method is unsuccessful for candidates where precipitation of the unionized forms occurs during titration. To prevent precipitation a co-solvent e.g. methanol or dimethylsulfoxide (DMSO) can be incorporated.

- Difference of solubility at various pH.

(iii) Effect of temperature on stability:

- Heat of solution, ΔH_S represents the heat released or absorbed when a mole of solute is dissolved in a large quantity of solvent.

Significance:

- Most normally, the solubility process is endothermic, e.g. non-electrolytes, unionized forms of weak acids and bases. if ΔH_s is positive, solubility increases if temperature increases.
- Solutes that are ionized when dissolved releases heat, the process is exothermic, ΔH_s is negative solubility increases as temperature decreases.

(iv) Solubilization:

- For drug candidates with poor water solubility, preformulation studies should include limited experiments to identify the possible mechanisms for solubilisation.
- Means of increasing the solubility are:
  (i) Addition of a cosolvent to the aqueous system e.g. ethanol, propylene glycol and glycerine.
  MOA: These co-solvents disrupt the hydrophobic interactions of water at the non-polar solute / water interfaces.
  (ii) Solubilisation in micellar solutions such as 0.01 M Tween 20 solution.
  (iii) Solubilisation by forming molecular complexes e.g. benzoic acid forms complex with caffeine.

(v) Partition coefficient:

- Partition coefficient is defined, as the ratio of un-ionized drug concentrations between the organic and aqueous phases, at equilibrium.
- Generally, 2-octanol and chloroform are taken as the oil phase. m equilibrium
  Significance: Drug molecules having higher $K_{O/W}$ will cross the lipid cell membrane.

(vi) Dissolution:

- The dissolution rate of a drug substance in which surface area is constant during disintegration is described by the modified Noyes-Whitney equation

$$\frac{dc}{dt} = \frac{DA}{hV}(C_s - C)$$

where, D = diffusion coefficient of the drug in the dissolution medium
h = thickness of the diffusion layer at the solid/liquid interface
A = surface area of drug exposed to dissolution medium.
V = volume of the medium
C_S = Concentration of saturated solution of the solute in the dissolution medium at the experimental temperature.
C = Concentration of drug in solution at time t.
When A = constant and CS >> C the equation can be rearranged to

$$\frac{dc}{dt} = \frac{DA}{hV}(C_s - C) \text{ or } \frac{dcV}{dt} = \frac{DA}{h}C_s \text{ or } W = kAt$$

where, W = weight (mg) of drug dissolved at time t
k = intrinsic dissolution rate constant $\frac{mg}{min\text{-}cm^2}$.

Determination of k:

- Pure drug powder is punched in a die and punch apparatus to give a uniform cylindrical shape. The tablet is covered with wax in all sides. One circular face is exposed to the dissolution medium. Thus, as dissolution precedes, the area, A, remains constant.
- Time to time dissolution medium is taken out and fresh medium added to the chamber.
- With two types of assembly, the experiments can be carried out.

pH and pKa Solubility Profile:

- **pKa Determination**: The Henderson – Hasseslebach equation provides an estimate of the ionized and unionized drug concentration at a particular pH.

  For acidic drugs,

  pH = pKa + log (ionized drug / un-ionized drug)

  For basic drugs,

  pH = pKa + log (unionized drug / ionized drug)
- Buffers, temperature, ionic strength and cosolvent can affect the pKa value.
- Potentiometric titration offers maximum sensitivity for compounds with pKa values in the range of 3-10.

Solubilization:

- Solubilization is increased by cosolvent addition.
- E.g. Propylene glycol solubilizes drug molecules by disrupting the hydrophobic interactions of water.

More non-polar the solute
↓
Greater is the solubilisation
achieved by cosolvent addition

Thermal/Heat Effects:

- Drugs which are unstable to heat requires refrigerative storage or lyophilisation (these products must be used within short periods)
- If it is endothermic → ΔH is + ve
  Increase in temperature → Increase in drug solubility
- If it is exothermic → ΔH is – ve
  Increase in temperature → Decrease in drug solubility
- For determining ΔH

$$\ln S = -\Delta H / RT + C$$

S = molar solubility at temperature, T = temperature in Kelvin, R = gas constant

Particle size:

- Fine particle characterization is very important property and here smallest particle should be tested to facilitate homogeneous sample preparation.
- **Coulter Counter Technique:** To check particle size and particle volume.
- **BET (Brunauer, Emmet, Teller) nitrogen absorption apparatus:** Measurement of surface area.
- **SEM (Scanning Electron Microscopy**): To check surface morphology.

1.2.3 Stability Analysis

Preformulation stability studies are the first quantitative assessment of chemical stability of a new drug. This may involve

1. Stability study in toxicology formulation
2. Stability study in solution state
3. Stability study in solid state.

1. Stability Study in Toxicology Formulation:

A new drug is administered to animals through oral route either by

(i) Mixing the drug in the feed
(ii) In the form of solution
(iii) In the form of suspension in aqueous vehicle

- Feed may contain water, vitamin, minerals (metal ions), enzymes and different functional groups that may severely reduce the stability of the new drug. So stability study should be carried out in the feed and at laboratory temperature.
- For solution and suspension, the chemical stability at different temperature and pH should be checked.
- For suspension-state the drug suspension is occasionally shaken to check dispersibility.

2. Solution Stability:

Objective: Identification of conditions necessary to form a stable solution.

Stability of a new drug may depend on: (i) pH, (ii) Ionic strength, (iii) Co-solvent, (iv) Light, (v) Temperature, (vi) Oxygen.

(i) pH Stability Study:

(a) Experiments to confirm decay at the extremes of pH and temperature. Three stability studies are carried out at the following conditions:

- 0.1 N HCl solution at 90°C
- Solution in water at 90°C
- 0.1 N NaOH solution at 90°C

These experiments are intentionally done to confirm the assay specificity and for maximum rates of degradation.

(b) Now aqueous buffers are used to produce solutions with wide range of pH values but with constant levels of drug concentration, co-solvent and ionic strength.

All the rate constants (k) at a single temperature are then plotted as a function of pH.

(ii) Ionic Strength: Since most pharmaceutical solutions are intended for parenteral routes of administration, the pH-stability studies should be carried out at a constant ionic strength that is compatible with body fluids. The ionic strength (μ) of an isotonic 0.9% w/v sodium chloride solution is 0.15.

Ionic strength for any buffer solution can be calculated by

$$\mu = \frac{1}{2} m_i Z_i^2$$

where, m_i = molar concentration of the ion

Z_i = valency of that ion

For computing, μ all the ionic species of the buffer solution and drugs are also taken into calculation.

(iii) Co-solvents: Some drugs are not sufficiently soluble to give concentrations of analytical sensitivity. In those cases, co-solvents may be used. However, presence of co-solvents will influence the rate constant. Hence, k values at different co-solvent concentrations are determined and plotted against % of co-solvent. Finally, the line is extrapolated to 0% co-solvent to produce the actual k value (i.e. in pure solvent).

(iv) Light: Drug solutions are kept in

(a) Clear glass ampoules
(b) Amber color glass container
(c) Yellow-green color glass container
(d) Container stored in card-board package or wrapped in aluminium foil – this one acts as the control.

Now the stability studies are carried out in the above containers.

(v) Temperature: The rate constant (k) of degradation reaction of a drug varies with temperature according to Arrhenius equation.

$$k = Ae^{\frac{-E_a}{RT}} \quad \text{or} \quad \ln = \ln A - \frac{E_a}{RT}\left(\frac{1}{T}\right) \quad \text{(In means natural logarithm)}$$

where, k = Rate constant
A = Frequency factor
E_a = Energy of activation
R = Ideal gas constant
T = Absolute temperature

Procedure: Buffer solutions were prepared and kept at different temperatures. Rate constants are determined at each temperature and the ln k value is plotted against (1/T).

Inference: The relationship is linear a constant decay mechanism over the temperature range has occurred.

A broken or non-linear relationship can change in the rate-limiting step of the reaction or change in decay mechanism.

Uses: Shelf life of the drug may be calculated.

e.g. Time Concentration of drug remaining

where, $t_{10\%}$= time for 10% decay to occur if the reaction follows 1st order kinetics $t_{10\%} = \frac{105}{K_1}$

Conclusion: If the drug is sufficiently stable, liquid formulation development may be started at once.

If the drug is unstable, further investigations may be necessary.

3. Solid State Stability:

Objectives: Identification of stable storage conditions for drug in the solid state and identification of compatible excipients for a formulation.

Characteristics:

- Solid state reactions are much slower, so the rate of appearance of decay product is measured (not the amount of drug remaining unchanged).
- To determine the mechanism of degradation thin layer chromatography (TLC), fluorescence or UV / Visible spectroscopy may be required.
- To study polymorphic changes DSC or IR-spectroscopy is required.
- In case of surface discoloration due to oxidation or reaction with excipients, surface reflectance equipment may be used.

Procedure:

1. Weighed samples are placed in open screw-capped vials and exposed to a variety of temperatures, humidities and light intensities. After the desired time samples are taken out and measured by HPLC (5 – 10 mg), DSC (10 to 50 mg), IR (2 to 20 mg).
2. To test for surface oxidation samples are stored in large (25ml) vials for injection capped with Teflon-lined rubber stopper. The stoppers are penetrated with needles

and the headspace is flooded with the desired gas. The resulting needle holes are sealed with wax to prevent degassing.

3. After fixed time those samples are removed and analyzed.

Drug-excipient Stability Profile:

Hypothetical dosage forms are prepared with various excipients and are exposed to various conditions to study the interactions of drug and excipients.

- **Melting point:** Each pure substance has a definite melting point. If not pure, the substance will exhibit a change in melting point. The pure substances have always higher melting points than their impure mixtures. This phenomenon is called melting point depression and commonly used to determine the purity of a drug substance.
- Unfortunately, many drug substances in use today are unpalatable and dosage forms containing such drugs (oral preparations) require the addition of flavors and/or colors.
- **Colours/Flavours:** Color is generally a function of a drug's inherent chemical structure relating to a certain level of unsaturation.
- Color intensity relates to the extent of conjugated unsaturation as well as the presence of chromophores.
- Some compound may appear to have color although structurally saturated.
- The substance may exhibit an inherent odor, characteristic of major functional groups present.
- Odour greatly affects the flavor of a preparation or food stuff.
- **Taste**: If taste is considered as unpalatable, consideration is to be given to the use of a less soluble chemical form of the drug.
- The odour and taste may be suppressed by using appropriate flavors and excipients or by coating the final product.
- **Particle Size:** Particle size can control variety of important factors :
  - Dissolution rate
  - Suspendability
  - Uniform distribution
  - Penetrability
  - Lack of grittiness

Particle Size Determination Methods:

1. Sieving
2. Microscopy
3. Sedimentation rate method
4. Light energy diffraction
5. Laser holography
6. Cascade impaction

1. Sieving method:

- Range: 50 - 150 μm
- Simple, inexpensive
- If powder is not dry, the apertures get clogged.

2. **Microscopy:**
   - Range: 0.2 - 100 µm
   - Particle size can be determined by the use of calibrated grid background.
   - Most direct method.
   - Slow and tedious method.
3. **Sedimentation method:**
   - Range: 1 - 200 µm
   - Andreasen pipette is used.
4. **Cascade impaction:**
   - The principle that a particle driven by an airstream will hit a surface in its path, provided that its inertia is sufficient to overcome the drug force that tends to keep in it in airstream.
5. **Light energy diffraction:**
   - Range: 0.5 - 500 µm
   - Particle size is determined by the reduction in light reaching the sensor as the particle, dispersed in a liquid or gas, passes through the sensing zone.
   - Quick and fast.
6. **Laser holography:**
   - Range: 1.4 - 100 µm
   - A pulsed laser is fired through an aerosolized particle spray & photographed in three dimensional with holographic camera, allowing the particles to be individually imaged & sized.
   - Particle size is characterized using these terms:
     - Very coarse (#8)
     - Coarse (#20)
     - Moderately coarse (#40)
     - Fine (#60)
     - Very fine (#80)

Powder Flow Properties:

Flowability of powder and chemical stability depends on the habit and internal structure of a drug.

Habit is the description of the outer appearance of a crystal. A single internal-structure for a compound can have several different habits, depending on the environment for growing crystals. Different habits of crystals are given below.

- Powder flow properties can be affected by change in particle size, shape and density.
- The flow properties depend upon following-

(i) Force of friction.

(ii) Cohesion between one particle to another.

- Fine particle possesses poor flow by filling void spaces between larger particles causing packing & densification of particles.
- By using glidant we can alter the flow properties.
- e.g. Starch, Talc.

Determination of Powder Flow Properties:

- By determining Angle of Repose.
- A greater angle of repose indicates poor flow.
- It should be less than 30° and can be determined by following equation:

$$\tan \theta = \frac{h}{r}$$

where, θ = angle of repose.
h = height of pile.
r = radius.

Angle of repose (in degree)	Type of flow
< 25	Excellent
25 - 30	Good
30 - 40	Passable
< 40	Very poor

Measurement of free-flowing powder by compressibility:

- Also known as Carr's index.

$$\text{Car's index (\%)} = \frac{(\text{Tapped density} - \text{Poured density})}{\text{Tapped density}} \times 100$$

Tapped Density:

- It is simple, fast and popular method of predicting powder flow characteristics.

Carr's Index	Type of flow
5-15	Excellent
12-16	Good
18- 21	Fair To Passable
23- 35	poor
33 - 38	Very Poor
> 40	Extremely Poor

Particle Shape:

- Particle shape will influence the surface area, flow of particles, packing & compaction properties of the particles.
- A sphere has minimum surface area per unit volume.
- Therefore, these properties can be compared for spheres & asymmetric particles, in order to decide the shape.

Surface Area:

- Particle size and surface area are inversely related to each other.
- Smaller the drug particle, greater the surface area.
- Specific surface is defined as the surface area per unit weight (Sw) or unit volume (Sv) of the material.

- However size reduction is not required in following cases when drug is unstable.
- Degrade in solution form.
- Produce undesirable effects.
- When sustained effect is desired.

Solubility Analysis:

- Preformulation solubility studies focus on drug solvent system that could occur during the delivery of drug candidate.
- e.g. A drug for oral administration should be examined for solubility in media having isotonic chloride ion concentration and acidic pH.
- Analytic methods that are particularly useful for solubility measurement include HPLC, UV spectroscopy, Fluorescence spectroscopy and Gas chromatography.
- Reverse phase HPLC offer accurate and efficient means of collecting solubility data of drug.

Descriptive Solubilities (I.P.):

Description	Parts of solvent required for one part of solute
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10 - 30
Sparingly Soluble	30 - 100
Slightly soluble	100 - 1000
Very Slightly soluble	1000 - 10000
Insoluble	> 10000

Partition Coefficient:

- It is the ratio of unionized drug distributed between organic and aqueous phase at equilibrium.
- $P_{o/w} = \left(\frac{C_{oil}}{C_{water}}\right)_{equilibrium}$

For determination of solubility the following points should be considered:

- The solvent & solute must be pure.
- A saturated solution must be obtained before any solution is removed for analysis.
- The method of separating a sample of saturated solution from undissolved solute must be satisfactory.
- The method of analyzing solution must be reliable
- Temperature must be adequately controlled.
- General Method of Increasing
- the Solubility

- Addition of co-solvent
- pH change method
- Reduction of particle size
- Temperature change method
- Addition of Surfactant
- Complexation
- Applications of solubilization
- Drugs with limited aqueous solubility can be solubilized. These include oil-soluble vitamins, steroid hormones and antimicrobial agents etc.
- Both oil-soluble and water-soluble compounds can be combined in a single phase system as in case of multivitamin preparations.
- Solubilization may lead to enhanced absorption and increased biological activity.
- Drug absorption from ointment bases and suppositories also increased.
- Aqueous concentrates of volatile oils can be prepared by solubilization.
- Example: soaps used for solubilising phenolic compounds for use as disinfectants-Lysol, Roxenol etc.
- Barbiturates, anticoagulant, alkloidal drugs are dissolved with polysorbate by solubilization.

Formulation Challenges with Poorly Soluble Compounds:

- Poor dissolution rate
- Low and variable bioavailability
- More potential for food effect
- Inability to deliver high doses for toxicity studies
- Difficulty in developing parenteral formulations

Stability:

- Stability is the extent to which a product retains (throughout its period of storage and use, i.e., its shelf life) the same properties that it possessed at the time of its manufacture.
- One of the principles of dosage form design is to ensure that the chemical integrity of drug substances is maintained during the usable life of the product.
- Three types of stability concern the pharmacists:
  - **(i) Chemical:** Each active ingredient retains its chemical integrity within the specified limits.
  - **(ii) Physical:** The original physical properties (including appearance, taste, color and odor) are retained.
  - **(iii) Biological:** Sterility is retained (No microbial growth).

1.3 CHEMICAL PROPERTIES

1.3.1 Hydrolysis

Drug molecules interact with water (drug) molecules to yield breakdown product. Susceptible to the hydrolytic process: esters, substituted amides, lactones, and lactams. E.g.: Anesthetics, antibiotics, vitamins and barbiturates.

1. Ester Hydrolysis:

Acid + Alcohol (involves rupture of a covalent linkage between a carbon atom and an oxygen). Catalysts – polar nature such as mineral acids, alkalies or λ certain enzymes – capable of supplying H^{++} and OH^{-} ions.

Kinetic study of hydrolysis of Aspirin was done in various buffer solutions. It was observed e.g. Aspirin is most stable at 2.4, at pH 5 to 7, degradation is pH independent and above pH 10 stability decreases with increase in pH.

Factors to be considered in Hydrolysis :

(i) pH

(ii) Type of solvent: solvent lower dielectric constant Eg.: ethanol, glycols, mannitol etc.

(iii) Complexation : steric or polar effects. Eg.: caffeine with benzocaine – electronic influence of complexing agent - alters affinity.

(iv) Surfactants: nonionic , cationic , anionic stabilizes drug against base catalysis. Eg: 5% SLS – 18 folds increase in $t_{1/2}$ of benzocaine Modification of chemical structure Salts and esters.

2. Amide Hydrolysis:

Hydrolytic reaction results Amide Acid + Amine. E.g.: Chloramphenicol, Nicinamides. Ring alterations: hydrolysis proceed as a result of ring cleavage. ring cleavage. E.g. Pilocarpine.

1.3.2 Oxidation and Reduction: Second Most Common Way

Oxidation: Presence of oxygen

- Initiated by heat, light or trace metal ions that Initiated by heat, light or trace metal ions that produce organic free radicals.
- These radicals propagate the oxidation reaction, which proceeds until inhibitors destroy the radicals or until side reactions eventually break radicals the chain.
- E.g. Dopamine.

Substance is oxidized when:

- If electrons are removed from it.
- Gains electronegative atoms or radicals or loses electropositive atoms or radicals.
- Addition of oxygen and removal of hydrogen.
- Most common: Autoxidation (free radical chain process).
- Involves homolytic bond fission of a covalent– each atom retains one of the electrons of original covalent bond.

Autoxidation:

- Initiation:

  $$RH \xrightarrow[\text{Light, Heat}]{\text{Activation}} R. + H.$$

- Propagation:

  $R. + O_2 \longrightarrow RO_2.$

  $RO_2. + RH \longrightarrow ROOH + R.$

- Hydroperoxide decomposition

  $ROOH \longrightarrow RO. + .OH$

- Termination.

  $RO_2. + X \longrightarrow$ Inactive product

  (X converts to peroxides group)

- $RO_2 + RO_2 \longrightarrow$ Inactive products
- Rate of prednisolone: Presence of aerobic and anaerobic conditions.
- Rancidity – oils and fats
- Oxygen content and Antioxidants

Photolysis:

- Photochemical
- Photosensitizer
- UV- violet portions – more active (shortet wavelength, more energy).

1.3.3 Racemization

Racemization is the process in which one enantiomer of a compound, such as an L-amino acid, converts to the other enantiomer.

- The compound then alternates between each form while the ratio between the (+) and (–) groups approaches 1 : 1, at which point it becomes optically inactive.
- If the racemization results in a mixture where the enantiomers are present in equal quantities, the resulting sample is described as racemeric or a racemate.
- The inter-conversion from one isomer to another can lead to a different pharmacokinetic properties (ADME) as well as of different pharmacological and of toxicological effect.
- Example: L-epinephrine is 15 to 20 times more active than D-form, while activity of racemic mixture is just one half of the L-form.
- It depends on temperature, solvent, catalyst and presence or absence of light.
- Biological significance: Many psychotropic drugs show differing activity or efficacy between isomers, e.g. Amphetamine is often dispensed as racemic salts while the more active dextro-amphetamine is reserved for severe indications; another example is Methadone, of which one isomer has activity as an opioid agonist and the other as an NMDA antagonist.

1.4 PARENTERAL DOSAGE FORM

Parenteral refers injectable route of administration. It derived from Greek words Para (Outside) and enteron (Intestine). So it is a route of administration other than the oral route. This route of administration bypasses the alimentary canal Pyrogens, fever-producing substances are primarily lipid polysaccharide product of metabolism of microorganism; they may be soluble, insoluble, or colloid,

Parenteral Dose Forms:

1. Parenteral preparations must be sterile - free of microorganisms.
2. To ensure sterility, parenterals are prepared using
   - aseptic techniques
   - special clothing (gowns, masks, hair net, gloves)
   - laminar flow hoods placed in special rooms.

Advantages of the Parenteral Route:

1. The IV route is the fastest method for delivering systemic drugs
   - preferred administration in an emergency situation.
2. It can provide fluids, electrolytes, and nutrition
   - patients who cannot take food or have serious problems with the GI tract.
3. It provides higher concentration of drug to bloodstream or tissues
   - advantageous in serious bacterial infection.
4. IV infusion provides a continuous amount of needed medication without fluctuation in blood levels of other routes.
5. Infusion rate can be adjusted
   - to provide more or less medication as the situation dictates, drug action can be prolonged by modifying the formulation.

Disadvantages of the Parenteral Route:

1. Traumatic injury from the insertion of needle.
2. Potential for introducing:
   - Toxic agents
   - Microbes
   - Pyrogens
3. Impossible to retrieve if adverse reaction occurs.
   - injected directly into the body.
4. Correct syringe, needle, and technique must be used.
5. Rotation of injection sites with long-term use
   - prevents scarring and other skin changes.
   - can influence drug absorption.

1.4.1 Routes of Administration of Parenteral Products

Various types of route of administration of Parenteral products are:

Intradermal Injection:

- Subcutaneous (Hypodermis) injection
- Intramuscular injection

- Intravenous injection
- Intra-arterial injection
- Intracardiac injection
- Intrathecal injection
- Intracisternal injection
- Peridural injection
- Intra-articular injection
- Intracerebral injection

Subcutaneous Injections:

- Given at a 45-degree angle 25- or 26-gauge needle, 3/8 to 5/8 inch length.
- No more than 1.5 ml should be injected into the site to avoid pressure on sensory nerves causing pain and discomfort.
- Administer medications below the skin into the subcutaneous fat outside of the upper arm top of the thigh lower portion of each side of the abdomen not into grossly adipose, hardened, inflamed, or swollen tissue.
- Often have a longer onset of action and a longer duration of action compared with IM or IV injection.

Intramuscular Injections:

- Care must be taken with deep IM injections to avoid hitting a vein, artery, or nerve.
- In adults, IM injections are given into upper, outer portion of the gluteus maximus large muscle on either side of the buttocks.
- For children and some adults, IM injections are given into the deltoid muscles of the shoulders.
- Typical needle is 22-25 gauge ½- to 1-inch needle.
- IM injections are administered at a 90^{o} angle volume limited to less than 3 ml.

Intravenous Injections or Infusions:

- Fast-acting route because the drug goes directly into the bloodstream often used in the emergency department and in critical care areas.
- Commonly used for fluid and electrolyte replacement to provide necessary nutrition to the patient who is critically ill.
- Intravenous (IV) injections are administered at a 15^{o} to 20^{o} angle.

Intra Arterial Injections:

- These injections are given directly in to the artery.

Intracardiac injections:

- These are given into the heart muscle or ventricle at the time of emergency only.

Intrathecal Injections:

- These are given into subachonoid space the surround the spinal cord. This route is used for spinal anaesthesia.

Official types of injections:

1. **Injection:** Liquid preparations that are drug substances or drug solutions thereof e.g. insulin injection USP.
2. **For injection:** Dry solid that, upon addition of suitable vehicles yield solutions confirming in all respect to the requirements to the injection. e.g. Cefuroxime injection USP.
3. **Injectable emulsions:** Liquid preparation of drug substance dispersed in a suitable emulsion medium. e.g. Propofol USP.
4. **Injectable suspension:** Liquid preparation of solid suspended in a suitable medium. e.g. Methyl Prednisolone Acetate Suspension USP.
5. **For injectable suspension:** Dry solid that upon addition of suitable vehicle yields preparation confirming in all respect to the requirements for Injectable suspension. e.g. Imipenem and Cilastatin Injectable suspension.

General Requirements of Parenteral Preparations:

- Stability
- Sterility
- Free from pyrogens
- Free from foreign particles
- Isotonicity
- Specific gravity
- Chemical purity

Formulation of Parenteral Products:

In the preparation of parenteral products, the following substances are added to make a stable preparation:

1. **The active drug**
2. **Vehicles:**
   - Aqueous vehicle (e.g. water for injection, water for injection free from CO_2)
   - Non-aqueous vehicle (e.g. Ethyl alcohol, propylene glycol, almond oil)
3. **Adjuvant:**
   - Solubilizing agents (e.g. Tweens and polysorbates)
   - Stabilizers and antioxidants (e.g. thiourea, ascorbic acid, tocopherol)
   - Buffering agents (e.g. citric acid, sodium citrate)
   - Antibacterial agents (e.g. benzyl alcohol, metacresol, phenol)
   - Chelating agents (e.g. EDTA)
   - Suspending, emulsifying and wetting agents (e.g. MC, CMC)
   - Tonicity factor (e.g. sodium chloride, dextrose)

1.5 PROCESSING OF PARENTERAL PREPARATION

Following steps are involved in the processing of parenteral preparation:

1. Cleaning of containers, closures and equipments.
2. Collection of materials.
3. Preparation of parenteral products.
4. Filtration.
5. Filling the preparation in final container.
6. Sealing the container.
7. Sterilization
8. Evaluation of the parenteral preparation.
9. Labelling and packaging.

1. Cleaning of containers, closures and equipments: Thoroughly cleaned with detergents with tap water distilled water finally rinsed with water for injection. Rubber closures are washed with 0.5% sodium pyrophosphate in water.

2. Collection of materials: All raw material of preparation should be collected from warehouse after accurate weighed. Water for injection should be Pyrogens free.

3. Preparation of parenteral products : The Parenteral preparation must be prepared in aseptic conditions. The ingredients are accurately weighed separately and dissolved in vehicle as per method of preparation to be followed.

4. Filtration: The Parenteral preparation must be filtered by bacteria proof filter such as, filter candle, membrane filter.

5. Filling the preparation in final container: The filling operation is carried out under strict aseptic precautions.

6. Sealing the container: Sealing should be done immediate after filling in aseptic environment.

7. Sterilization: For thermostable substances, the Parenteral products are sterilized by autoclaving method at different temperature and pressure. E.g. 10 lb pressure (115.5^{o}C, or 240^{o}F) for 30 minutes, 15 lb pressure (121.5^{o}C, or 250^{o}F) for 20 minutes, 20 lb pressure (126.5^{o}C, or 260^{o}F) for 15 minutes. Heat sensitive or moisture sensitive materials are sterilized by exposure to ethylene oxide or propylene oxide gas.

8. Evaluation of the Parenteral preparation: The following tests are performed in order to maintain quality control:

- Sterility test
- Clarity test
- Leakage test
- Pyrogen test
- Assay

9. Labelling & packaging

1.5.1 Evaluation of Parenteral Products

- Sterility testing
- Particulate matter monitoring
- Faculty seal packaging or leakage test

- Pyrogens testing
- LAL test
- Assay or drug content uniformity .

Sterility testing:

Definition: It is a procedure carried out to detect and conform absence of any viable form of microbes in or on pharmacopeia preparation or product.

Principle: Sterility testing only shows that organisms capable of growing in selected conditions are absent from the fraction of batch that has been tested. If the microorganism are present in the product can be indicated by a turbidity in the clear medium.

1.5.2 Objectives of Sterility Testing

- For validation of sterilization process.
- To check presence of microorganisms in preparation which are sterile.
- To prevent issue of contaminated product in market.

1.5.3 Steps involved in Sterility Testing

- Sampling
- Selection of the quantity of the product to be used
- Methods of sterility testing:
  (i) Method 1: Membrane filtration method
  (ii) Method 2: Direct inoculation method
- Observation and interpretation must be carried out under aseptic condition.

1. Sampling: The sample must be representative of the whole of the bulk material and a lot of final containers.

It is mainly followed by two rules:

- A fixed percentage of the final container are selected.
- A fixed number of containers are taken independent of the lot or batch size.

2. Selection of the quantity of the product to be used: Selection of the quantity of the product to be used for sterility testing depends mainly on the volume or weight in the container.

3. Methods of sterility testing :

(i) Membrane filtration method (Method 1):

- Membrane filtration method is appropriate for :
  - Filterable aqueous preparations
  - Alcoholic preparations
  - Oily preparations
  - Preparations miscible with or soluble in aqueous or oily (solvents with no antimicrobial effect.
- All steps of this procedure are performed aseptically in a Class 100 Laminar Flow Hood.

Membrane filter 0.45 µ porosity, Filter the test solution. After filtration remove the filter. Cut the filter in to two halves. First half (for Bacteria) and Second half (for fungi), Transfer in 100 ml culture media (Fluid Thioglycollate medium). Incubate at 30-35^{o}C for not less than 7 days. Transfer in 100 ml culture media (Soyabeans-Casein Digest medium). Again incubate at 20-25^{o}C for not less than 7 days. Observe the growth in the media.

(ii) Direct inoculation method (Method 2):

- Suitable for samples with small volumes.
- Volume of the product is not more than 10% of the volume of the medium.
- Suitable method for aqueous solution, oily liquids, ointments and creams.
- Suitable quantity of the preparation to be examined is transferred directly into the appropriate culture medium and incubate for not less than 14 days.

Observation and results:

Culture media is examined during and after at the end of incubation.

The following observations are possible:

- No evidence of growth pass the test for sterility.
- There is evidence of growth re-testing is performed same number of sample, volume and media as in original test. No evidence of growth pass the test for sterility.
- There is evidence of growth isolate and identify the organism. Re-testing is performed with twice number of sample if: No evidence of growth pass the test for sterility. There is evidence of growth Fail the test for sterility.

1.6 THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

- The BCS is a scientific framework for classifying drug substances based on their Aqueous Solubility and Intestinal Permeability.
- When combined with the dissolution of the drug product, the BCS take into account three major factors that govern the rate and extent of drug adsorption from IR solid oral dosage forms. These factors are Dissolution, Solubility and Intestinal Permeability.
- The aim of the BCS is to provide a regulatory tool for the replacement of certain BE studies by conducting accurate in-vitro dissolution tests.

According to the BCS, Drug substances are classified as follows:

- Class I - High Permeability, High Solubility
- Class II - High Permeability, Low Solubility
- Class III - Low Permeability, High Solubility
- Class IV - Low Permeability, Low Solubility

Class I - High Permeability, High Solubility

- Drugs dissolved rapidly.
- Drugs absorbed rapidly.
- Rapid therapeutic action.
- Excellent property.
- Ideal for oral route.
- e.g. Metoprolol, Diltiazem, Verapamil, Propranolol.

Class II - High Permeability, Low Solubility

- Drugs dissolved slowly.
- Drugs absorbed rapidly.
- Controlled released drugs.
- Oral / IV route for administration.
- e.g. Glibenclamide, Ezetimibe, Phenytoin, Nifedipine.

Class III - Low Permeability, High Solubility

- Dissolved rapidly
- Absorbance is limited
- Incomplete bioavailability
- Oral / IV route for administration
- e.g. Cimetidine, Acyclovir, Captopril

Class IV - Low Permeability, Low Solubility

- Low dissolution rate
- Low permeability property
- Slow or low therapeutic action
- IV or other routes are required
- e.g. Hydrochlorothiazide

Significance of BCS

- Regulatory toll for replacement of certain BE studies.
- It can save both time and money - if the immediate - release, orally administered drug meets specific criteria, and the FDA will grant a waiver for expensive and time consuming bio-equivalence studies.
- Valuable tool for formulation scientist for selection of design of formulated drug substance.
- When integrated with other information provides a tremendous tool for efficient drug development.
- Reduces cost and time of approving scale-up and post approval challenges.
- Applicable in both pre-clinical and clinical drug development process.
- Works as a guiding tool in development of various oral drug delivery systems.

QUESTIONS

Long essay Questions: (10 marks each)

1. Define preformulation. Explain the preformulation study of solid in details.
2. Define stability. Explain stability study of solid and liquid dosage form.
3. Explain the objective of preformulation study in parentral preparation.

Short essay questions: (5 marks each)

1. Define BCS classification. Explain the objectives of BCS class in brief.
2. What is polymorphism? Differentiate between crystalline form and amorphous form.
3. Explain the effect of light in different dosage forms.

Short answer questions: (2 marks each)

1. Define Prodrug with a suitable example.
2. What is recemization?
3. Define molecular adducts and list out its types.

☆☆☆

Chapter 2 ...

TABLETS

Upon completion of the chapter, students will be able to understand:

- *Ideal Characteristics of Tablets*
- *Classification of Tablets*
- *Excipients*
- *Formulation of Tablets*
- *Granulation Methods*
- *Compression and Processing Problems*
- *Equipments*
- *Tablet Cooling*

2.1 INTRODUCTION

Per oral tablets occupy the broadest and the most significant place among all pharmaceutical dosage forms. Taking one or two tablets a day with a glass of water is the easiest and the most acceptable way of administration of a drug to a patient.

Solid-dosage forms broadly encompass two types of formulation, namely tablets and capsules. It has been estimated that solid-dosage forms constitute circa 90% of all dosage forms used to provide systemic administration of therapeutic agents. This highlights the importance of these dosage forms in the treatment and management of disease states. The widespread use of tablets has been achieved as a result of their convenience and also the diversity of tablet types.

From the point of view of ease of manufacture, tablet production, compared with other dosage forms, provides the highest output per manufacturing hour, and is the most economical, especially if one considers modern manufacturing methods involving processes such as the direct compression (DC) or fluidized-bed granulation.

Tablets are solid dosage forms usually prepared with the aid of suitable pharmaceutical excipients. They may vary in size, shape, weight, hardness, thickness, disintegration, and dissolution characteristics and in other aspects, depending on their intended use and method of manufacture. Most tablets are used in the oral administration of drugs. Many of these are prepared with colorants and coatings of various types. Other tablets, such as those administered sublingually, buccally, or vaginally, are prepared to have features most applicable to their particular route of administration.

Tablets are prepared primarily by compression, with a limited number prepared by molding. Compressed tablets are manufactured with tablet machines capable of exerting great pressure in compacting the powdered or granulated material.

Their shape and dimensions are determined by the use of various shaped punches and dies. Molded tablets are prepared on a large scale by tablet machinery or on a small scale by manually forcing dampened powder material into a mold from which the formed tablet is then ejected and allowed to dry. Some tablets are scored, or grooved, which allows them to be easily broken into two or more parts. This enables the patient to swallow smaller portions as may be desired, or when prescribed, it allows the tablet to be taken in reduced or divided dosage. Some tablets that are not scored are not intended to be broken or cut by the patient since they may have special coatings and/or drug-release features that would be compromised by altering the tablet's physical integrity.

While tableting may appear from what has been said to be a facile process, it is often far from straightforward. Drug molecules show various differences in physical and chemical properties. These include differences in their crystalline structure, particle size, water solubility, dose, and sensitivity to hydrolysis or oxidation, Hence, every drug molecule must be treated as a unique entity for formulation. Drugs synthesized in the last 30 years have been increasingly showing limited water solubility, poor flow and compression properties, and sensitivity to moisture and heat. Preparing a tablet dosage form from such molecules is a challenge, since the market demands easy and cost-effective manufacturing, an acceptable dissolution rate, and of course high bioavailability, and mechanically strong tablets that resist fracture during packaging, transport, and ultimately, in patient use. Furthermore, the tablets must fulfill the requirements for bioavailability and, eventually, bioequivalence. When considering all these factors, designing and manufacturing a successful tablet requires optimization of the formulation and processing parameters, which can be achieved by the application of a thorough knowledge of excipients, and the subsequent selection of the most suitable manufacturing process.

2.1 IDEAL CHARACTERISTICS OF TABLETS

Like all other dosage forms, tablets should fulfil a number of specifications regarding their chemical, physical and biological properties. Quality issues relating to the final product are worth considering early in the development process (and thus early in this chapter) as they give an indication of the goal to be achieved during the development and manufacture of tablets.

Tests and specifications for some of these properties are given in pharmacopoeias. The most important of these are dose content and dose uniformity, the release of the drug in terms of tablet disintegration and drug dissolution, and the microbial quality of the preparation. In addition, the authorities and manufacturers define a set of other specifications. One such important property is the resistance of the tablet towards attrition and fracture.

The quality attributes of a tablet can be summarized as follows:

1. The tablet should include the correct dose of the drug.
2. The appearance of the tablet should be elegant and its weight, size and appearance should be consistent.

3. The drug should be released from the tablet in a controlled and reproducible way.
4. The tablet should be biocompatible, i.e. not include excipients, contaminants and microorganisms that could cause harm to patients.
5. The tablet should be of sufficient mechanical strength to withstand fracture and erosion during handling.
6. The tablet should be chemically, physically and microbiologically stable during the lifetime of the product.

2.3 CLASSIFICATION OF TABLETS

Types of Tablets and Tablet Design:

Tablet design is based on the experience and knowledge of excipients, which are materials serving the purpose of making a good tablet when combined with a drug. The mechanical and chemical properties of excipients have the utmost importance, and the area is closely related to materials engineering as well as pharmacy. Expected properties of a modern tablet include mechanical strength suitable for coating, packaging, and transportation; an optimum size, shape, and color for identification; ease of swallowing; and, finally, fulfilling the pharmacopoeial requirements for drug content and release rates as well as stability and bioavailability.

Some of the pharmaceutical tablet types based on the way of administration or presentation to the patient are listed below:

1. Simple uncoated tablets
2. Coated tablets
3. Effervescent tablets
4. Buccal and sublingual tablets
5. Chewable tablets
6. Multilayered tablets
7. Sugarcoated tablets
8. Fast-disintegrating tablets
9. Vaginal tablets
10. Osmotic tablets
11. Controlled-release tablets
12. Multicomponent tablets

1. **Simple uncoated tablets:** The simplest form of a pharmaceutical tablet consists of a combination of a drug and some functional excipients compressed directly. This tablet should be formed by compression without difficulty using binders, disintegrants, and lubricants, and when used by a patient, it should disintegrate in the stomach and should of course be bioavailable. Such simple tablets are manufactured by mixing the drug and excipients in a V-shaped mixer and are compressed in a tablet press using dies and punches of suitable size.

2. **Film-coated tablets:** A tablet can be coated with a polymer film to provide greater ease of swallowing, protection against light or moisture, protection of the drug from gastric acidity, and modification or control of drug release rate. Identification of a formulation by color or logo is extremely important today not only for patient safety but also because of the problem of counterfeiting. Polymers and processes are available to achieve all of these properties.

2.4 EXCIPIENTS

Tablet formulation design starts with a predetermined value, which is the dose size. The amount of drug in a tablet can be a limiting step in formulation design. Tablet excipients can be classified on the basis of their functionality as listed below:

1. Fillers/diluents
2. Binders
3. Disintegrants
4. Lubricants
5. Glidants
6. Buffering agents
7. Sweeteners
8. Wetting agents
9. Coating agents
10. Matrix formers

2.4.1 Fillers/Diluents

Fillers are used to arrive at a tablet of reasonable size when a drug forms a small portion of the formula, as in the case of 25 mg estradiol vaginal tablets. Depending on the physiological conditions and formulation, one needs a tablet of around 100 mg for ease of handling and administration, and therefore, fillers are used to increase bulk. Usually, a lactose monohydrate is the first material to be considered. This water-soluble disaccharide is obtained from whey by crystallization and drying after cheese production. Lactose is a water-soluble diluent, 216 mg dissolving in 1-mL water. Using three different drying techniques, fluidized-bed methods, roller drying, and spray drying, a-lactose monohydrate, anhydrous b-lactose, and spray-dried lactose are obtained, respectively. The three different lactose grades differ considerably in their mechanical properties in relation to tableting. For instance, anhydrous b-lactose shows a steep compression force–tablet crushing strength relation. On the other hand, a-lactose monohydrate and even spray-dried lactose are inferior grades in this respect. Spray drying of lactose forms partial amorphous structures, and that contributes to its better compressibility. Spray-dried lactose flows well because of its spherical granule shape.

Therefore, the mechanical properties and the size distribution of lactose types must be known before making a selection out of many lactose grades. A partial list of excipients used in tablet manufacturing is following:

Fillers/Diluents Used in Tablet Formulations are:

- Lactose (a-lactose monohydrate, anhydrite b-lactose, spray-dried lactose)
- Microcrystalline cellulose (Avicel PH 101, Avicel PH 200, Emcocel)
- Starch (Corn starch, partially hydrolyzed starch)
- Dibasic calcium phosphate (Emcompress, Di-Tab)
- Mannitol (Parteck, Delta M)
- Sorbitol (Neosorb 60)
- Calcium sulfate (Delaflo)
- Compressible sucrose (Di-Pac, Des-tab, Nu-Tab)

1. Starch:

Starch has been used as a tablet/capsule excipient for a long time. Unlike lactose, starch has a multifunctional use in solid dosage forms. It serves as a filler/diluent as well as a disintegrant, and also as a binder in the form of starch paste. Depending on the region, starch can be obtained from corn, potatoes, wheat or rice. It contains amylase and amylopectin units. Starch is not water soluble. For pharmaceutical purposes, starch does not flow well and cannot be compressed into strong compacts. Hence, partially pregelatinized starch is obtained by mechanical means such as rupturing the starch granules between hot rollers to render it partial water soluble. This contributes to its binding properties because of about 15% free amylopectin, 5% free amylose, and 80% unmodified starch. Starch normally has the highest equilibrium moisture content among all pharmaceutical excipients, that is to say, about 11% to 14%. In general, starch or modified starch does not have good mechanical properties for tableting processes without the contribution of other plastic deformation-showing materials. On the other hand, starch is a good disintegrant in tablets, especially in the form of its semisynthetic derivative such as sodium carboxymethyl starch, which is extremely important. Its abundance and low cost make it a major pharmaceutical excipient.

2. Microcrystalline Cellulose:

Since its introduction to the pharmaceutical industry in 1964 by FMC, microcrystalline cellulose (MCC) has revolutionized tablet formulation. MCC forms very strong compacts under even low compression pressures. It is obtained from wood pulp after controlled acid hydrolysis, which produces a high degree of crystallinity to the cellulose chains. After neutralization, filtering, and spray drying a white granular powder is obtained.

MCC has at least nine different commercial grades (Avicel PH grades, FMC, U.S.A.) according to its average particle size (20 –180 mm), moisture content (1.5–5.0%), bulk density (0.25–0.44 g/ml), and volumetric flow (1.5–5.0 lit/min) for applications ranging from wet granulation to direct compression. MCC shows a strong plastic deformation under pressure and a high dilution potential. Therefore, good compressibility can be matched with good flow only by selecting the right grade or making a wet granulation to a certain size and shape. As a diluent, it is used in combination with spray-dried lactose or dicalcium phosphate dihydrate during the DC tableting to balance the cost or flow properties. In a compression force–crushing strength plot, MCC shows the steepest line among all excipients reaching 20- kg tablet crushing strength at about 750 kg force. MCC is not water soluble but

absorbs water. In a fluidized-bed granulation process, MCC requires the highest amount of water for the same granule size when compared to starch and lactose monohydrate.

3. Dicalcium Phosphate Dihydrate:

This water-insoluble material is among the top five excipients in modern tablet formulations. The true density of dicalcium phosphate dihydrate is 2.3 g/ml, which makes it one of the heaviest pharmaceutical excipients per volume with a reported tapped density of 0.7 g/ml. Dicalcium phosphate anhydrous is also available. At 2000 kg-f compression, tablet crushing strength reaches a maximum of 100 N with this excipient.

Therefore, its binding properties are inferior to those of MCC. The main mechanism of compaction of dicalcium phosphate is brittle fracture, creating new surfaces, which therefore shows much less lubricant sensitivity: This can be an advantage over plastically deforming materials such as MCC or some starches. Dicalcium phosphate dihydrate, like other inorganic salts, has a detrimental effect on tablet tooling.

4. Mannitol:

Mannitol in various polymorphic forms is the main excipient of chewable tablets due to its negative heat of solution, which results in a pleasant mouth feel. A new mannitol grade, namely, d-mannitol (Parteck, Delta M) has been reported to be superior to the other polymorphs such as a or b-mannitol in terms of mechanical properties and chemical reactivity. Hence, tablets with higher crushing strengths can be manufactured. Mannitol is nonhygroscopic and shows a low reactivity with drug substances. Therefore, it has the potential to be utilized more in future tablet formulations.

5. Coprocessed Excipient Products:

Some flexibility is necessary in the design of tablet formulations. Selecting each excipient depends on the physical and chemical properties of the drug, the drug dose, and the required final form and function of the tablet. There are however aids for the formulator.

There are some coprocessed excipients containing usually a diluent and binder, and sometimes, even a disintegrant in a readymade granulation. LudipressTM (BASF, Germany) contains a-lactose monohydrate, polyvinylpyrrolidone (PVP), and Kollidon CL. Cellactose 80TM (Meggle, Germany) contains a-lactose monohydrate and cellulose powder, ProsolvTM SMCC (JRS Pharma, Germany), silicified MCC, contains 98% MCC and 2% colloidal silicon dioxide, which provides a better granule flow and an opportunity for smaller and denser tablets upon direct compression. There are also coprocessed actives like ascorbic acid, thiamine, riboflavine, pyridoxine, paracetamol, and acetyl salicylic acid. For those drugs that are manufactured in huge volumes, the use of coprocessed excipients is efficient, since the small capacity of many pharmaceutical manufacturing plants for wet or dry granulation cannot deal with huge volumes.

Materials that contribute to plastic deformation, which means stronger compacts upon compression or forming a matrix such as methyl cellulose (MC), HPMC, hydoxy propyl cellulose (HPC), cellulose powder, gelatine, and mannitol are used. Coprocessed products are so designed that by simple addition of the drug, compressed tablets may be produced. Using coprocessed active allows minimum excipient addition and manipulation.

2.4.2 Binders

Binders used in Tablet Formulation are:

- Polyvinylpyrrolidone (PVP)
- Sodium carboxymethyl cellulose
- HPMC (Low molecular weight, 5 cps)
- Starch paste
- Simple syrup

Binders in tablet technology serve the purpose of binding small drug or excipient particles together to impart cohesiveness, and to form a granulate of a designed size range, usually larger than the initial material that flows freely and is also compressible, and eventually to be compressed into tablets or to be filled into capsules. A binder will help the tablet to remain intact after compression. Binders can be added as dry powders to form a matrix that will include the drug, as in the case of dry granulation or in direct compression. Sometimes, the binders are dissolved in liquids such as water or alcohol and then sprayed onto the powder mixture as with wet granulation. Materials such as MCC act as a binder/ diluent in the case of direct compression. However, a polymer such as PVP is solely used as a binder. One of the commercial products of PVP is KollidonTM (BASF), which has grades on the basis of molecular weight of the polymer: Kollidon K 25 (MW 28,000– 34,000), K 30 (MW 44,000–54,000), and K 90 (MW 1,000,000–1,500,000) contain PVP of increasing molecular weights. PVP has some advantages over other binders: it is used in relatively small concentrations such as 1% to 5% to prepare a binder solution, it is soluble to above 10% in water, ethanol, and glycerol, which provides an opportunity for water-free granulation. One of the most significant advantages of PVP is its low viscosity (5–10 mPa.sec) even up to concentrations as high as 20% (w/v). A low-viscosity solution can easily be sprayed using peristaltic pumps during a fluidized-bed granulation. Starch paste has been a traditional binder, at concentrations between 5% and 10%. Starch is dispersed in cold water, and then slowly heated up to boiling with constant stirring. When a translucent paste is formed, it can be diluted with cold water. On the other hand, preparing a starch paste with modified starch will not require boiling, since it dissolves in warm water because of the free amylopectin. In modern granulation processes using high shear mixers, starch paste finds few applications. HPMC, MC, HPC, and ethyl cellulose can be used as binders in tablet formulations. These cellulose-based binders perform as well as PVP in modern granulation processes. Hydrophilic polymers, especially of low molecular weight, for instance HPMC E6 (6 CP viscosity grade), can be dissolved in water to obtain a low-viscosity solution, and they bind well and contribute to plastic deformation during tableting. The high-molecular weight grades of these cellulose-based materials can be used as matrix formers, and incorporated into formulations as dry binders. Ethyl cellulose is not water soluble, so it is used as an alcoholic solution. Materials such as PVP and HPMC have largely replaced other binders such as gelatine, sucrose, simple syrup, or acacia.

2.4.3 Disintegrants

Disintegrants serve the purpose of facilitating the disintegration of tablets into its components either after administration in the GI tract or just before administration, such as in the case of the fast-disintegrating tablets. Disintegrants may play an important role in the bioavailability of a drug in tablet dose forms. When disintegrants come into contact with water, they usually swell, as their cross-linked molecular structure, such as in amylose in starch or in cross-linked PVP, imbibes water and swells, providing the force to disperse the tablet. Depending on the formulation design, some tablets containing higher percentages of MCC may disintegrate readily during disintegration tests without an additional disintegrant. Addition of starches externally to the final granulation before tableting is best justified for disintegration purposes. Starch is a "mild" tablet disintegrant. In the past, there was concern that tablet compression forces should not exceed certain limits or tablet crushing strengths 70 to 80 N because of the probability of prolonged disintegration times. However, with the advent of modern excipients, mechanically strong tablets with 200 to 300 N crushing strengths can be produced, and these tablets will disintegrate within five minutes or less using the super-disintegrants. Super-disintegrants are materials added to tablet formulations in a range of 1% to 5% to assure disintegration within 1 to 10 minutes. Among these are sodium carboxymethyl starch (ExplotabTM, Mendell, U.S.A.), cross-linked sodium carboxymethyl cellulose (PharmacelTM XL, DMV, Netherlands), and cross-linked PVP (KollidonTM XL, BASF). The rank order of the degree of swelling in water in two minutes for those disintegrants has been reported to be sodium carboxymethyl starch > sodium carboxymethyl cellulose > L-HPC 11 > cross-linked PVP > starch > MCC.

2.4.4 Lubricants

Lubricants and Glidants used in Tablet Formulations are:

- Magnesium stearate
- Stearic acid
- Sodium stearyl fumarate
- Hydrogenated vegetable oil
- PEG 4000, 6000
- Hexagonal boron nitride
- DL-Leucine
- Sodium lauryl sulfate
- Gliceryl behenate
- Sodium benzoate
- Colloidal silicone dioxide
- Talc
- Starch
- Super disintegrants
- Sodium starch glycolate (Explotab)
- Cross-linked PVP (Polyplasdone XL)
- Cross-linked carboxymethyl cellulose (Ac-Di-Sol)

Pharmaceutical lubricants are materials used in tablet formulations to reduce the friction between the lower punch and the die and the tablet. Friction damages both the tablet and the tablet press during the ejection cycle. Lubricants are a mechanical necessity, without which modern tablet manufacturing would be impossible. Glidants are materials that reduce interparticular friction, covering the particle surfaces with a thin layer, and as a result helping in better granule flow. Colloidal silicon dioxide, talc, and starch can be used as glidants; colloidal silicon dioxide is effective as low as 0.5% as a glidant. Lubricants are added to pharmaceutical granules just before the tabletting stage. Mixing the main granule mass with a lubricant has been an intensively investigated subject. Prolonged mixing with a surface-covering lubricant such as magnesium stearate negatively affects the binding capacity of a granule mass. Hence, tablet formation might be inhibited, unless the granule mass undergoes brittle fracture and creates new clean surfaces. Especially, materials exhibiting plastic deformation with a limited surface area would show a strong sensitivity to lubricants. Therefore, the specific surface area of a lubricant as well as the surface area of the granule mass are both important parameters in selecting lubricant type, concentration, and mixing times. Boundary lubricants will adhere on the metal surfaces of the tablet press, die, and punches and will form a boundary layer with the tablet. Alkaline stearates such as magnesium stearate are an example of a boundary lubricant. Magnesium stearate is still the most effective pharmaceutical lubricant. Its usual concentration range is between 0.1% and 2%, and its effectiveness shows a biphasic profile, a region of a fast reduction in friction up to 1 %, and a slower friction-reducing effect after 1%. Magnesium stearate reduces not only the lower punch ejection force by about 70% but also tablet tensile strength. Stearic acid is the second most important lubricant. It is not as effective as magnesium stearate, the minimum effective stearic acid concentration is about 1%, and it reduces the lower punch ejection force no more than 30%. This fatty acid is however useful when an alkaline ingredient in a tablet formula is undesirable. The hexagonal form of boron nitride (HBN) has been reported as a potential tablet lubricant. HBN is similar to graphite, which is soft and lubricious. This inorganic solid powder retains its ability to lubricate in extreme cold or heat.

It was reported that boron nitride reduced the lower punch ejection force as efficiently as magnesium stearate, but its ability to reduce the tablet tensile strength is less than magnesium stearate. The result is mechanically stronger tablets. Therefore, there is a good potential for HBN to be used as a tablet lubricant. For effervescent tablets, water-soluble lubricants are required since insoluble alkaline lubricants would accumulate on the surface of final solution or form a cloudy solution with an alkaline taste, all of which is undesirable. Sodium lauryl sulfate, DL-leucine, or various PEGs can be used as water-soluble lubricants. Liquid paraffin and hydrogenated vegetable oil are also among the lubricants, but their effectiveness is lower than that of magnesium stearate and stearic acid.

2.5 FORMULATION OF TABLETS

The size and, to some extent, the shape of the tablet are determined by the active ingredient(s). Drugs having very small doses in the microgram range (e.g. folic acid, digitoxin, reserpine, dexamethasone, etc.) require the addition of fillers also called excipients

to be added to produce a mass or volume of material that can be made into tablets of a size that is convenient for patients. A common and convenient size for such low-dosage drugs is a 1/4-in. round tablet or equivalent in some other shape. It is difficult for some patients to count and handle tablets smaller than this.

Tablets of this size ordinarily weigh 150 mg or more depending on the density of the excipients used to make up the tablet mass.

As the dose increases, so does the size of the tablet. Drugs with a dose of 100 to 200 mg may require tablet weights of 150 to 300 mg and round die diameters of 1/4 to 7/16 in. in diameter depending on the density and compressibility of the powders used. As the dose of the active ingredient(s) increases, the amount of the excipients and the size of the tablet may vary considerably depending on requirements of each to produce an acceptable tablet. While the diameter of the tablet may in some cases be fixed, the thickness is variable thus allowing the formulator considerable latitude and flexibility in adjusting formulations.

As the dose, and therefore the size, of the tablet increases, the formulator uses his expertise and knowledge of excipients to keep the size of the tablet as small as possible without sacrificing its necessary attributes. Formulation of a tablet requires the following considerations:

1. Size of dose or quantity of active ingredients
2. Stability of active ingredient(s)
3. Solubility of active ingredient(s)
4. Density of active ingredient(s)
5. Compressibility of active ingredient(s)
6. Selection of excipients
7. Method of granulation (preparation for compression)
8. Character of granulation
9. Tablet press, type, size, capacity
10. Environmental conditions (ambient or humidity control)
11. Stability of the final product
12. Bioavailability of the active drug content of the tablet

The selection of excipients is critical in the formulation of tablets. Once the formulator has become familiar with the physical and chemical properties of the drug, the process of selecting excipients begins. The stability of the drug should be determined with each proposed excipient. This can be accomplished as follows: In the laboratory, prepare an intimate mixture of the drug with an excess of each individual excipient and hold at 60 DC for 72 hr in a glass container. At the end of this period, analyze for the drug using a stability-indicating assay.

2.6 GRANULATION METHODS

Granulation Process:

Once a tablet formulation is designed with drug, binder, disintegrant, diluent, pH buffer, lubricant, or a matrix former polymer, a manufacturing method must also be determined.

The manufacturing method will depend on the dose of active ingredient, the limitations of drug substance such as heat sensitivity or water insolubility, availability of specialized equipment such as high-shear granulators or fluidized beds, the time frame for manufacturing, and the batch size. Certain manufacturing methods can be used interchangeably. On the other hand, sometimes a specific manufacturing method must be employed, for instance, passing the formulation three times through a roller compactor and compressing a 1500-mg formulation to produce a tablet of reasonable size.

Therefore, deciding on a manufacturing method is a complex task that requires time, equipment, and formulation optimization, as well as a close collaboration between formulation scientists and process engineers. In general terms, there are three manufacturing processes for tablets: (1) wet granulation, (2) dry granulation, and (3) direct compression as discussed below.

2.6.1 Wet Granulation - [Aqueous Granulation Technique]

The purpose of wet granulation is to convert the drug and excipient mixture into granules that flow well into dies, and which are compressible into mechanically strong and acceptable tablets. Wet granulation has many subtypes.

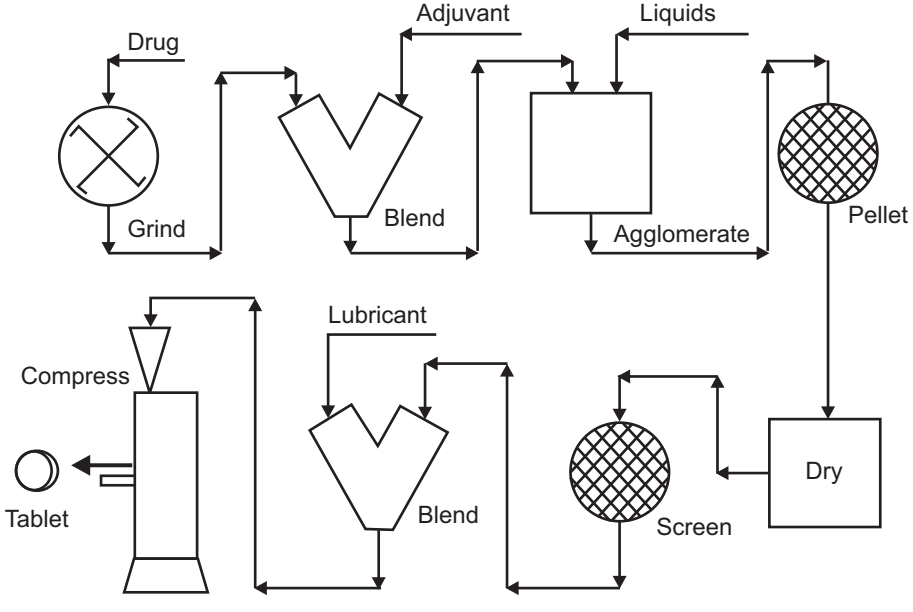


Fig. 2.1: Wet granulation method

The classical traditional wet granulation operation consists of the following processes:

- Premixing drug with other ingredients using a V-shaped mixer.

- Transferring the mixture into a traditional low shear granulator where a binder solution is added under a mechanical shear until a certain granule size and binding are obtained.
- Wet sieving of granules through a desired screen size.
- Drying of granules in a tray-oven dryer.
- Dry sieving/milling of granules to a certain particle size distribution.
- Adding a lubricant to the dry granules.
- Compressing the granules into tablets.

The wet granulation operation as described above has been used for more than 50 years in the pharmaceutical industry, and there is a great expertise on this area. However, introduction of new materials and equipment, changing manufacturing needs, and time limitations for manufacturing have brought new modifications to classical wet granulation. Two different modified wet granulation operations are summarized below:

Modification to traditional wet granulation involves the following:

- Premixing drug with other ingredients using a V-shaped mixer or a high-shear mixer/granulator
- Transferring the mixture into a high-shear granulator where a binder solution is added, and a certain granule size is obtained in a very short time.
- Wet sieving of granules through a desired screen size may or may not be required because of very uniform and narrow particle size distribution.
- Drying of granules in a fluidized bed or in a microwave dryer.
- Alternatively, drying the wet mass in the same high-shear mixer/granulator.
- Dry sieving/milling of granules to a certain particle size distribution.
- Adding a lubricant to dry granules.
- Compressing the granules into tablets.

Modification to traditional wet granulation-II involves the following:

- Premixing drug with other ingredients using a V-shaped mixer.
- Transferring the mixture into a fluidized-bed granulator where a binder solution is sprayed until a certain granule size and simultaneous drying occur.
- Dry sieving/milling of granules to a certain particle size distribution.
- Adding a lubricant to dry granules.
- Compressing the granules into tablets.

On the basis of the modifications summarized above, traditional wet granulation has become a more feasible, time-saving, and economical operation. In a regular workday, many batches can be manufactured with a high reproducibility. The high-shear granulators and/or fluidized-bed granulators/dryers are at the center of these operations. Among the advantages of wet granulation are better drug content uniformity for low-dose drugs, better mechanical tablet properties such as high crushing strength, and low friability due to well-distributed binder molecules over the drug and diluent particles. Expensive equipment, limited batch capacity, and the need for drying are among the disadvantages of wet granulation operations.

2.6.2 Dry Granulation - [Non-Aqueous Granulation Technique]

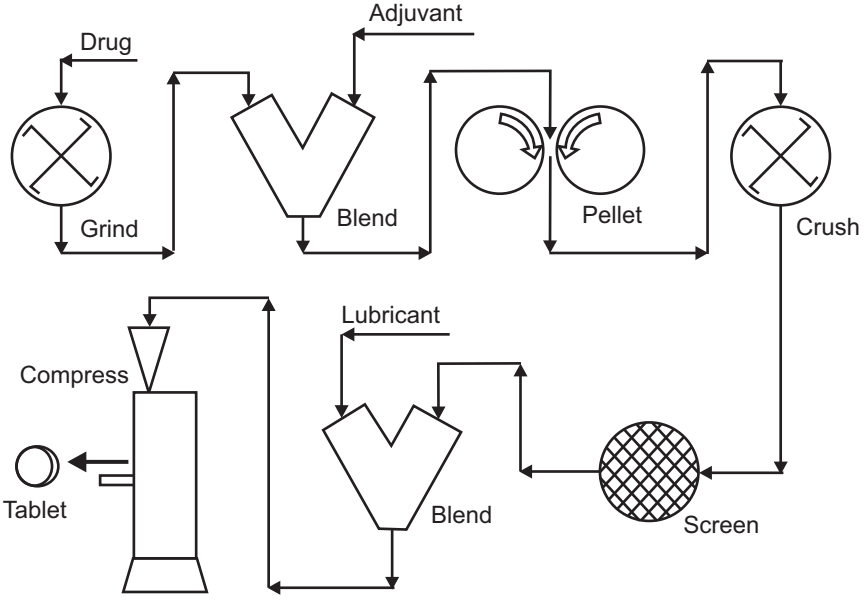


Fig. 2.2: Dry granulation method

Dry granulation is the method of producing granules without any solvent use or drying prior to tablet manufacturing. The flow and compressibility are attained by mechanical compression. A dry binder such as MCC or a polymer such as HPMC that will contribute to plastic deformation can be added to the mixture. In the past, before the availability of continuous roller compactors, compressing briquette tablets in specialized tablet presses and breaking those tablets into granules was the method of choice, but this operation produced dust and had other problems. Therefore, dry granulation was not a preferred way of manufacturing tablets. In modern application of dry granulation, counter-rotating steel rollers are used to apply pressure to the powder. The surface of these rollers can be smooth or grooved depending on the properties of the powder. The compressed product has a higher density upon processing between the rollers. Some formulations may require double or triple pass through roller compactor for maximum densification. The final product will require size reduction and sieving. Modern dry granulation using roller compactors is a straightforward, reproducible operation with few steps. Hence, it is a rapid and economical way of producing pharmaceutical granules. The selection and concentration of formulation ingredients as well as their mechanical properties are more critical in this process than in wet granulation.

Basic steps in Dry Granulation are:

- Premixing drug with other ingredients using a V-shaped mixer.
- Transferring the mixture into a roller compactor using a closed-circuit vacuum equipment to prevent dust formation.
- Milling/sieving of the resulting flakes or ribbons into granules.
- Adding lubricant and/or disintegrant to granules, and finally.
- Compressing the granules into tablets.

The operation parameters that affect the product properties as might be anticipated include roll pressure, speed, surface texture, and the gap between the rollers. The powders are fed to a roller compactor by a screw feeder under positive pressure. For those tablets that approach or exceed 1000 mg such as the 825 mg amoxicillin and 125 mg potassium clavulanate combination, dry granulation is the most feasible way of manufacture.

2.6.3 Direct Compression

As the name implies, this method involves no further processing of powders before tableting. A formulation is well mixed to ensure uniform drug distribution, and after adding a lubricant, tablets are compressed. However, the requirements for flowability and compressibility must be met by the excipients or the drug substance requires to be coated or processed. Since direct compression involves only mixing and compressing steps, it is the most preferred way of making tablets, given appropriate choice of excipients.

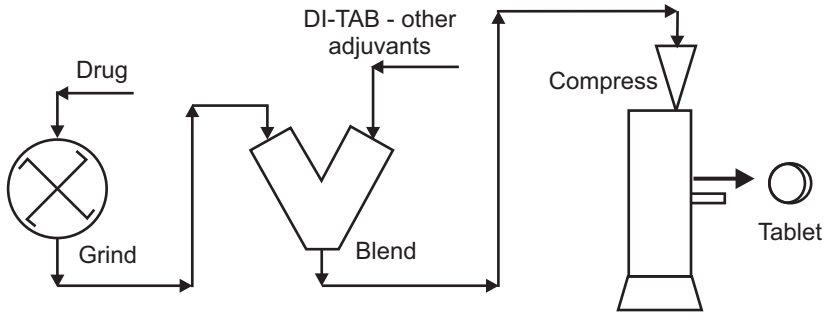


Fig. 2.3: Direction compression method

Steps in Direct Compression are:

- Premixing drug with other ingredients using a V-shaped mixer
- Adding a lubricant to the granules
- Mixing with lubricant 3 to10 minutes
- Compressing the granules

Availability of DC excipients does not guarantee the success of DC tabletting. The drug substance must also have appropriate compressibility and flowability if the drug represents more than one-third of tablet formulation. In that case, DC excipients may compensate for flowability and compressibility. If a drug powder with an insufficient flow and compressibility forms a large portion of a tablet, the DC method cannot be used.

Active materials such as acetaminophen, amoxicillin, ascorbic acid, thiamine, and riboflavine have DC grades. The DC grades are produced by coprocessing the actives with polymers such as MC, hydroxypropyl MC, acrylates, or PVP through a spray-drying or fluidized-bed coating process. Direct compression requires the use of directly compressible excipients, and thus limits a formulator's ability for further processing.

However, once a compressible formulation is designed, manufacturing is straightforward and simple. A pharmaceutical company that manufactures tablets only with DC method needs only powder-powder mixers and tablet presses, which means lower investment costs. MCC is the most important DC excipient. Other DC excipients include anhydrous b-lactose, spray-dried lactose, unmilled dicalcium phosphate dihydrate, pregelatinized starch, and mannitol DC.

2.7 COMPRESSION AND PROCESSING PROBLEMS

Defects related to tableting process:

1. **Capping:** It is partial or complete separation of the top or bottom of tablet due air-entrapment in the granular material.
2. **Lamination:** It is separation of tablet into two or more layers due to air-entrapment in the granular material.
3. **Cracking:** It is due to rapid expansion of tablets when deep concave punches are used.

Defects related to excipient:

1. **Chipping:** It is due to very dry granules.
2. **Sticking:** It is the adhesion of granulation material to the die wall
3. **Picking:** It is the removal of material from the surface of tablet and its adherance to the face of punch.
4. **Binding:** These problems (v, vi, vii) are due to more amount of binder in the granules or wet granules.

Defect related to more than one factors:

1. **Mottling:** It is either due to any one or more of these factors: Due to a colored drug, which has different color than the rest of the granular material (Excipient- related); improper mixing of granular material (Process-related); dirt in the granular material or on punch faces; oil spots by using oily lubricant.

Defect related to machine:

1. **Double Impression:** It is due to free rotation of the punches, which have some engraving on the punch faces. Further, in this section, each problem is described along-with its causes and remedies which may be related to either of formulation (granulation) or of machine (dies, punches and entire tablet press).

2.7.1 Capping

Capping is the term used, when the upper or lower segment of the tablet separates horizontally, either partially or completely from the main body of a tablet and comes off as a cap, during ejection from the tablet press, or during subsequent handling.

Reason: Capping is usually due to the air–entrapment in a compact during compression, and subsequent expansion of tablet on ejection of a tablet from a die.

Causes and Remedies of Capping related to Formulation (Granulation):

Causes:

- Large amount of fines in the granulation.
- Too dry or very low moisture content (leading to loss of proper binding action).
- Not thoroughly dried granules.
- Insufficient amount of binder or improper binder.
- Insufficient or improper lubricant.
- Granular mass too cold.

Remedies:

- Remove some or all fines through 100 to 200 mesh screen.
- Moisten the granules suitably. Add hygroscopic substance e.g. sorbitol, methyl-cellulose or PEG-4000.
- Dry the granules properly.
- Increasing the amount of binder.
- Adding dry binder such as pre-gelatinized starch, gum acacia, powdered sorbitol, PVP, hydrophilic silica or powdered sugar.
- Increase the amount of lubricant or change the type of lubricant.
- Compress at room temperature.

Causes and Remedies of Capping related to Machine (Dies, Punches and Tablet Press):

Causes:

- Poorly finished dies.
- Deep concave punches or beveled-edge faces of punches.
- Lower punch remains below the face of die during ejection.
- Incorrect adjustment of sweep-off blade.
- High turret speed.

Remedies:

- Polish dies properly. Investigate other steels or other materials.
- Use flat punches.
- Make proper setting of lower punch during ejection.
- Adjust sweep-off blade correctly to facilitate proper ejection.
- Reduce speed of turret (Increase dwell time).

2.7.2 Lamination

Lamination is the separation of a tablet into two or more distinct horizontal layers.

Reason: Air–entrapment during compression and subsequent release on ejection. The condition is exaggerated by higher speed of turret.

Causes and Remedies of Lamination related to Formulation (Granulation):

Causes:

- Oily or waxy materials in granules.
- Too much of hydrophobic lubricant.
- Magnesium-stearate.

Remedies:

- Modify mixing process. Add adsorbent or absorbent.
- Use a less amount of lubricant or change the type of lubricant.

Causes and Remedies of Lamination related to Machine (Dies, Punches & Tablet Press):

Causes:

- Rapid relaxation of the peripheral regions of a tablet, on ejection from a die.
- Rapid decompression.

Remedies:

- Use tapered dies, i.e. upper part of the die bore has an outward taper of 3° to 5°.
- Use pre-compression step.
- Reduce turret speed and reduce the final compression pressure.

2.7.3 Chipping

Chipping is defined as the breaking of tablet edges, while the tablet leaves the press or during subsequent handling and coating operations.

Reason: Incorrect machine settings, specially mis-set ejection take-off.

Causes and Remedies of Chipping related to Formulation (Granulation):

Causes:

- Sticking on punch faces.
- Too dry granules.
- Too much binding causes chipping at bottom.

Remedies:

- Dry the granules properly or increase lubrication.
- Moisten the granules to plasticize.
- Add hygroscopic substances.
- Optimize binding, or use dry binders.

Causes and Remedies of Chipping related to Machine (Dies, Punches and Tablet Press):

Causes:

- Groove of die worn at compression point.
- Barreled die (center of the die wider than ends).
- Edge of punch face turned inside/inward.
- Concavity too deep to compress properly.

Remedies:

- Polish to open end, reverse or replace the die.
- Polish the die to make it cylindrical.
- Polish the punch edges.
- Reduce concavity of punch faces.
- Use flat punches.

2.7.4 Cracking

Small, fine cracks observed on the upper and lower central surface of tablets, or very rarely on the sidewall are referred to as cracks.

Reason: It is observed as a result of rapid expansion of tablets, especially when deep concave punches are used.

Causes and Remedies of Cracking related to Formulation (Granulation):

Causes:

- Large size of granules.
- Too dry granules.

- Tablets expand.
- Granulation too cold.

Remedies:

- Reduce granule size.
- Add fines.
- Moisten the granules properly and add proper amount of binder.
- Improve granulation.
- Add dry binders.
- Compress at room temperature.

Causes and Remedies of Cracking related to Machine (Dies, Punches and Tablet Press):

Causes:

- Tablet expands on ejection due to air entrapment.
- Deep concavities cause cracking while removing tablets.

Remedies:

- Use tapered die.
- Use special take-off.

2.7.5 Sticking

Sticking refers to the tablet material adhering to the die wall. Filming is a slow form of sticking and is largely due to excess moisture in the granulation.

Reason: Improperly dried or improperly lubricated granules.

Causes and Remedies of Sticking related to Formulation (Granulation):

Causes:

- Granules not dried properly.
- Too little or improper lubrication.
- Too much binder.
- Hygroscopic granular material.
- Oily or way materials.
- Too soft or weak granules.

Remedies:

- Dry the granules properly. Make moisture analysis to determine limits.
- Increase or change lubricant.
- Reduce the amount of binder or use a different type of binder.
- Modify granulation and compress under controlled humidity.
- Modify mixing process. Add an absorbent.
- Optimize the amount of binder and granulation technique.

Causes and Remedies of Sticking related to Machine (Dies, Punches and Tablet Press):

Causes:

- Concavity too deep for granulation.
- Too little pressure.
- Compressing too fast.

Remedies:

- Reduce concavity to optimum.
- Increase pressure.
- Reduce speed.

2.7.6 Picking

Picking is the term used when a small amount of material from a tablet is sticking to and being removed off from the tablet-surface by a punch face.

The problem is more prevalent on the upper punch faces than on the lower ones. The problem worsens, if tablets are repeatedly manufactured in this station of tooling because of the more and more material getting added to the already stuck material on the punch face.

Reason: Picking is of particular concern when punch tips have engraving or embossing letters, as well as the granular material is improperly dried.

Causes and Remedies of Picking related to Formulation (Granulation):

Causes:

- Excessive moisture in granules.
- Too little or improper lubrication.
- Low melting point substances, may soften from the heat of compression and lead to picking.
- Low melting point medicament in high concentration.
- Too warm granules when compressing.
- Too much amount of binder.

Remedies:

- Dry properly the granules, determine optimum limit.
- Increase lubrication; use colloidal silica as a polishing agent, so that material does not cling to punch faces.
- Add high melting-point materials. Use high melting point lubricants.
- Refrigerate granules and the entire tablet press.
- Compress at room temperature. Cool sufficiently before compression.
- Reduce the amount of binder, change the type or use dry binders.

Causes and Remedies of Picking related to Machine (Dies, Punches and Tablet Press):

Causes:

- Rough or scratched punch faces.
- Bevels or dividing lines too deep.
- Pressure applied is not enough; too soft tablets.

Remedies:

- Polish faces to high luster.
- Design lettering as large as possible.

- Plate the punch faces with chromium to produce a smooth and non-adherent face.
- Reduce depths and sharpness.
- Increase pressure to optimum.

2.7.7 Binding

Binding in the die, is the term used when the tablets adhere, seize or tear in the die. A film is formed in the die and ejection of tablet is hindered. With excessive binding, the tablet sides are cracked and it may crumble apart.

Reason: Binding is usually due to excessive amount of moisture in granules, lack of lubrication and/or use of worn dies.

Causes and Remedies of Binding related to Formulation (Granulation):

Causes:

- Too moist granules and extrudes around lower punch.
- Insufficient or improper lubricant.
- Too coarse granules.
- Too hard granules for the lubricant to be effective.
- Granular material very abrasive and cutting into dies.
- Granular material too warm.
- Sticks to the die.

Remedies:

- Dry the granules properly.
- Increase the amount of lubricant or use a more effective lubricant.
- Reduce granular size, add more fines, and increase the quantity of lubricant.
- Modify granulation. Reduce granular size.
- If coarse granules, reduce its size.
- Use wear-resistant dies.
- Reduce temperature.
- Increase clearance if it is extruding.

Causes and Remedies of Binding related to Machine (Dies, Punches and Tablet Press):

Causes:

- Poorly finished dies.
- Rough dies due to abrasion, corrosion.
- Undersized dies. Too little clearance.
- Too much pressure in the tablet press.

Remedies:

- Polish the dies properly.
- Investigate other steels or other materials or modify granulation.
- Rework to proper size. Increase clearance.
- Reduce pressure, or Modify granulation.

2.7.8 Mottling

Mottling is the term used to describe an unequal distribution of colour on a tablet, with light or dark spots standing out in an otherwise uniform surface. Reason: One cause of mottling may be a coloured drug, whose colour differs from the colour of excipients used for granulation of a tablet.

Causes and Remedies of Mottling:

Causes:

- A coloured drug used along with colourless or white-coloured excipients.
- A dye migrates to the surface of granulation while drying.
- Improperly mixed dye, especially during Direct Compression.
- Improper mixing of a coloured binder solution.

Remedies:

- Use appropriate colourants.
- Change the solvent system, Change the binder, Reduce drying temperature and use a smaller particle size.
- Mix properly and reduce size if it is of a larger size to prevent segregation.
- Incorporate dry colour additive during powder blending step, then add fine powdered adhesives such as acacia and tragacanth and mix well and finally add granulating liquid.

2.7.9 Double Impression

Double impression involves only those punches, which have a monogram or other engraving on them.

Reason: At the moment of compression, the tablet receives the imprint of the punch. Now, on some machines, the lower punch freely drops and travels uncontrolled for a short distance before riding up the ejection cam to push the tablet out of the die, now during this free travel, the punch rotates and at this point, the punch may make a new impression on the bottom of the tablet, resulting in 'Double Impression'.

Causes and Remedies of Double Impression:

Causes:

- Free rotation of either upper punch or lower punch during ejection of a tablet.

Remedies:

- Use keying in tooling, i.e. inset a key alongside of the punch, so that it fits the punch and prevents punch rotation.
- Newer presses have anti-turning devices, which prevent punch rotation.

2.8 TABLET WEIGHT

Sources of Variation:

The tablet weight is mainly affected by following reasons:

(i) Product variation: This type of variation can be due to inconsistent powder density and particle size distribution. Density can change on the press, often because of overfilling of the die and re-circulation of the powder on the tablet press, whereas particle size

distribution may change when the product becomes unblended during transfer or because of static electricity. This may also change because the product cannot withstand the handling and the mechanical stress it undergoes before reaching the tablet press.

(ii) Machine condition: The problems caused by a tablet press that is poorly prepared or operated are legion. The up and down motion under load on a new die table should be within 0.003 inch of the setting. Care must be taken to ensure that the pressure rolls and cams are in very good condition.

(iii) Tooling condition: The punch working length should be taken in consideration. Working length is an important factor in how punches affect tablet weight. New tools are made to a tolerance of one-thousandth of an inch, the length of each punch is correct and identical.

(iv) Powder flow and feed rates: Various defects are related to powder flow and feed-rates stem, therefore powder flow and feed rates should be taken in account while manufacturing of tablets.

2.9 PROBLEMS AND REMEDIES FOR TABLET COATING

2.9.1 Blistering

It is local detachment of film from the substrate forming blister.

Reason: Entrapment of gases in or underneath the film due to overheating either during spraying or at the end of the coating run.

Cause and Remedy of Blistering:

Cause: Effect of temperature on the strength, elasticity and adhesion of the film.

Remedy: Use mild drying condition.

2.9.2 Cratering

It is defect of film coating whereby volcanic-like craters appears exposing the tablet surface.

Reason: The coating solution penetrates the surface of the tablet, often at the crown where the surface is more porous, causing localized disintegration of the core and disruption of the coating.

Causes and Remedies of Cratering:

Causes:

- Inefficient drying.
- Higher rate of application of coating solution.

Remedies:

- Use efficient and optimum drying conditions.
- Increase viscosity of coating solution to decrease spray application rate.

2.9.3 Picking

It is defect where isolated areas of film are pulled away from the surface when the tablet sticks together and then part.

Reason: Conditions similar to cratering that produces an overly wet tablet bed where adjacent tablets can stick together and then break apart.

Causes and Remedies of Picking:

Causes:

- Inefficient drying.
- Higher rate of application of coating solution.

Remedies:

- Use optimum and efficient drying conditions or increase the inlet air temperature.
- Decrease the rater of application of coating solution by increasing viscosity of coating solution.

2.9.4 Pitting

It is defect whereby pits occur in the surface of a tablet core without any visible disruption of the film coating.

Reason: Temperature of the tablet core is greater than the melting point of the materials used in the tablet formulation.

Cause and Remedy of Pitting:

Cause: Inappropriate drying (inlet air) temperature.

Remedy: Dispensing with preheating procedures at the initiation of coating and modifying the drying (inlet air) temperature such that the temperature of the tablet core is not greater than the melting point of the batch of additives used.

2.9.5 Blooming

It is defect where coating becomes dull immediately or after prolonged storage at high temperatures.

Reason: It is due to collection on the surface of low molecular weight ingredients included in the coating formulation. In most circumstances the ingredient will be plasticizer.

Cause and Remedy of Blooming:

Cause: High concentration and low molecular weight of plasticizer.

Remedy: Decrease plasticizer concentration and increase molecular weight of plasticizer.

2.9.6 Blushing

It is defect best described as whitish specks or haziness in the film.

Reason: It is thought to be due to precipitated polymer exacerbated by the use of high coating temperature at or above the thermal gelation temperature of the polymers.

Causes and Remedies of Blushing:

Causes:

- High coating temperature.
- Use of sorbitol in formulation which causes largest fall in the thermal gelation temperature of the Hydroxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose, Methyl Cellulose and Cellulose ethers.

Remedies:

- Decrease the drying air temperature.
- Avoid use of sorbitol with Hydroxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose, Methyl Cellulose and Cellulose ethers.

2.9.7 Colour Variation

It is a defect which involves variation in colour of the film.

Reason: Alteration of the frequency and duration of appearance of tablets in the spray zone or the size/shape of the spray zone.

Cause and Remedy of Colour Variation:

Cause: Improper mixing, uneven spray pattern, insufficient coating, migration of soluble dyes-plasticizers and other additives during drying.

Remedy: Go for geometric mixing, reformulation with different plasticizers and additives or use mild drying conditions.

2.9.8 Infilling

It is defect that renders the intagliations indistinctness.

Reason: Inability of foam, formed by air spraying of a polymer solution, to break. The foam droplets on the surface of the tablet breakdown readily due to attrition but the intagliations form a protected area allowing the foam to accumulate and set. Once the foam has accumulated to a level approaching the outer contour of the tablet surface, normal attrition can occur allowing the structure to be covered with a continuous film.

Cause and Remedy of Infilling:

Cause: Bubble or foam formation because of air spraying of a polymer solution.

Remedy: Add alcohol or use spray nozzle capable of finer atomization.

2.9.9 Orange Peel/Roughness

It is surface defect resulting in the film being rough and non-glossy. Appearance is similar to that of an orange.

Reason: Inadequate spreading of the coating solution before drying.

Causes and Remedies of Orange Peel/Roughness:

Causes:

- Rapid Drying.
- High solution viscosity

Remedies:

- Use mild drying conditions.
- Use additional solvents to decrease viscosity of solution.

2.9.10 Cracking/Splitting

It is defect in which the film either cracks across the crown of the tablet (cracking) or splits around the edges of the tablet (Splitting).

Reason: Internal stress in the film exceeds tensile strength of the film.

Cause of Cracking/Splitting:

- Use of higher molecular weight polymers or polymeric blends.
- Use lower molecular weight polymers or polymeric blends. Also adjust plasticizer type and concentration.

2.9.11 Bridging

This occurs when the coating fills in the lettering or logo on the tablet and is typically caused by improper application of the solution, poor design of the tablet embossing, high coating viscosity, high percentage of solids in the solution, or improper atomization pressure. During drying, the film may shrink and pull away from the sharp corners of an intagliation or bisect, resulting in a bridging of the surface. This defect can be so severe that the monogram or bisect is completely obscured. Remedy: Increasing the plasticizer content or changing the plasticizer can decrease the incidence of bridging.

2.10 TABLET EQUIPMENTS

2.10.1 Rotary Tablet Press

Pharmaceutical tablets are generally produced on rotary tablet presses shown in the Fig. 2.4, where upper and lower punches reside in the upper and lower turret, respectively. The dies are inserted in the die table and secured by die lock screws. The upper and lower turret and the die table are precisely aligned. The movement of the punches is controlled by cam tracks and compression rollers. As the entire assembly rotates, the upper and lower punches move along the cam tracks to accomplish die fill, tablet compression, ejection, and scrape-off.

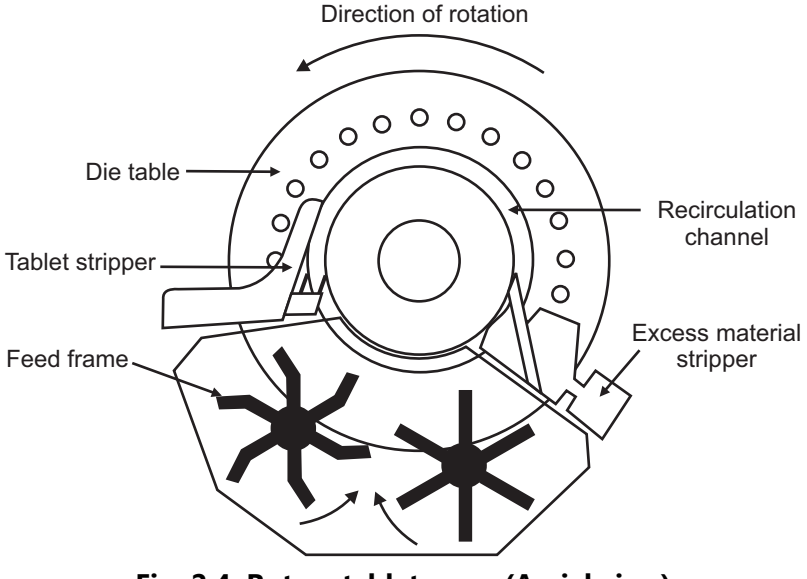


Fig. 2.4: Rotary tablet press (Aerial view)

Tablet Compression:

Tablet compression can be separated into the two distinct yet equally important phases of die fill-weight adjustment and tablet formation as shown in Fig. 2.5. As die fill begins, the

lower punch face is initially flush with the die table surface as the lower punch enters the overfill cam at the entry of the feeder. The lower punch travels under the feeder and is pulled down by the overfill cam. At this point the lower punch has passed through approximately 50% of the feeder and the die cavity contains more material than required.

After overfilling the die cavity, the lower punch is adjusted to a constant height as it passes into the weight-regulation unit. The constant height, known as the fill depth, is measured as the distance between the lower punch face and the die table surface. Since die fill is volumetric, the constant height of the lower punch in the weight-regulation unit provides a constant volume of material. Therefore, the fill depth is affected by the density of the granulation. Variation of granulation density between batches results in different fill depths, whereas variable granulation density within a batch results in fluctuating fill depth requirements.

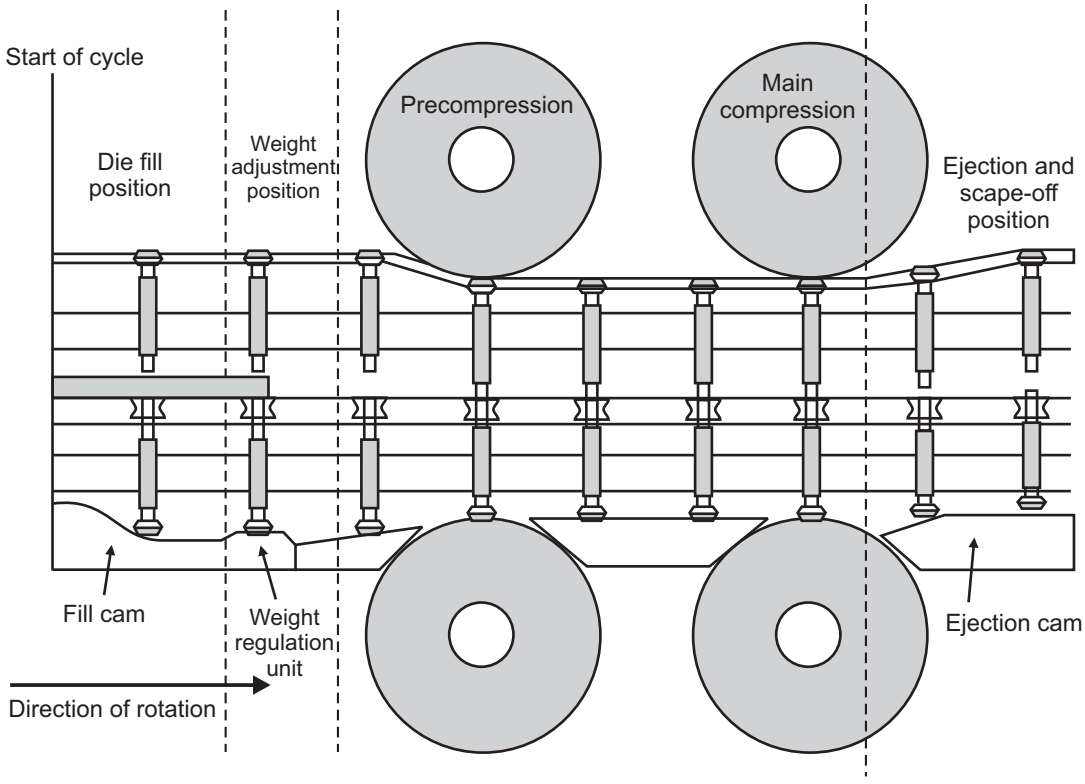


Fig. 2.5: Rotary press (Sequences of compression)

As the lower punch passes from the fill cam to the weight-regulation cam, the excess material is pushed back into the feeder and scraped off at the top of the die table by the excess material stripper and directed into a recirculation channel. On many modern presses, the lower punch is lowered by approximately 2-4 mm relative to the top of the die table after the excess material stripper. This lowers the material away from the top of the die table, minimizing uncontrolled loss as the upper punch enters into the die cavity after scrape-off. Under these circumstances the upper punch does not contact the top of the material until it

enters into the die, minimizing material loss and weight variation. Additionally, lowering the slug of material away from the die table surface reduces material loss due to the centrifugal force of the rotating die table.

Overfilling of the die cavity is necessary to achieve uniform tablet weights and to optimize machine running conditions. However, at times excessive overfilling can lead to other problems such as excessive wear for abrasive raw materials, particle size reduction for friable granulations, material segregation and over-mixing of lubricant. Therefore, the effect of different machine running conditions must be evaluated for each different product separately.

The material that is directed into the recirculation channel is subsequently introduced back into the feeder at the tablet stripper or at the inside edge of the feeder. It is worth noting that the paddle in the feeder at the point of material entry rotates in the opposite direction as the turret to aid in die fill and induce flow back into the feeder.

Frequently the maximum machine speed may depend on die fill characteristics due to excess tablet weight variation at high machine speeds. However, because the compression characteristics of most pharmaceutical products exhibit visco-elastic properties, the press speed may also have a major effect on the compressibility of the material. For this reason, the ability to compress a tablet adequately is often the overriding factor to consider in tablet compression.

The process of tablet formation begins as the upper punch is lowered directly into the die cavity after the excess material stripper. As mentioned previously, it is advantageous if the slug of material is lower than the die table surface as the upper punch enters to minimize uncontrolled material loss and weight variation.

After the upper punch enters into the die, the upper and lower punches begin to move toward each other as the punches ride along cam tracks toward the pre-compression rollers. At the pre-compression stage, the initial (and typically the lower) compression force is applied. Traditionally, tablet presses were equipped to apply a 20 kN maximum pre-compression force using relatively small compression rollers (approximately 100 mm (4 in.) diameter rollers). However, to improve flexibility, many modern rotary tablet presses are equipped with identical pre-compression and main compression force capabilities, allowing the application of 80-100 kN forces using 250–300-mm-diameter compression rollers.

After application of the pre-compression force, the punches move toward the main compression rollers where the final (main) force is applied. As the punches impact the rollers, the compression force increases until the punch head flat is tangent to the compression roller and maximum force is applied (Fig. 2.3). The applied compression force is a measured value and depends on the distance between the punches and the quantity of material in the die. After main compression, the upper punch is pulled out of the die cavity while the lower punch impacts the ejection cam to begin the ejection process. As the die table continues to rotate, the lower punch raises the tablet out of the die cavity to eject the tablet to the point of scrape-off.

2.10.2 Press Design and Layout

Typical sections to provide separation and isolation of the compression area from the other components are as follows:

- Upper cam section
- Compression section
- Lower cam section
- Lower mechanical section
- Electrical section
- Lubrication system

With the proper separation of these areas, only the compression zone is exposed to material, thus reducing cleaning and change-over time of the tablet press. In addition to the machine sections, an understanding of other machine subsystems is necessary, such as the lubrication system and the diagnostic systems (safety systems) to achieve optimal machine performance.

Modern rotary tablet presses are either single-sided or double-sided. A single-sided machine has one feeding station, one set of pre-compression and main compression rollers, and one discharge station. These machines produce one tablet per punch station per die table revolution. A double-sided machine has two feeding stations, two sets of pre-compression and main compression rollers, and two discharge stations, and produces two tablets per punch station per die table revolution. The double-sided machine operates identically to the single-sided machine with the exception that the excess material from the first feeding station passes into the second feeding station. A double-sided machine has a higher output than a single-sided machine. Its pitch circle diameter is also greater, which could result in weight uniformity and compressibility issues

(A) Upper Cam Section:

The upper cam section is typically shrouded and sealed to prevent exposure of material. It consists of the upper cam track, all upper compression rollers, and all adjustments to the position of the upper compression rollers. The primary components of the upper cam section are as follows:

1. Upper punch removal/dwell cams: The upper punches are loaded and removed from the machine at this location. These cams typically reside directly above the material feeder. In many press designs, the upper punch dwell cam is designed to measure the tightness of the upper punches in the turret. A spring loaded cam designed to raise the upper punch slightly (1-4 mm) is connected to a proximity sensor. If the punches are too tight then the spring loaded cam falls instead of raising the upper punches, thus tripping the proximity sensor and shutting down the machine. In alternative press designs, the upper punch tightness is measured in the upper-punch pull-up cam, typically by a strain gauge measurement of the lifting force.

2. Upper punch lowering cam: The upper punches are lowered into the die cavity by the upper punch lowering cam. This cam is typically CAD optimized to minimize the

acceleration and velocity of the upper punch as it enters into the die cavity. In this way, the upper punch travels in a smooth and controlled manner as it enters the die cavity, thus improving weight uniformity.

3. Upper pre-compression and main compression rollers insertion depth adjustments: Insertion depth for both pre-compression and main compression is adjusted in the upper cam section. The insertion depth determines the location of tablet formation in the die cavity relative to the top of the die table as shown in Fig. ????. It is measured as the distance at which the upper punch enters into the die at the tangent between the upper punch head and the compression roller.

4. Upper punch pull-up cam: After compression, the upper punch enters into the upper-punch pull-up cam, which removes the upper punch from the die cavity. This cam provides an excellent location to measure the upper punch pull-up force that determines the tightness of the upper punches. Compared to the upper punch dwell cam, this location has the advantage of determining the punch tightness not only in the turret but also in the die cavity. Detection of tight punches at this location prevents almost all possibility of machine damage.

5. Cam material of construction: Both the upper and lower cam sections use cams to guide the punches while the turret rotates. These cams are typically made of various materials such as steel, bronze, or alloy. Most of the cam tracks in the turret are designed to smoothly guide the punches. However, cams that undergo impact (e.g. ejection cam) and stress (e.g. weight regulation cam) require metal construction with good impact resistance. For this purpose, an aluminum–bronze alloy provides superior abrasion resistance and excellent impact strength.

(B) Compression Section:

The compression section contains all components that are exposed to the material, such as the material hopper, the feeder, the excess material stripper, the upper and lower turrets, the die table, and the tablet stripper. Additionally, the dust-collection shrouds are located in the compression section. Proper shrouding of this area ensures that none of the upper and lower punch heads, compression rollers, and cam tracks are exposed to material. Proper maintenance and setup of the compression section is critical for optimal press performance.

The primary components of the compression section are explained in the following sections:

- Material hopper.
- Gravity feed frame.
- Force feeder.
- Excess-material stripper.
- Pre-compression and main compression rollers.
- Tablet stripper.
- Material recirculation.
- Dust extraction.

1. Material hopper: The material hopper is an integral part of the feeding system. Typically, it is capable of holding approximately 5-10 kg of material. Low level sensors are mounted in the hopper to signal an alarm, shut off the machine or activate a feeding mechanism to deliver more material when the product falls below this level. The material hopper should be symmetrical with steep discharge angles to promote mass flow and prevent funnel flow (rat holing) in the granulation. The discharge outlet of the hopper should be as large as possible reaching into the feeder to prevent material bridging.

2. Gravity feed frame: These feed frames provide good performance for materials with good flow properties but are typically limited to slow machine speeds. On the other hand, gravity feeders do not agitate the product and impart no energy. Therefore, they offer advantages for products where material segregation and over-mixing are of concern. For example, products that are sensitive to over-blending of magnesium stearate (i.e., exhibit capping when over-blended) may exhibit improved compressibility by using a gravity feeder as opposed to a force feeder.

3. Force feeder: Force feeders are typically multi-chamber and multi-paddle feeders. These feeders are critical to allow optimal press performance at high machine speeds with minimal weight variation. For products with good flow properties, the feeder should move the material from the overhead hopper to the dies with minimal mixing. Most force feeders contain two or three chambers and paddles. The three chamber/paddle system typically performs better than the two chamber/paddle designs. The top paddle and feed chamber are connected directly to the hopper and move the material from the overhead hopper to the filling chambers located directly above the die cavities. The top chamber eliminates the effect of the head pressure on material flow, thus providing uniform die fill regardless of the quantity of material in the hopper.

4. Excess-material stripper: The excess-material stripper is located immediately after the feeding system and scrapes off the excess material on the die table after weight adjustment. It is often overlooked during setup although it is one of the most critical components of the tablet press. A brass stripper is employed, which sits flush on the die table under spring tension. The material is scraped off just before the lowering cam. The brass stripper directs the excess material into the recirculation channel. A tail-over-die covers the die cavity after scrape-off to the point of upper punch entry. This design minimizes uncontrolled material loss due to flinging of material out of the die cavity at high rotational speeds.

5. Pre-compression and main compression collers: After die fill and scrape-off, the punches rotate to the pre-compression station where an initial force is applied to the compact. The tablet is frequently partially formed during the pre-compression stage. Subsequently, the upper and lower punches move together under the main compression rollers where the final tablet is formed. The main compression roller is usually larger than the pre-compression roller.

6. Tablet stripper: The tablet stripper scrapes off the tablets from the lower punch and directs them down the discharge chute. On high-speed machines, special attention must be

paid to the tablet takeoff to prevent tablet backup; modifications are necessary for shaped tablets. On high-speed machines it is critical to move the tablets off the die table as quickly as possible.

7. Material recirculation: Material is re-circulated from the center of the turret into the feed frame. Some press designs include recessed recirculation channels to minimize particle attrition and prevent excess material loss to the vacuum system. It is critical not to re-circulate too much material because this can result in low product yields and can have a detrimental effect on the powder's physical properties, which could result in poor compressibility, uniformity, and final properties (e.g. reduced dissolution rate).

8. Dust extraction: Adequate dust extraction is necessary to maintain high-speed operation for extended periods of time. The entire compression area should be shrouded to minimize dust infiltration into other press areas. Effective dust extraction minimizes dust and oil contamination on the surface of the tablets, which could produce black specs. Insufficient dust extraction results in excessive material build-up on the lower and upper punches leading to tight punches.

(C) Lower Cam Section

The lower cam section is completely sealed from the compression section. It houses the lower compression rollers, the entire lower cam track that guides the lower punches as the turret rotates, and all adjustments for the lower pre-compression and main compression roller positions. Additionally, any motors necessary for automatic machine adjustment are contained in this section.

- Fill cam.
- Weight regulation cam.
- Lower punch brakes.
- Pre-compression and main compression rails.
- Adjustment of lower pre-compression and main compression roller thickness.
- Ejection rail.
- Scrape-off rail.
- Force overload system.

1. Fill cam: The fill cam is designed to lower the punch to overfill the die cavity. Lower-punch fill cams are typically available in a variety of sizes that are changed depending on the final fill depth as determined by the weight regulation cam. Press manufacturers recommend a fill cam in which the weight regulation cam operates in the approximate center of the fill cam.

2. Weight regulation cam: The lower punch travels from the fill cam to the weight regulation cam, which determines the final volume of material that remains in the die cavity after scrape-off. Proper design and operation of this unit is essential to ensure uniform tablet weights. In general, the unit should operate in a manner to ensure smooth punch travel minimizing punch chatter as the lower punch is raised to a precise and constant height.

3. Lower Punch Brakes: Most rotary tablet presses are equipped with lower-punch brakes that are Teflon tipped and spring loaded to apply constant pressure to the lower punches. Alternatively, some manufacturers apply pressure to a friction belt that provides resistance on the lower punches. The lower-punch brakes act as a ''retention'' system for holding the lower punches in place during press setup. More importantly, these systems help to minimize lower punch chatter at high press speeds thus minimizing tablet weight variation.

2.11 TABLET TOOLING

2.11.1 Basics of Tablet Tooling

Tablet compression machines are made keeping in view the type of dies and punches will be used on them. The dies and punches and their setup on compression machine is called tooling, it is classified as B and D mainly.

The B tooling dies and punch can further have specifications as BB and D tooling can also be dies and punches can be utilized on B tooling machine which is called as DB.

Mainly there are two standards, D and B, in US specification provided by Tableting Specification Manual (TSM) is followed where as in Europe European standard known as the EU, or "Euronorm" standard. There is not much difference in both the specifications but both are very different.

2.11.2 Punch

1. **Head:** The end of the punch that guides it through the cam track of tablet machine during Rotation.
2. **Head flat (Dwell Flat):** The flat area of the head that receives the compression force from Rollers (in upper punches) and determines the weight and ejection height (in lower punches).
3. **Outside head Angle:** The area gets in touch with the roller prior to head flat , while Compression.
4. **Inside Head Angle:** This is the area, which pulls down the lower punches after ejection and lifts the upper punches after compression.
5. **Neck:** The relived area between the head and barrel, which provides clearance for the cams.
6. **Barrel:** This area guides the punch (while going up and down) with reference to turret guides.
7. **Stem:** The area of the punch opposite the head, beginning at the tip and extending to the point where the full diameter of the barrel begins. If the chamfer is present the barrel usually reaches its full diameter just above the chamfer.
8. **Tip:** This determines size, shape & profile
9. **Tip face:** This area of punch is where the tablet is formed. Good surface finish is required here to get quality tablets.
10. **Working length:** This distance between bottom of the cup and the head flat is called as working length which determines weight and thickness of the tablet.
11. **Overall length:** Distance between top of the cup and the head flat.

12. **Key Angle:** The relationship of the punch key to the tablet shape. The keys position is influenced by the tablet shape, take-off angle, and turret rotation.
13. **Domed Heads:** Increases the dwell time and hence help to achieve the better tablet hardness.
14. **Dwell time –** The time punches spends below the pressure roller while rotating in the machine.
15. **Clearance:** Die bore dia – punch tip dia = Clearance.
16. **Hardness:** Usually measured in HRC (Rockwell 'C' scale) and optimum readings are as follows:

Steel	Hardness
OHNS O1	58-59
HCHC D2	59-60
HCHC D3	61-62

2.11.3 Die

It is a hardened steel (HCHC) mould to make the shape of a tablet.

Die Terminology:

1. **Die O.D.:** The outside diameter of the die, which is compatible with the die pockets in the press.
2. **Die Height:** The overall height of the die.
3. **Die Bore:** The cavity where the tablet is made. The Cavity's shape and size determine the same form of tablet.
4. **Chamfer:** Entry angle of the die bore.
5. **Taper dies:** dies with tapered bore on one or both sides. They are used for easy ejection of tablets (mainly for double layered tablets.
6. **Die Groove:** The groove around the periphery of the die, which allows the die to be fixed in the press.
7. **Lined (Insert) Dies**: Dies fitted with a linear insert made from a much harder, more wear resistant material such as tungsten carbide and ceramic.

There are following types of tooling available:

- 'B' -Tooling
- 'D' – Tooling
- 'BB' -Tooling
- 'DB' – Tooling

Type of tooling	Punch Length (mm)	Punch diameter (mm)	Die Diameter (mm)	Height of dies (mm)	Max. Tab. size (mm) Round/Capsule
B	133.6	19	30.15	22.22	16/19
D	133.6	25.4	38.1	23.82	25/25
BB	133.6	19	24.0	22.22	13/14
DB	133.6	25.4	30.15	23.22	19/19

Tip diameter of punches:

Check the tip diameter with the help of a Vernier caliper. Check and set the zero reading of the Vernier caliper. Place the punch tip in a vertical position. Check the fine setting of the Vernier caliper and record the reading. The readings should be within ± 0.1 mm of the standard dimension.

Difference in height of the punches:

Set the dial gauge of the inspection kit at zero position with the help of the standard punch height 133.60 mm. Keep the punches one by one inside the punch holder over the metal pad of the inspection kit and check the difference in deflection from the zero position. The difference should not be more than ±0.08 mm of the standard dimension.

Body diameter of punches:

Check the body diameter with the help of a Vernier caliper. Check and set the zero reading of the Vernier caliper. Check the fine setting of the Vernier caliper and record the reading. The standard dimensions and limit are as in table.

Embossing of punches:

Visually check the embossing and record the observation.

Difference in concentricity of punches:

Keep the punch over a 'V' block pad horizontally by keeping the magnet on and set the dial gauge at zero position over the punch body. Rotate the punch in the clockwise direction, take two readings each from the punch (one from the top and one from the bottom of the punch body) and record the observations. The deflection should be within ± 0.05 mm of the standard dimension. Keep the punch over a 'V' block pad horizontally by keeping the magnet ON and set the dial gauge at zero position over the highest point on tip diameter. Rotate the punch in the clockwise direction and record the observations. The deflection should be within ± 0.025 mm of the standard dimension.

Go and No-Go of punch head:

Take "B" or "D" type tooling "Go-No Go" punch head tester for checking punch head. Move the punch head through "go" side of punch head tester it should pass easily. Move the punch head through "no go" side of punch head tester & it should not pass through it. Record the observations.

Outer diameter of dies:

Set the dial gauge of the inspection kit at zero position with the help of the standard die master piece. Keep the dies horizontal position one by one over the metal pad (V BLOCK) of the inspection kit and check the outer dimension deflection from the zero position. Record the reading.

Height of the die:

Set the dial gauge of the inspection kit at zero position with the help of the standard die master piece. Place the dies in vertical position one by one over the metal pad of the inspection kit and check the height deflection from the zero position. Record the reading.

Difference in concentricity of dies:

Keep the die over a 'V' block in horizontal position and set the dial gauge at zero position over the die body. Rotate the die in the clockwise direction, take two readings each from the die (both side) and record the observations. The deflection should be within ± 0.05 mm.

Frequency:

Inspection of punches and dies to be done after receiving of a new punch set and after compression of two million tablets per subset.

2.12 QUALITY STANDARDS AND COMPENDIAL REQUIREMENTS

These include criteria for weight, weight variation, content uniformity, thickness, hardness, disintegration, and dissolution. These factors must be controlled during production (in-process controls) and verified after the production of each batch to ensure that established product quality standards are met.

FINISHED PRODUCT

1. Tablet Weight and USP Weight Variation Test:

The quantity of fill in the die of a tablet press determines the weight of the tablet. The volume of fill is adjusted with the first few tablets to yield the desired weight and content. For example, if a tablet is to contain 20 mg of a drug substance and if 100,000 tablets are to be produced, 2,000 g of drug is included in the formula.

The USP contains a test for determination of dosage form uniformity by weight variation for uncoated tablets.

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

2. Content Uniformity:

By the USP method, 10 dosage units are individually assayed for their content according to the method described in the individual monograph.

3. Tablet Thickness:

The thickness of a tablet is determined by the diameter of the die, the amount of fill permitted to enter the die, the compaction characteristics of the fill material and the force or pressure applied during compression.

The degree of pressure affects not only thickness but also hardness of the tablet; hardness is perhaps the more important criterion since it can affect disintegration and dissolution.

4. Tablet Hardness and Friability

The greater the pressure applied, the harder the tablets, although the characteristics of the granulation also have a bearing on hardness. In general, tablets should be sufficiently

hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing.

A tablet's durability may be determined through the use of a friabilator. This apparatus determines the tablet's friability, or tendency to crumble, by allowing it to roll and fall within the drum.

Conventional compressed tablets that lose less than 0.5% to 1% of weight are considered acceptable, less than 0.5% shows superior friability of tablets.

5. Tablet Disintegration:

The tablet must first disintegrate and discharge the drug to the body fluids for dissolution. Tablet disintegration also is important for tablets containing medicinal agents (such as antacids and anti diarrheal) that are not intended to be absorbed but rather to act locally within the gastrointestinal tract.

The apparatus consists of a basket and rack assembly containing six open-ended transparent tubes of USP-specified dimensions, held vertically upon a 10-mesh stainless steel wire screen.

During testing, a tablet is placed in each of the six tubes of the basket, and through the use of a mechanical device, the basket is raised and lowered in the immersion fluid at 29 to 32 cycles per minute, the wire screen is always below the level of the fluid.

The state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core .....

Type of capsule	Disintegration time
Uncoated tablets	15 minutes
Coated tablets: Film-coated	30 minutes
Other coated tablets	60 minutes
Enteric-coated tablets:	
0.1 M hydrochloric acid	Should not disintegrate in 120 minutes
Mixed phosphate buffer pH 6.8	60 minutes
Dispersible and soluble tablets	Within 3 minutes
Effervescent tablets	5 minutes

6. Tablet Dissolution:

In vitro dissolution testing of solid dosage forms is important for a number of reasons:

- It guides formulation and product development toward product optimization.
- Manufacturing may be monitored by dissolution testing as a component of the overall quality assurance program.
- Consistent in vitro dissolution testing ensures bioequivalence from batch to batch.
- It is a requirement for regulatory approval of marketing for products registered with the FDA and regulatory agencies of other countries.

For a high-solubility and high-permeability Category I drug, an IVIVC may be expected if the dissolution rate is slower than the rate of gastric emptying (the rate-limiting factor).

A number of formulation and manufacturing factors can affect the disintegration and dissolution of a tablet, including particle size of the drug substance; solubility and hygroscopicity of the formulation; type and concentration of the disintegrant, binder, and lubricant; manufacturing method, particularly the compactness of the granulation and compression force used in tableting and any in-process variables.

In addition to formulation and manufacturing controls, the method of dissolution testing must be controlled to minimize important variables such as paddle rotational speed, vibration, and disturbances by sampling probes.

Dissolution testing for oral dosage forms has been a component of evaluating product quality in the USP when only 12 monographs contained such a requirement. Today the requirement is standard for tablets and capsules.

2.13 COATING OF TABLETS

Tablet coating is one of the oldest pharmaceutical processes. It involves application of sugar or polymeric coat on the tablet. The advantage of coating tablet are taste masking, odour masking, physical and chemical protection, protect the drug in the stomach and to control its release profile.

A summary of the rationale for tablet coatings is provided below:

- To protect the drug from degradation in the stomach (an enteric coating).
- To prevent drug-induced irritation at a specific site within the gastrointestinal tract, e.g. the stomach for non-steroidal anti-inflammatory drugs.
- To provide controlled release of the drug throughout the gastrointestinal tract.
- To target drug release to a specific site in the gastrointestinal tract, e.g. the delivery of drug to the colon for the treatment of inflammatory conditions.
- To mask the taste of drugs.
- To improve the appearance of the tablet.

General Description of Tablet Coating:

The main steps involved in the coating of tablets are as follows:

- The tablets (or granules) are placed within the coating apparatus and agitated.
- The coating solution is sprayed on to the surface of the tablets.
- Warm air is passed over the tablets to facilitate removal of the solvent from the adsorbed layer of coating solution on the surface of the tablets.
- When the solvent has evaporated, the tablets will be coated with the solid component of the original coating solution.

2.13.1 Coating Formation

Coating solutions are available in two main formulation types : (1) Solutions and (2) Emulsions.

1. Coating solutions: Coating solutions contain the coating material (polymers or sugar), the coating solvent and other excipients that are required to improve the performance of the tablet coating, e.g. colourants/opacifiers, plasticisers (to render the film flexible). The choice of the solvent/solvent blend is according to the physicochemical properties of the coating material (i.e. the compatibility of the material with the solvent); however, other considerations include the volatility and the flammability of the solvent. The concentration of the coating material within the solution is also a consideration. Increasing the concentration of coating material within the solvent will reduce the processing time; however, by increasing the concentration of material, the viscosity of the solution may be unacceptably high to achieve the correct spray properties during coating.

2. Coating emulsions: More recently emulsions have been developed as tablet-coating systems. In these the polymer is dissolved in a volatile organic phase (with plasticizer and colourants/opacifiers, as required) and this is emulsified within an external aqueous phase. The initial stage in the coating process involves the deposition and subsequent spreading of the atomized coating solution/emulsion on the surface of the tablet (or granule). To achieve a uniform surface distribution of the coating solution/emulsion on the tablet, consideration of the wetting properties of the solution/emulsion on the surface of the tablet is required. Following spreading, evaporation of the solvent initially enables coalescence of the organic droplets, and hence initial film formation on the surface of the tablet. As drying continues, the saturation solubility of the coating material in the solvent is exceeded and the solid coating is formed on the surface of the tablet. It should be noted that contact, spreading, droplet coalescence and solvent evaporation occur almost instantaneously.

2.13.2 Tablet Coating in Practice

There are several designs of systems that are used in industrial practice to coat tablets (or granules).

Examples of these systems are:

1. Pan Coater:

The pan coating system is generically composed of a metal pan (drum) into which the tablets are placed and that may be rotated at a range of speeds. The coating solution is sprayed on to the surface of the tablets within the pan whilst the drum is rotated. Simultaneously warm air is passed over the surface of the tablets to facilitate the evaporation of the solvent in which the coating material has been dissolved.

Control of the coating process is obtained by modifying the following parameters:

- Rotation rate of the drum/pan
- Airflow rate
- Temperature of the air
- Concentration of sugar/polymer within the coating solution/emulsion

More recently, pan coaters have been developed in which the pan is perforated (e.g. the Accela-Cota and Hi-Coater systems). In these systems the warmed air is passed into

the drum and through the tablet bed before being exhausted (with the solvent from the coating solution) via the perforated drum. In the Driacoater system, the drum is composed of a serious of perforated fins (typically 8 per drum) from which the warmed air is provided. As the drum rotates, the tablets in the tablet bed are mixed by and collected on the fins before being suspended in the warmed air. The tablets are then dropped into the tablet bed and the process is repeated. The warmed air is then exited from the rear of the pan.

2. Air Suspension Coaters:

Air suspension coaters are highly efficient coating systems in which the coating solution is sprayed on to tablets (or granules) that have been suspended in a positive (warmed) airflow. This ability simultaneously to suspend and coat tablets leads to high coating efficiency. Typically the tablets are initially suspended in the centre of the chamber and then move to the periphery of the chamber before falling to the bottom, at which stage the process is continuously repeated. The coating solution is fed into the fluidization chamber (usually at the bottom of the chamber) as an atomized spray that has been generated either by passage of the coating solution through a nozzle under high pressure or by passage of the coating solution through a nozzle at low pressure, at which point the solution comes into contact with two high pressure air streams.

Process Variables in Fluidized Air Coating

There are several process factors that control both the efficiency of the coating process and the quality of the formed coat. These are:

(a) Evaporation rate of the solvent.

(b) Fluidized air volume.

(c) Specific humidity.

(d) Coating sprays rate and duration.

(a) Evaporation rate of the solvent: The rate of evaporation of the solvent directly affects both the quality (in particular the mechanical properties) of the tablet coating and the time required to form the tablet coating. Whilst it is important to process the coating in the minimum time, increasing the evaporation rate of the solvent decreases the time available for polymer–polymer interactions to occur. Therefore, if solvent evaporation rate is too rapid, the mechanical properties of the films will be compromised due to the adverse effects on polymer interactions. Both the solvent vapour pressure and the process temperature affect the rate of evaporation of a solvent. Therefore, a low process temperature is normally employed for coating solutions/solvents containing a solvent of high vapour pressure, e.g. dichloromethane. Small fluctuations in processing temperature will have greater effects on the quality of the tablet coatings prepared using organic solvents than when processed using an aqueous coating solution.

(b) Fluidized air volume: The fluidized air volume will affect both the velocity of the droplets of coating solutions/emulsions and their fluidized pattern within the coating chamber.

(c) Specific humidity: It is important to control the specific humidity within the warmed air and hence in the coating chamber to ensure that the quality of the tablet coating is optimized. If the relative humidity in the coating chamber is high, evaporative cooling by the solvent may occur. This will, in turn, lower the temperature of the air to below the dew point, resulting in the condensation of water on to the tablet surface. This will interfere with the coating process, resulting in poor adhesion of hydrophobic coatings to the tablet surface and visual imperfections in the formed coating. Therefore, control (but not elimination) of the relative humidity within the coating process is required. The presence of humidity within the coating chamber may be useful in dispelling static electricity that may occur after the coating process has been completed.

(d) Coating spray rate and duration: The coating spray rate is controlled within the coating process and is selected according to the solubility of the coating solvent in the air volume and the viscosity of the atomized droplets. It should be noted that excessive spray rates will produce coatings that exhibit poor adhesion to the tablet surface. Typically the coating process will involve several passes through the coating apparatus. Therefore one method by which the thickness of the coating on the tablet may be modified is to increase the time spent within the coating chamber. Alternatively, the concentration of coating material may be increased within the coating solution. The viscosity of the solution must be considered to ensure that the increased viscosity does not compromise the atomization process, and specifically the droplet size.

2.13.3 Problems Associated with Tablet Coatings

There are several problems associated with tablet coatings, including:

1. Poor adhesion of the coating to the tablet;
2. Tablet abrasion;
3. Filling tablet markings;
4. Rough surface;
5. Formation of cracks in the coating; and
6. Variations in the colour of the coating.

1. Poor Adhesion of the Coating to the Tablet:

This phenomenon may be due to:

- High relative humidity within the coating chamber when coating tablets using an organic solvent system.
- High coating spray rate.
- Concentration of polymer in the coating solution/emulsion is too low.
- Temperature of air is too low, resulting in a slow rate of solvent evaporation (particularly valid for coating systems that employ solvents of low vapour pressure, e.g. water).
- Air fluidization rate or pan rotation rate is too slow.
- The tablet substrate has minimal curvature. Typically curved surfaces are easier to coat than flat surfaces.

2. Tablet Abrasion:

The coating process involves exposing the tablets to shearing stresses that are generated as a result of collisions with other tablets and also with the walls of the coating chamber. This may result in damage to the tablet surface. This problem may occur due to:

- Inappropriate tablet hardness.
- Irregular tablet shape.
- Tablet bed is too heavy during coating.
- The speed of rotation of the pan or the air fluidization rate is excessive.

(a) Inappropriate tablet hardness: Tablet hardness may be improved by increasing the compaction pressure or binder concentration (in wet granulation). Generally, the hardness of tablets produced by wet granulation is greater than by other methods and therefore the tablets produced by this method are generally suitable for coating

(b) Irregular tablet shape: Irregular tablet shapes are more prone to abrasion than regular tablet shapes. This problem may therefore be overcome by changing the tablet shape.

(c) Tablet bed is too heavy during coating: This leads to increased tablet–tablet contact. To correct this problem the loading of tablets within the coating chamber is reduced.

(d) The speed of rotation of the pan or the air fluidization rate is excessive: By reducing the speed of pan rotation or air fluidization rate, tablet–tablet contact is decreased.

3. Filling Tablet Markings:

Manufacturers may wish to identify their product with a particular mark/name (performed by using a tablet punch that has been embossed with the specified mark). If the coating conditions are unsuitable, the coating will excessively deposit within the mark/name and, in so doing, the marking will be partially obscured. This may occur due to:

- The use of deep markings.
- Use of an excessive volume of coating solution.
- Air temperature is too low.
- Pan rotation speed/fluidization flow rate is too low.

4. Rough Surface:

One of the major problems of tablet coating is the production of tablets that exhibit a rough surface. This phenomenon is often associated with drying of the coating droplets prior to reaching the surface of the tablet. To correct this problem the spray rate may be increased and the inlet air temperature decreased.

5. Formation of Cracks in the Coating:

The formation of cracks in tablet coatings is principally due to the use of an inappropriate coating formulation. Plasticizers are employed to lower the glass transition

temperature of polymer coatings. This in turn renders the film more flexible and less brittle. Therefore cracking in polymer coatings may indicate that either the plasticizer concentration should be increased or, alternatively, a different plasticizer that is more compatible with the polymer chosen for the coating should be considered. In certain situations cracking of polymer coats may occur due to the use of a polymer that has a low stress resistance and is therefore prone to stress failure. To rectify this situation either the molecular weight of the polymer should be increased or, alternatively, a different polymer should be used that has a greater resistance to the applied stress (i.e. an increased ultimate tensile strength).

6. Variations in the Colour of the Coating:

Tablets that have been coated with a polymer containing a colourant should show uniform colour. Variations in the colour of a tablet coating may be due to:

- Improper mixing of the colour within the coating formulation.
- Uneven coating process, resulting in regional differences in the thickness of the applied coating.
- Migration of coloured components within the tablet core into the coating. This may be resolved by the use of a coloured coating that will mask the effects of the migration or by the use of a coating in which the components within the table core are insoluble.

2.14 IN-PROCESS QUALITY CONTROL TESTS FOR PHARMACEUTICAL TABLETS

The quality in the pharmaceutical industry has become a very important and sensitive issue. Since the world has gathered together to unite its practices, guides and the launching of the Food and Drug Administration (FDA) current good manufacturing practices (cGMP) for the 21st century - there has been a growing awareness for the significance of the quality of the pharmaceutical products.

The purposes of Quality control are to produce a perfect finished product by preventing or eliminating errors at every stage in production. Quality control is a team work and we have to remember that quality must be built into a drug product during product and process design and it is influenced by the physical plant design, space, ventilation, cleanliness and sanitation during routine production.

Process testing enables easier identification of problems.

In-process quality control (IPQC) tests was important to remove problems from every stage in production and maintain the quality of the In-process product with standards as specified in the pharmacopoeias

In-Process Quality Control Tests (IPQC) are accurate and specific for testing of raw materials (RM) to the release of the finished dosage (FD) forms IPQC tests was performed in production area.

If a defective product batch is identified, that can be corrected by rework. Whereas once that batch has been completed, this may not be possible.

Failure to meet IPC specification indicates either those procedures were not followed or some factors were out of control. Standard operating procedures (SOPs) should be established in the pharmaceutical industry and followed that describe the IPQCs and tests:

1. Size and shape: The size and shape of the tablet can be dimensionally described monitored and controlled. It is determined by the tooling during the compression process.

2. Colour and odour: Many pharmaceutical tablets use colour as a vital means of rapid identification and consumer acceptance. But it must be uniform within a single tablet, from tablet to tablet and from lot to lot.

The presence of an odour in a batch of tablets could indicate a stability problem e.g. the characteristic odour of acetic acid in degrading aspirin tablets or could be characteristic of the drugs e.g. vitamins have a characteristic odor. Taste is important in consumer acceptance of chewable tablets.

3. Thickness: The thickness of a tablet is the only dimensional variable related to the process. Thickness of individual tablets may be measured by a micrometer. Other techniques involve placing 5 or 10 tablets in a holding tray, where their total thickness may be measured by a sliding caliper scale. Tablet thickness should be controlled within a ± 5 % variation of a standard. Thickness must be controlled to facilitate packaging. It is expressed in mm.

4. Unique identification markings: Pharmaceutical companies often use some type of unique markings on tablets in addition to color, for rapid identification of their product these markings utilize some form of embossing, engraving or printing of the company name or symbol or a product code.

5. Moisture content of granules: Granules should possess sufficient strength to withstand normal handling and mixing processes without breaking down and producing large amounts of fine powder. On the other hand, some size reduction during compaction into tablets is desirable to expose the areas of clean surface necessary for optimum bonding to take place so moisture content is very important factor for producing good pharmaceutical product.

6. Assay: In a tablet an active ingredient is present which is called Active pharmaceutical ingredient. So to prepare the tablet assay has to be done by using suitable analytical method to produce good finished product

7. Uniformity of content: A physically sound tablet may not produce the desired effects. To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet and batch to batch.

For this test according to BP using a suitable analytical method, determine the individual contents of active substance(s) of 10 tablets taken at random

The tablet complies with the test according to BP, if each individual content is between 85% and 115% of the average content. The tablet fails to comply with the test if more than

one individual contents are outside these limits or if one individual content is outside the limits of 75% to 125% of the average content. If one individual content is outside the limits of 85% to 115%, but within the limits of 75% to 125%, determine the individual contents of another 20 tablets taken at random. The tablet complies with the test if not more than one of the individual contents of the 30 tablets is outside 85% to 115% of the average content and none is outside the limits of 75% to 125% of the average content

8. Uniformity of mass: This test is applicable for uncoated and film coated tablets. For this test according to BP weigh individually 20 tablets taken at random and determine the average mass. As per BP the tablet complies with the test if not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation and none deviates by more than twice that percentage.

Average mass (mg)	Percentage deviation (%)
80 or less	10.0
More than 80 and less than 250	7.5
250 or more	5.0

9. Weight variation test: According to the USP weight variation test is run by weighting 20 tablets individually calculating the average weights and comparing the individual tablet weights to the average. The value of weight variation test is expressed in percentage.

Average mass (mg)	Percentage deviation (%)
130 or less	10.0
More than 130 and less than 324	7.5
More than 324	5.0

$$\text{Weight Variation} = \frac{I_w - A_w}{A_w} \times 100\%$$

where, I_w = Individual weight of tablet; and A_w = Average weight of tablet.

10. Content of Active Ingredients: For this test according to IP determine the amount of active ingredient(s) by the method described in the assay and calculate the amount of active ingredient(s) per tablet. The result lies within the range for the content of active ingredient(s) stated in the monograph.

11. Hardness Test: For this test one of the earliest testers was Ketan tablet hardness tester, which is a type of the Monsanto hardness tester to evaluate tablet hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet and zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded in kilogram.

QUESTIONS

Long essay questions: (10 marks each)

1. Discuss problems encountered in tableting. Give reasons and causes and suggest remedies for the same.
2. Discuss various machines used to compress tablets.
3. Discuss working principle, construction and operation of single press tablet machine.
4. Discuss in detail working principle, construction and operation of multi-station press tablet manufacturing machine.
5. Discuss various tools of tablet compression machine.
6. Write about meanings of various tablets tooling terms.
7. What is tablet coating? Give its objectives.
8. Discuss various types of tablet coatings.
9. Elaborate on formulation of tablet coating compositions.
10. Discuss various excipients used in tablet coating compositions.

Short essay questions: (5 marks each)

1. Write note on solvent system for making coating compositions.
2. Enlist and elaborate on various equipments employed in tablet coating.
3. Write in detail about tablet coating process.
4. Elaborate upon quality of a tablet for coating applications.
5. Discuss various defects in tablet coating along with reason, causes and remedies for the same.
6. Write notes on:
   (a) Sugar coating
   (b) Film coating
   (c) Enteric coating
   (d) Gelatin coating
   (e) Compression coating

Short answer questions: (2 marks each)

1. What is tablet? Classify them with examples of each.
2. What are advantages and disadvantages of tablets over other dosage forms?
3. Give ideal characteristics of tablet dosage forms.
4. Define following terms:
   (a) Compressed tablet
   (b) Chewable tablet

(c) Dispensing tablet
(d) Immediate release tablet
(e) Sugar coated tablet
(f) Buccal tablet
(g) Gelatin coated tablet
(h) Sustain release tablet
(i) Film coated tablet

5. Describe various excipients used in manufacturing of compressed tablets.
6. Write short note on formulation of a tablet.

☆☆☆

Chapter 3 ...

LIQUID ORALS

Upon completion of the chapter, students will be able to understand:

- *The key building blocks of liquid dosage forms.*
- *The technologies used in preparation and evaluation of various liquid dosage forms .*
- *The knowledge to develop liquid dosage forms with desired safety, sensory, stability and efficacy.*

3.1 INTRODUCTION

Liquid orals are the liquid dosage formulations containing one or more active ingredients with or without additives dissolved in a suitable vehicle, meant for oral administration. Examples of liquid orals are syrups, elixirs, linctuses, mixtures, oral drops, solutions, suspensions, emulsions etc. Here formulation of monophasic liquids is discussed.

Liquid orals are the big category of formulations in the pharmaceutical dosage formulations market. 25-30% of monographs in pharmacopoeia are liquids. They are used so widely even though solid dosage formulations are dominating now-a-days because of certain advantages mentioned below.

Advantages of Liquid Orals:

1. Liquid dosage formulations are preferred dosage formulations for the children who feel difficulty in swallowing solids. This is also true with elderly patients.
2. Bioavailability of liquids is more than solids, sometimes equal to that of intra muscular injections.
3. The solution is the only form in which certain compounds can be obtained. For example hydrogen peroxide solution.
4. The liquid, sometimes, is more stable and convenient than the solid compound. For example, ferric chloride solution.
5. The substance is formed by chemical interaction in solution, and as the latter is the form in which it is most frequently required, there would be no advantage gained in isolating the solid compound. For example, strong ammonium acetate solution.
6. A liquid provides a convenient form for prescribing and dispensing substances the dose of which is a small fraction of a grain. For example solution of strychnine hydrochloride.
7. Sometimes the patients expect the drug in liquid dosage formulation for certain diseases. Examples are cough syrups and antacids.

8. Liquid dosage formulations can be made more pleasant by adding suitable colours, flavours and sweeteners, if necessary viscolizers can be added to increase the viscosity.
9. The drug is uniformly distributed, therefore, no need to shake the container.
10. Some drugs are irritating to the gastric mucosa. When given in a tablet or capsule form. This irritation may be reduced when the drug is given in solution because of the dilution factor.

Disadvantages of Liquid Orals:

1. Most of the drugs are known to undergo reactions like hydrolysis, oxidation etc. Such reactions are more severe in liquids.
2. Many drugs pose problems in solubilizing them in the given solvent. Special techniques should be followed to dissolve such poorly soluble drugs.
3. Formulation of liquids, sometimes, includes more number of steps than solids.
4. Liquids are stored in the containers which create problems like sorption, leaching, air permeability etc.
5. It is difficult to mask unpleasant flavours.
6. The bulk and weight of dosage form are high.
7. Contents are vulnerable loss by breakage of the container.
8. Patient is instructed to measure the dose. Hence drug administered depends on the measurer and accuracy of the patient.
9. Liquids are more prone to bacterial contamination.
10. The pleasant taste of liquid formulations may result in overdosage. This is especially hazardous with children.

Preformulation of Liquid Orals:

A successful liquid oral is one that is developed to satisfy the ideal requirements of stability, therapeutic effectiveness, and pleasing appearance. The knowledge of the factors influencing the manufacture of liquid orals is essential to solve the formulation problems.

3.2 SOLUBILITY

In the preparation of liquids the drug is dissolved in the solvent of intended use. But the dissolution of drug depends on;

- Nature of solvent
- Nature of solute
- Intensity of the forces present in solute-solvent
- Solute-solvent interactions
- Steric factors
- Electronic factors

Determination of Solubility:

Before attempting to formulate a solution the solubilities of any ingredients must be determined. This can be done by placing an excess of finely divided drug in a tightly closed container along with the solvent. This container is then agitated at constant temperature bath for 72 hours. Samples are withdrawn to determine the solubility of the drug by suitable analytical technique.

Factors Influencing Solubility:

1. **pH:** Most of the drugs are either weak acids or weak bases. They are insoluble or slightly soluble in water while their salts are soluble. The solubility of these agents is markedly influenced by pH of their environment.

   The values for the solubility constant K_s and the dissociation constants K_a or K_b that are reported in the literature are usually for the drug in distilled water. These values are not always helpful as such. Because these values differ for the dosage formulation like elixir containing more amount of solid and cosolvents. In general, cosolvents such as alcohol or glycerin have the effect of increasing solubility constant and decreasing the dissociation constant.

   The drug's pH environment should be fixed by keeping certain points in mind.
   - The solvent used for the dosage formulation.
   - The concentration of the drug required in the formulation.
   - pH should not decrease the stability of the product.
   - pH should encourage physiologic compatibility.

   During the formulation of solutions of acidic and basic drugs, the following factors must be considered.
   - The solubility of ionized and unionized forms of the drug.
   - The chemical stability of the drug as functions of the pH and the buffer components.
   - The therapeutic or pharmaceutical efficacy of the drug.

   The buffer pH and buffer type are selected to maintain a proper balance between these three variables.
2. **Buffers:** After fixing pH of the drug's environment, the formulation must be supplied in such a way as to maintain the pH throughout its life. But in certain cases there is a possibility of change in the pH. To avoid consequences of pH change, suitable buffers must be added. The selection of a buffer must be consistent with the following criteria:
   - The buffer must have adequate capacity in the desired pH range.
   - The buffer must be biologically safe for the intended use.
   - The buffer should have little or no deleterious effect on the stability of the final product.
   - The buffer should permit acceptable flavouring and colouring of the product.
   - The pKa of the acid used in buffer should be close to the desired pH of the final dosage form.

Typical buffer systems used in pharmaceutical preparations are acetate-acetic acid, bicarbonate-carbonate, borate-boric acid, and Na_2HPO_4-$Na_2H_2PO_4$.

3. **Cosolvency:** The solubility of certain drugs in water is insufficient. In such cases their solubility is increased by using water-miscible solvents in which the drugs are soluble. This process is known as *cosolvency* and the solvents used for the purpose are known as *cosolvents*.

   Mechanism: (i) Modification of polarity of the solvent system in such a way as to approach the polarity of the solute. (ii) The formation of a completely new solvent whose interactions cannot be easily predicted from the interactions of the individual components of the solvent mixture.

   It is easy to predict solubilities of nonpolar or semipolar compounds in 20% ethanol in water than to predict solubilities of the same compounds in water-ethanol-glycerin-sorbitol solvent system. The sum of solubility values in individual solvents is usually not equal to its solubility in blend of solvents.

   Auxiliary use: Cosolvents are also used to facilitate the incorporation of volatile oils in the formulations to impart odour.

   Examples: Cosolvents used in liquid orals are ethanol, sorbitol, glycerin, syrups, propylene glycol, PEGs etc.

   If ethanol is used as a cosolvent, then the amount of ethanol is kept to a minimum because of its pharmacological effect, burning taste in high concentration and cost.

4. **Dielectric Constant:** The well known rule "like dissolves like" is based on the observation that molecules of similar charge distribution are mutually soluble. Molecules which have asymmetric charge distribution, i.e. polar molecules, are soluble in polar media, while non polar molecules can easily be placed in non polar media.

   The dielectric constant is a measure of the polarizability of a molecule. Compounds are often classified according to their dielectric constants as polar, semipolar or nonpolar.

Polarity	Dielectric constant
Non-polar	1 – 20
Semi-polar	20 – 50
Polar	> 50

   It should be remembered that dielectric constant is not necessarily an accurate and sufficient predictive tool for solubility. Dielectric constant for sucrose is 3.3, yet it is very soluble in water. The dielectric constants of dioxane (2.26) and mineral oil (2.5) are essentially similar, yet dioxane is completely miscible with water whereas mineral oil is immiscible with water.

   The dielectric constant of water decreases with an increase in temperature, yet the solubility of most compounds increases with an increase in temperature. Therefore solubility cannot be predicted from combination of dielectric constant alone.

   The dielectric constant of a combination two solvents lies between the values for the individual components. The solvent properties of solvent blends having the same

dielectric constant are not similar. Dielectric constant for 70% w/w ethanol is 61.1 which is very close to dielectric constant for 40% w/w sucrose 59.9%, yet these two solvents have different solvent properties.

The dielectric constant of a solvent, therefore, gives only a rough qualitative prediction of the solvent properties and the degree of solubility of polar and non polar compounds.

5. **Solubilization:** Solubilization is an alternative method for increasing the solubility of poorly water-soluble drugs. *Solubilization* is defined as the spontaneous passage of poorly water soluble solute molecules into an aqueous solution of soap or a detergent, in which a thermodynamically stable solution is formed.

   When surfactants are added to a liquid at low concentrations, they tend to orient at the air-liquid interface. With the increased concentrations of surfactant, the molecules are forced into the bulk of the liquid. At still higher concentrations, the molecules of surfactant in the bulk of the liquid begin to form micelles. The concentration of surfactant at which it occurs is known as the *critical micelle concentration (*CMC).

   Solubilization effects when micelles entrap or adsorb solute molecules. Therefore, the surface active agent must be present in solution at or above the CMC. For oral preparations polysorbates are used as surfactants.

   For example, (1) cresol with soap solution in which cresol solubility is increased with increased CMC formation (2) Cholesterol is more soluble in aqueous soap solutions than in pure water.

6. **Complexation:** Organic compounds in solution generally tend to associate with each other to some extent. Every substance has specific, reproducible equilibrium solubility in a given solvent at a given temperature. Any deviation from this inherent solubility must be due to the formation of new species (complexes) in solution.

   Insoluble compounds often interact with a soluble ingredient to form a soluble complex. For example, preparation of iodine solutions. Insoluble iodine (I_2) reacts with soluble I^- of KI to form soluble KII_2 soluble complex.

   In the case of weakly acidic and basic compounds, the total solubility is equal to the inherent solubility of the undissociated compound plus the concentration of the dissociated species. Similarly when complex formation occurs, the total solubility is equal to the inherent solubility of the uncomplexed drug plus the concentration of drug complex in solution.

   In utilizing this approach for increasing the solubility of a compound, one has to make sure that the complex is reversible, dissociates easily and releases the active ingredient, otherwise the active ingredient becomes therapeutically ineffective.

7. **Hydrotrophy:** The term hydrotrophy has been used to designate the increase in solubility in water of various substances due to the presence of large amounts of additives.

   Mechanism: A complex is formed between solute and hydrotrophic agent by weak interaction.

Limitations:

- Large amount (20 to 50%) of additive is necessary to produce the effect.
- The extent to which solubility is increased is not sufficient.
- Many of the complexing agents are either physiologically active substances or are of unknown biologic character.

Examples:

- Sodium benzoate increases the solubility of caffeine.
- Sodium acetate increases the solubility of theophyllin.
- Sodium benzoate increases the solubility of benzoic acid.
- PVP increases the solubility of iodine.

8. **Chemical Modification of the Drug:** The solubility of poorly soluble drugs can be increased by chemical modification of the drug.

   Example: The solubility of betamethasone alcohol in water is 5.8 mg/100 ml at 25°C. The solubility of chemically modified drug betamethasone alcohol 21 disodium phosphate in water is 10 g/100 ml.

   Limitation: Chemically modified drugs must be subjected to the prolonged testing protocol as the parent compound, including biologic activity studies, acute and chronic toxicity, pharmaceutical evaluation, and clinical testing. This procedure is time consuming and expensive. Therefore this procedure is approached only when other procedures are not possible.
9. **Temperature:** Solubility of most of the drugs/additives increases with the increase in temperature.
10. **Salting-out:** The addition of large amounts of highly soluble salts to aqueous solutions of organic compounds often leads to precipitation or separation of organic solutes. This phenomenon is called as salting out and is attributed to competition between the salts and the organic compounds for solvent molecules (water). The salting-out power of a salt depends on the size and relevance of its ions.
11. **Salting-in:** This is a process of increasing the solubility of an organic compound upon the addition of a salt. For example, salting-in of globulins (proteins) in water in presence of salts.
12. **Particle Size:** Solubility increases with decrease in particle size at submicron levels, an increase of about 10% in solubility is then observed. This is due to the large surface free energy associated with small particles.
13. **Molecular Size of Solvent Molecules:** The solvent properties of water are due to the small size of its molecules. Any other liquids which are similar to water in polarity, dielectric constant, and hydrogen-bonding may be poor solvents for ionic compounds. The reason is because of the larger size of the liquid molecules when compared to water molecules. It is difficult for these liquid molecules to penetrate and dissolve the crystals.
14. **Molecular Shape of Solute Molecules:** The shape of the solute molecule influences the solubility. The high solubility of ammonia in water is due to its shape which fits without

difficulty in the structure of water. The effect of the shape of the solute molecules on its solubility in a given solvent is predominantly an entropy effect.

15. **Macromolecules:** These are the compounds with molecular weight ranging from 10,000 to millions. Examples are plasma proteins, enzymes, natural polysaccharides, cellulose derivatives, PVP, carbapol etc. Solubility behaviour of macromolecules depends on molecular weight ionic character, shape, pH, temperature and added salts. Aqueous solutions are generally highly viscous and many form gels at low concentrations. These properties are the basis for the extensive use of macromolecules as thickening and suspending agents in dosage forms.

3.3 FORMULATION AND MANUFACTURING CONSIDERATIONS OF SYRUPS

Liquid orals mainly constitute drug/s in a solvent/s along with essential additives. A list of additives with examples is given here. Suitable additives are selected for the preparation.

Additives and Components:

1. Preservatives:

Liquid orals must be preserved using preservatives so as to get protection from microorganisms. No Single Preservatives exists that satisfies all of those requirements for all formulations. The Selection of a preservative system must be made on individual basis using published information and in-house microbiologic studies for guidance. Frequently a combination of two or more preservatives are needed to achieve the desired antimicrobial effect

Microorganisms can enter into the liquid orals through the following sources:

(i) Raw materials (Solutes & solvents)
(ii) Containers
(iii) Equipment
(iv) Manufacturing environment
(v) Operators
(vi) Packaging materials

Examples of Some Pharmaceutically Useful Preservatives:

(i) Acidic: Phenol (0.2-0.5), Chlorocresol (0.05-0.1), o-phenyl phenol (0.005-0.01), Alkyl esters of parahydroxy-benzoic acid (0.001-0.2), Benzoic acid and its salts (0.1-0.3), Boric acid and its salts (0.5-1.0), Sorbic acid and its salts (0.05-0.2).

(ii) Neutral: Chlorbutanol (0.5), Benzyl alcohol (1.0), 0-phenylethylethyl alcohol (0.2-1.0), Mercurial Thimerosal (0.001-0.1), Phenyl Mercuric Acetate and nitrate (0.002-0.005), Nitromersol (0.001-0.1)

(iii) Quartenary ammonium compounds: Benzalkonium chloride (0.004-0.02), Cetylpyridinium chloride (0.01-0.02)

An effectively designed preservative system must retain its antimicrobial activity for the shelf life of the product. To ensure compliance with this precept the preservative characteristics of the product in its final form (including formulation and package) must be studied as a function of age. The best method of demonstrating preservative characteristics is by microbiologic evaluation.

Specific organisms generally recognized as undesirable in oral liquids include salmonella species, Escherichiacoli, Enterobacterspecies, Pseudomonas species (commonly P.aeruginosa), proteolytic species of clostridium and candida albicans.

2. Sweetening Agents:

Sweetening agents generally constitute a major portion of the solid content in those dosage forms requiring them.

Examples of sweetening agents: Sucrose, Liquid glucose, Aspartame, Saccharin,

(i) Sucrose has had a long history of use. It is soluble in aqueous media (solutions containing approximately 85 % sucrose can be prepared). It is chemically and physically stable in the Ph range of 4.0 to 8.0.it is frequently used in conjunction with sorbitol, glycerin and other polyols which reduce the tendency of sucrose to crystallize

(ii) Liquid Glucose is an extremely viscid substance that imparts sweetness to liquid formulations. Although liquid glucose is not a pure chemical entity, its method of manufacture can be well controlled, and batch to batch variability is usually not a significant problem.

(iii) Saccharin is used to supplement sugars and polyols as sweeteners. It is approximately 250 to 500 times as sweet as sugar, but it can have a bitter aftertaste if not properly used in the formula.

(iv) A New Synthetic Sweetener, Aspartame has been approved in numerous countries for use as a food and/or drug ingredient. Aspartame is the methyl ester of aspartic and phenylalanine. It is approximately 200 times sweeter than sucrose and has none of the aftertaste of saccharin.

3. Viscosity Controlling Agents:

It is sometimes desirable to increase the viscosity of a liquid either to serve as an adjunct for palatability or to improve pourability. This can be achieved by increasing the sugar concentration or by incorporating viscosity-controlling agents such as polyvinyl pyrrolidone or various cellulosic derivatives (e.g methyl cellulose or sodium carboxy methyl cellulose). These compounds form solutions in water that are stable over a wide pH range. Viscosity - inducing polymers should be used with a degree of caution. They are known to form molecular complexes with a variety of organic and inorganic compounds and thus influence the activity of these compounds.

4. Buffers:

During storage of liquid preparations, degradation of the product, interactions with container components or dissolution of gases and vapours causes change in their pH level, which can be prevented by addition of buffer. A suitable buffer system should have adequate buffer capacity to maintain the pH level of the product. Commonly used buffer systems are phosphates, acetates, citrates and glutamates. Although buffers ensure pH stability, the buffer system can affect other properties such as solubility and stability. The ionic strength contributions of the buffer systems can affect stability. Buffers can also act adversely as general-acid or general-base catalysts and cause degradation of the drug substance. Therefore before selecting any buffer system, the effect of buffer species should be studied.

5. Antioxidants:

Various drugs in solution are subject to oxidative degradation. Oxidation is defined as a loss of electrons from a compound leading to change in the oxidation state of the molecule. Drugs possessing favorable oxidative potential are especially vulnerable to degradation. Additionally certain properties of the selected primary packaging (such as polymer degradation, oxygen transmission rates, impurities etc) can readily lead to oxidation of drug molecules in solution and hence may require the addition of antioxidants to maintain product stability.

Examples: Ascorbic acid, Butylated hydroxyanisole, Butylated hydroxytoluene

6. Flavours:

A combination of flavouring agents is usually required to mask these taste sensations effectively. Menthol, Chloroform and various salts are frequently used as flavor adjuncts. Menthol and Chloroform are sometimes referred to as de-sensitizing agents. They impart a flavor and odour of their own to the product and have a mild anaesthetic effect on the sensory receptor organs associated with taste.

7. Solvents:

A vehicle for a liquid dosage form may be a pharmaceutical solvent, a solution, an emulsion, or a suspension. The desired or required properties of the vehicle depend on the route of administration for the preparation and the type of solvent system needed or desired.

Example: Sugar-free, artificially sweetened vehicles, Water, Alcohol, Glycerin, Propylene glycol.

3.4 FORMULATION AND MANUFACTURING CONSIDERATIONS OF ELIXIRS

The USP XVII defines elixirs as clear, sweetened hydroalcohol liquids intended for oral use containing flavoring substances or active medicinal agents. Their primary solvents are alcohol and water, with glycerin, sorbitol and syrup sometimes as an additional solvent and/or sweetening agents. They are prepared by simple solution or admixture of the several ingredients. They are used either as vehicles or for the therapeutic effect of the medicinal substances that they contain.

Main Ingredients: Alcohol, Water, Glycerin, Preservatives, Sorbital, Flavouring agents.

Types of Elixirs: Medicated Elixirs and Non-medicated Elixirs.

Simple, no therapeutic agents ʊ May only contain alcohol, sweetening agents, colouring agents ʊ Self preserve Uses: ʊ They are used purely as diluting agents ʊ solvents for drugs [containing approximately 25 percent alcohol, e.g., simple elixir, Iso-alcoholic elixir or low alcohol elixir (containing 8-10% alcohol), High alcoholic elixir (containing 75-78% alcohol)] Example Aromatic elixir, Isoalcoholic Elixir

3.4.1 Formulation of Elixirs

Generally elixirs contain following ingredients:

1. Vehicles: About 10-20% of alcohol is used for keeping oils, vegetable extracts, tannins etc in solution form. Glycerol and propylene glycol are used as solvent .

2. Stabilizers: In neomycin elixir, citric acid is used to adjust pH 4.0 to 5.0 to minimize the darkening that occurs on storage. Disodium edetate should be used to sequester heavy metals that catalyse decomposition of the antibiotics.

3. Flavouring agents: Sweetening agents and fruit flavours are used in many medicinal preparation. e. g. (i) Black currant syrup in chloral Elixir, (ii) Compound orange spirits with glycerol in phenobarbital elixir.

4. Preservatives: In elixir, fermentation and mold growth are inhibited when it contains more than 20% of alcohol, propylene glycol or glycerol. The commonly used preservatives are double strength chloroform, spirit, and benzoic acid and methyl ester of p- hydroxy benzoic acid.

3.4.2 Method of Preparation

Dissolve the water-soluble ingredients in part of the water, add and dissolve the sucrose in it. Dissolve the other ingredients in the alcohol. (Concentration of alcohol should be 5-40% to make clear solution) The aqueous solution is then added to the alcoholic solution with constant stirring and make up the volume with the solvent or vehicle specified in the formulation. Sucrose increases viscosity but decreases the solubility properties of water and so must be added after primary solution has been carried out. A high alcoholic content is maintained during preparation by adding aqueous phase to the alcoholic solution. Elixirs should be brilliantly clear and therefore strained or filtered, if necessary, subjected to clarifying action of purified talc or siliceous earth.

Dry Elixirs: Dry elixirs containing a non-steroidal anti-inflammatory drug and ethanol were encapsulated in a dextrin. The dissolution rate constant of the drug from the microcapsules usually increased considerably compared to the drug alone, possibly due to the cosolvent ethanol.

3.4.3 Manufacturing Considerations

1. Raw Materials:

The raw materials used in manufacturing of liquids should conform to well though out specifications. These specifications should assure identity, purity, uniformity and free from excessive microbial contamination. Incoming raw materials should be impounded and thoroughly tested before they are released for manufacturing.

Aside from the active ingredient water is usually the most important constituent in a liquid product. It should meet the USP requirements for purified water. It may be obtained by distillation or ion exchange treatment. In recent years, manufacturers have devoted considerable effort to upgrading the microbial purity of the water supply used in oral liquids. Techniques employed include reverse osmosis purification, ultraviolet sterilization, membrane filtration, and constant circulation in piping systems that have no "dead ends" where microorganisms can thrive. In general, the most difficult microbes to remove from a purified water system are the Pseudomonas shows a purified water system designed to minimize microbial growth.

2. Equipments:

The equipments used include:

- **Mixing tanks:** These are usually made up of stainless steel. They are available in different sizes. Sometimes heating and cooling of the solution is necessary during the manufacture of liquid orals. In such cases, tanks are jacketed through which either steam or cold water can be supplied for the purpose. They are facilitated by see through charging ports and illuminated. With these facilities the contents inside can be observed.
- **Agitators:** During mixing the contents must be stirred thoroughly to ensure complete solubility of the contents. The mixing of liquids is easy if they are miscible and mobile. A simple mixing device is essential to encourage flow of liquids. High capacity electric stirrer may be used if the liquids are of high viscosity. Agitating systems fixed to the mixing tanks serve this purpose.
- **Measuring devices:** Measuring devices of different capacity are required for measuring the liquids.
- **Filtration systems:** The solvents used are filtered before using them for preparation. Even such systems, sometimes, are used for sterilization of liquids. Though liquid orals are always not necessary to be sterile, liquids are filtered to polish the preparation.
- **Bins:** The liquids are stored in the bins after filtration until for further use.
- **Piping:** Piping system is required for the transport of the liquids from storage bins to filling equipment. The distance between the storage bin and filling equipment must be as short as possible. Because more the distance more will be the chances of microbial contamination.

All the equipments used must be thoroughly cleaned using well validated cleaning procedure. Finally the equipments must be sterilized. For sterilizing the following agents can be used.

- Dilute solutions of hydrogen peroxide
- Phenol derivatives
- Peracetic acid
- Alcohol
- Boiling water
- Autoclave
- Steam
- Dry heat

3. Personal:

One important source of contamination is personal working. To avoid the contamination, the person must wear head covering, gloves and face masks at all times. In addition a continuous education program is essential to keep the person aware of the procedure.

4. Compounding Procedure:

Dilute solutions, prepared from rapidly dissolving materials, are simply prepared by charging the solute to the solvent and agitating until the solution is homogeneous. When

more concentrated solutions are being made, or when the solute is slowly dissolving, it may be advantageous to employ heat.

Compounding Instructions:

- Charge 2000 L of purified water through the water meter into the compounding tank. Check the volume against the outage chart. Heat to approximately 50°C.
- To the water in the compounding tank, charge the following materials in the amounts specified in the batch sheet. Dissolve each one, with agitation, before adding the next (a) drug, (b) sodium benzoate, (c) standard granulated sugar. Agitate the contents of the compounding tank until homogeneous, and then cool to 30°C.
- Charge the specified amount of glycerin to the compounding tank. Agitate until, batch is homogeneous.
- Charge the specified amount of sorbitol solution to the compounding tank. Agitate until the batch is homogeneous.
- Measure 20 L of alcohol into a suitable stainless steel container. Add and dissolve the specified charge of menthol. Add and dissolve the specified charge of flavour.
- Charge the alcoholic solution of menthol and flavour to the batch in the-compounding tank. Agitate until homogeneous.
- Charge the balance of the specified amount of alcohol to the batch. Agitate until homogeneous.
- Charge 10 L of purified water to a clean stainless steel container. Add to the water and dissolve the specified amount of FD and C Yellow No. 6.
- Charge the dye solution to the batch in the compounding tank, and agitate until homogeneous.
- Add to the compounding tank sufficient purified water to bring the batch volume to 5000 L.
- Weight out 2.5 kg of filter aid, and charge it to the contents of the compounding tank. Agitate for 10 min. The batch is now ready to filter.
- Cycle the batch through the filter and back to the compounding tank until the filtrate is clear. At this point, the filtrate may be discharged and collected in the designated holding tank.
- Sample the batch, and submit for testing in accordance with standard procedure.

3.5 SUSPENSIONS AND EMULSIONS

Biphasic liquids such as suspensions and emulsions are unique dosage forms because many of their properties are due to the presence of a boundary region between two phases. In suspensions, a liquid and an insoluble solid meet to form an interface. In the case of emulsions, two immiscible liquids, usually oil and water, form an interface.

3.5.1 Formulation of Suspensions

1. **Wetting agents:** They are added to disperse solids in continuous liquid phase .
   Example: Polysorbate 80, 20, span etc.
2. **Suspending agents:** They are added to flocs the drug particles.

3. **Thickeners:** They are added to increase the viscosity of suspension.
   Example: gaur gum, xanthan gum.

4. **Buffers and pH adjusting agents:** They are added to stabilize the suspension to a desired pH range.

5. **Colouring agents:** They are added to impart desired colour to suspension and improve elegance.

6. **Preservatives:** They are added to prevent microbial growth.

3.5.2 Preparation of Suspensions

Step 1: Suspensions are prepared by grinding the insoluble materials in the mortar to a smooth paste with a vehicle containing the wetting agent.

Step 2: All soluble ingredients are dissolved in same portion of the vehicle and added to the smooth paste to step 1 to get slurry.

Step 3: The slurry is transformed to a graduated cylinder, the mortar is rinsed with successive portion of the vehicle.

Step 4: Decide whether the solids are

- Suspended in a structured vehicle
- Flocculated
- Flocculated and then suspended

Add the vehicle containing the suspending agent (or) flocculating agent.

Step 5: Make up the dispersion to the final volume .Thus suspension is prepared.

3.5.3 Stability of Suspension

Factors that contribute to appreciable stability of a suspension include:

1. **Small Particle Size:**
   - Reduced size of the dispersed particle increases the total surface area of the solid.
   - The greater the degree of subdivision of a given solid the larger the surface area.
   - The increase in surface area means also an increase in interface between the solids and liquids leading to an increase in viscosity of a system.
2. **Increasing the Viscosity:**
   - Increased viscosity of the continuous phase can lead to the stability of suspensions.
   - This is so because the rate of sedimentation can be reduced by increase in viscosity. Viscosity increase is brought about by addition of thickening agents to the external phase.
   - It is important to note that the rate of release of a drug from a suspension is also dependent on viscosity.
3. **Temperature:**
   - Another factor which negatively affects the stability and usefulness of pharmaceutical suspensions is fluctuation of temperature. Temperature fluctuations can lead to caking and claying.

3.6 FORMULATION OF EMULSIONS

Emulsifying Agents (Emulsifiers): An emulsifying agent is the material that enhances the stability of an emulsion (i.e. Prevention of coalescence and reducing creaming).

The ideal emulsifying agent is colourless, odourless, tasteless, non-toxic, non-irritant and able to produce stable emulsions at low concentrations.

Examples of Emulsifying Agents:

1. **Carbohydrate Materials:** Acacia, Tragacanth, Agar, Pectin. o/w emulsion.
2. **Protein Substances:** Gelatin, Egg yolk, Caesin o/w emulsion.
3. **High Molecular Weight Alcohols:** Stearyl Alcohol, Cetyl Alcohol, Glyceryl Mono stearate o/w emulsion, cholesterol w/o emulsion.
4. **Wetting Agents:**
   - Anionic, Cationic, Nonionic
   - o/w emulsion -w/o emulsion
5. **Finely divided solids:** Bentonite, Magnesium Hydroxide, Aluminum Hydroxide o/w emulsion.

Tests for Identification of Emulsion Type:

- Dilution test (Miscibility test)
- Staining test (Dye solubility test)
- Conductivity measurement
- Fluorescence test

3.6.1 Preparation of Emulsions

The methods commonly used to prepare emulsions can be divided into two categories:

1. Trituration Method:

This method consists of dry gum method and wet gum method.

(i) Dry Gum Method: In this method the oil is first triturated with gum with a little amount of water to form the primary emulsion. The trituration is continued till a characteristic 'clicking' sound is heard and a thick white cream is formed. Once the primary emulsion is formed, the remaining quantity of water is slowly added to form the final emulsion.

4 : 2 : 1 formula 4 parts (volumes) of oil 2 parts of water 1 part of gum

(ii) Wet Gum Method: As the name implies, in this method first gum and water are triturated together to form a mucilage. The required quantity of oil is then added gradually in small proportions with thorough trituration to form the primary emulsion. Once the primary emulsion has been formed remaining quantity of water is added to make the final emulsion.

4 : 2 : 1 formula 4 parts (volumes) of oil 2 parts of water 1 part of gum Homogenizer /Mortar and Pestle.

2. Bottle Method:

- This method is employed for preparing emulsions containing volatile and other non-viscous oils. Both dry gum and wet gum methods can be employed for the preparation.

- As volatile oils have a low viscosity as compared to fixed oils, they require comparatively large quantity of gum for emulsification.
- In this method, oil or water is first shaken thoroughly and vigorously with the calculated amount of gum. Once this has emulsified completely, the second liquid (either oil or water) is then added all at once and the bottle is again shaken vigorously to form the primary emulsion. More of water is added in small portions with constant agitation after each addition to produce the final volume.

3.6.2 Stability of Emulsion

- An emulsion is said to be stable if it remains as such after its preparation, i.e. the dispersed globules are uniformly distributed throughout the dispersion medium during its storage. The emulsion should be chemically stable and there should not be any bacterial growth during it shelf life.
- Emulsion instability may either reversible or irreversible and manifest in the following ways:
  - Cracking (irreversible instability)
  - Flocculation
  - Creaming
  - Phase inversion

1. Cracking:

Cracking means the separation of two layers of disperse and continuous phase, due to the coalescence of disperse phase globules which are difficult to redisperse by shaking.

Cracking may occur due to following reasons:

- By addition of emulsifying agent of opposite type
- By decomposition or precipitation of emulsifying agent
- By addition of common solvent
- By microorganisms
- Change in temperature
- By creaming

2. Flocculation:

In flocculated state the secondary interaction (Van der Waals' forces) maintains the droplets at a defined distance of separation. Application of shearing stress to the formulation (shaking) will redisperse these droplets to form a homogeneous formulation. Although flocculation may stabilize the formulation, there is also possibility that the close location of droplets would enable droplet coalescence to occur if the mechanical properties of the interfacial film are compromised.

3. Creaming:

Creaming may be defined as the upward movement of dispersed globules to form a thick layer at the surface of emulsion. Creaming is temporary phase because it can be re-distributed by mild shaking or stirring to get again a homogenous emulsion.

The factors affecting creaming are described by Stoke's law:

$$V = \frac{2r^2 (d_1 - d_2) f}{9\eta}$$

where V = rate of creaming
r = radius of globules
d_1 = density of dispersed phase
d_2 = density of dispersion medium
g = gravitational constant
η = viscosity of the dispersion medium

Following approaches can be used for decreasing creaming:

- Radius of globules
- Difference in density of disperse phase and continuous phase
- Viscosity of dispersion medium
- Storage condition

4. Phase inversion:

Phase inversion means the change of one type of emulsion into other type, i.e. oil in water emulsion changes into water in oil type and vice-versa.

Due to the following reasons the phase inversion takes place:

- By the addition of an electrolyte
- By changing the phase-volume ratio
- By temperature change
- By changing the emulsifying agent

The phase inversion can be minimized by keeping concentration of disperse phase between 30 to 60 %, storing the emulsion in cool place and using a proper emulsifying agent in adequate concentration.

3.7 PACKAGING, LABELING AND STORAGE OF EMULSIONS

- Depending on the use, emulsions should be packed in suitable containers. Emulsions meant for oral use are usually packed in well filled bottles having an air tight closure.
- Light sensitive products are packed in amber coloured bottles.
- For viscous emulsions, wide mouth bottles should be used. The label on the emulsion should mention that these products have to be shaken thoroughly before use.
- External use products should clearly mention on their label that they are meant for external use only.
- Emulsions should be stored in a cool place but refrigeration should be avoided as this low temperature can adversely affect the stability of preparation.

Selection of Method: Liquid orals are filled into containers by different methods. The method selected for filling depends on the following;

- Characteristics of liquid
  - Viscosity
  - Surface tension

- Foam producing qualities
- Compatibility with the materials of construction of the filling machine

- The type of package
- The required production output

3.8 METHODS OF FILLING

1. Gravimetric filling method
2. Volumetric filling method
3. Constant level filling method
   (a) Vacuum filling
   (b) Gravity-vacuum filling
   (c) Pressure-vacuum filling

1. Gravimetric Filling Method:

In this method liquid from the bulk liquid tank is allowed to flow into the containers upto a given weight.

Advantage: This is a useful technique for filling large quantities of the preparation and for highly viscous products.

Disadvantage: This method is not suitable for high speed production rates and for automatic equipment.

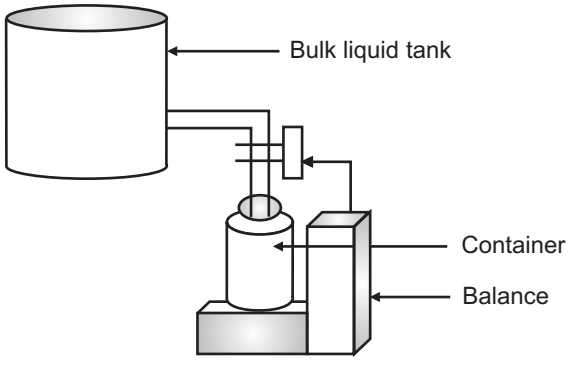


Fig. 3.1: Gravimetric filling method

2. Volumetric Filing Method:

In this method liquid is filled by positive displacement piston action. Filling station is equipped with a measuring piston and cylinder. The quality of the liquid to be filled is measured by the stroke of the piston.

Advantage: This type of arrangement can fill accurately to within fraction of a millilitre.

Disadvantages:

- Highly viscous liquids may seize the piston resulting in either loss of fill accuracy or line breakdown.
- Very low viscous liquids flow very fast. This leads to dripping from the filling piston resulting in fill inaccuracies. ***Solution*****:** The problems can be controlled by proper engineering of the filling equipment.

Containers of uniform dimensions must be used for filing to have uniform appearance. Otherwise even though the fill amount is accurate, the fill height varies inversely with the container capacity. An oversized package appears to have insufficient fill, whereas an undersized package appears to have an excessive fill.

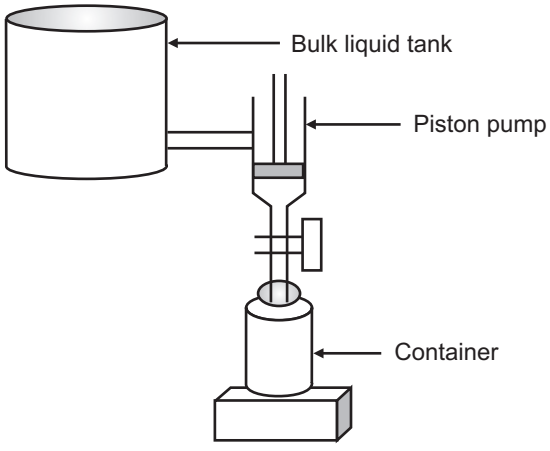


Fig. 3.2: Volumetric filling method

3. Constant Level Filling Method:

In this method container is used as the means for controlling the fill of each unit. The fill amount is varied by adjusting the height to which the container is filled.

Limitation: Any dimensional variations in the containers result in comparable variations in the net fill per unit.

The filling machines make use of a siphon principle. In addition high pressure difference is created between the liquid discharge nozzle and the constant level overflow system.

(a) Vacuum filling: A container is connected to the bulk liquid tank through vacuum head. The connections must be air-tight. Container, on the other hand, is connected to vacuum pump. A vacuum is then developed within the container. The developed vacuum causes the liquid to flow from the bulk liquid tank to the container. The liquid level rises until it reaches the vacuum tube, which is positioned at the desired constant level. If excess liquid is drawn through the vacuum tube, from there the liquid is recycled to the bulk liquid tank.

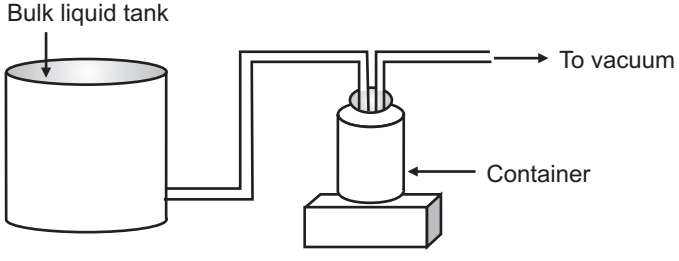


Fig. 3.3: Vacuum filling

(b) Gravity-vacuum filling: In this method, the bulk liquid tank is placed a level above the container. Connections are made air-tight. Vacuum is applied for filling. In addition gravitational force also acts to aid filling.

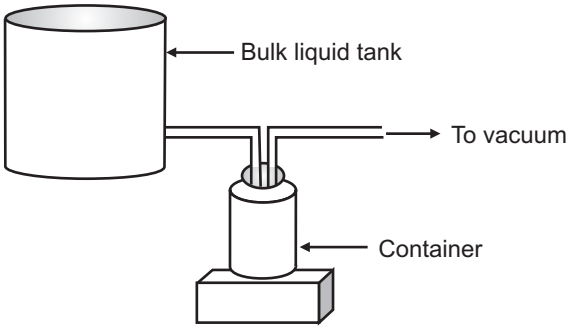


Fig. 3.4: Gravity-vacuum filling

(c) Pressure-vacuum filling: Here also connections are made air-tight. Container is connected to vacuum pump and bulk liquid tank is connected to positive pressure inducing pump. Vacuum in the container and positive pressure above the bulk liquid synergistically act to fill the liquid.

Advantage: Suitable for high viscous liquids.

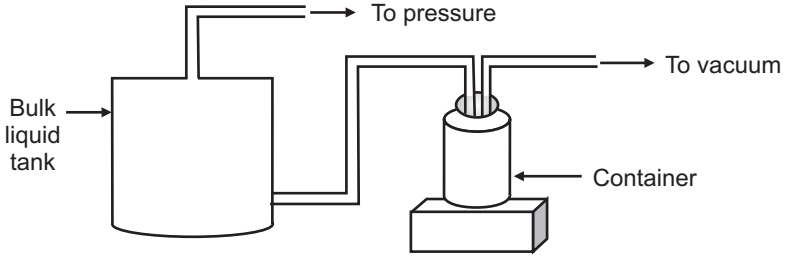


Fig. 3.5: Pressure-vacuum filling

Foam production – Problem: Foam is produced during the filling with all these methods. This is a severe problem when high production rates are required.

Solution: The problem of foam formation cannot be totally solved. However the intensity of the problem can be decreased by any of the following techniques;

(a) Using equipment that minimizes product turbulence.
(b) Using closed system filling equipment that prevents the entry of air or other gases which participate in the formation of foam.
(c) Using mechanical defoaming devices.
(d) Using low filling rates.

3.9 PACKAGE

Most liquid orals are packaged in either amber or flint glass containers with plastic or metal caps. Glass is generally inert to aqueous solutions in the pH range appropriate for oral liquids. But cap and liner may react. Plastic caps may undergo stress cracking on contact with some liquids. Metal caps may undergo corrosion. Therefore compatible closures must be selected on an individual basis.

3.10 EVALUATION OF LIQUID ORALS

A solution is a liquid preparation that contains one or more soluble chemical substances dissolved in a specified solvent.

3.10.1 Non-Sterile Liquid Dosage Forms

1. Evaluation Tests for Syrups:

A concentrated solution of a sugar, such as sucrose, in water or other aqueous liquid, sometimes with a medicinal agent added; usually used as a flavored vehicle for drugs. It is commonly expanded to include any liquid dosage form (e.g., oral suspension) in a sweet and viscid vehicle.

Following tests are carried out for the evaluation of syrups:

(a) Transmittance of light: A light transmittance meter is a newer tool that is used to check syrup colour. In a light transmittance meter, a syrup sample is checked for colour by passing light through the sample. The percent of light transmission is compared to light transmission rates set for different grades. When using one, you need to be sure there are no finger prints on the syrup test bottle, and that the syrup sample has no bubbles or cloudiness. Any of these conditions may diminish the light that is transmitted through the sample and therefore lowers the grade of the sample.

(b) Visual inspection: With visual inspection, the ingredients and the final products are carefully examined for purity and for appearance. Physical appearance of products for patient adherence and compliance is critical so it should be

- Good looking
- Elegance in appearance

(c) pH measurement: The measurement and maintenance pH is also very important step in the quality control testing. Generally there are two different types of methods used in the measurement of pH.

Methods for pH measurement:

- The simplest and cheapest is to dip a piece of pH paper into the sample. The paper is impregnated with chemicals that change colour and the colour may be compared to a chart supplied with the paper to give pH of the sample.
- If greatest accuracy is required a pH meter should be used. A typical pH meter consists of a special measuring glass electrode connected to and electronic meter that measures and displays the pH reading.

(d) Sucrose concentration: The determination of sucrose concentrations is also very important in quality control testing of syrups. If the concentration of sucrose in the syrup is very high it may crystallize the syrup and less sucrose concentrations give favor for the microbial growth.

There is no specific method for the determination of sucrose in syrup, HPLC and UV-spectroscopy for this purpose is used.

(e) Physical stability in syrups: The syrups must be stable physically.

Example:

- Its appearance (no crystallization and microbial growth)
- Colour must be completely soluble with other ingredients
- Odour and taste(palatable) .
- Solid material is completely miscible in liquid

2. Evaluation of Elixirs:

Definition: Elixirs are clear, sweetened hydro-alcoholic solutions intended for oral use and are usually flavored to enhance their palatability.

Evaluation Parameters:

(a) Determination of alcohol content: Elixir usually contains 5 to 40% alcohol. The determination of alcohol unless otherwise specified in the individual monograph. It is suitable for examining most fluid extracts, tinctures and elixirs provided the capacity of the distilling flask is sufficient (commonly two to four times the volume of the liquid to be heated) and the rate of distillation is such that clear distillates are produced. Cloudy distillates may be clarified by agitation with talc, or with calcium carbonate. And filtration is done. After which the temperature of the filtrate is adjusted and the alcohol content determined from the specific gravity. During all manipulations, take precautions to minimize the loss of alcohol by evaporation. For liquids it is presumed to contain less than 30% of alcohol.

(b) Viscosity measurement: Viscosity is a property of liquids that is directly related to the resistance to flow. Viscosity measurement is very important quality control test in case of syrups an elixirs. Viscosity and consistency directly relates with stability of solutions. If viscosity increases, then there is a chance of increase in stability.

3. Evaluation of Suspensions:

A pharmaceutical suspension is a coarse dispersion in which insoluble particles, generally greater than 1 μm in diameter, are dispersed in a liquid medium, usually aqueous.

Following tests are carried out for the evaluation of suspensions:

(a) Sedimentation method: Two parameters are studied for determination of sedimentation. They are: (i) Sedimentation volume, and (ii) Degree of flocculation.

(i) Sedimentation Volume: The suspension formulation (50 ml) is poured separately into 100 ml measuring cylinders and sedimentation volume is read after 1, 2, 3 and 7 days, and thereafter at weekly intervals for 12 weeks. Triplicate results are obtained for each formulation. Sedimentation volume is calculated according to the equation:

$$F = \frac{V_u}{V_o}$$

where, F = sedimentation volume

V_u = ultimate height of sediment

V_o = initial height of total suspension

(ii) Degree of flocculation (β): It is the ratio of the sedimentation volume of the flocculated suspension (F), to the sedimentation volume of the deflocculated suspension, (F_∞).

$$\beta = \frac{F}{F_\infty} = \frac{\text{Floculated sedimentation volume}}{\text{Defloculated sedimentation volume}}$$

F has values ranging from less than one to greater than one.

Normally F < 1.

When $F < 1 \leftrightarrow V_u < V_o$

When $F = 1 \leftrightarrow V_u < V_o$

The system is in flocculated equilibrium and show no clear supernatant on standing.

When $F > 1 \leftrightarrow V_u > V_o$

Higher the value, higher will be the stability.

(b) Rheological method: Viscosity of suspensions is of great importance for stability and pourability of suspensions. As we know suspensions have least physical stability amongst all dosage forms due to sedimentation and cake formation. So as the viscosity of the dispersion medium increases, the terminal settling velocity decreases thus the dispersed phase settle at a slower rate and they remain dispersed for longer time yielding higher stability to the suspension. On the other hand as the viscosity of the suspension increases, it's pourability decreases and inconvenience to the patients for dosing increases. Thus, the viscosity of suspension should be maintained within optimum range to yield stable and easily pourable suspensions.

- A practical rheological method involves the use of Brookfield viscometer mounted on a helipath stand. The T-bar spindle is made to descend slowly into the suspension, and the dial reading on the viscometer is then measure of the resistance the spindle meets at various levels in a sediment.
- Data obtained on samples variously aged and stored indicate whether undesired changes are taking place. This measurement is made on undisturbed samples of different ages. The results indicate how the particles are settling with time.
- In screening study, the better suspensions show a lesser rate of dial reading with spindle turns, i.e., the curve is horizontal for a longer period.

Fig. 3.6

(c) Electro kinetic method: In this zeta potential is measured by using micro electrophoresis apparatus and zeta plus (Brookhaven instruments corporation, USA). It shows the stability of a disperse system.

E.g. micro-electrophoresis apparatus MK-1.

Zeta potential: The zeta potential of the formulated suspensions is determined using a zeta plus (Brookhaven instruments corporation, USA). Approximately 1 ml of suspension is transferred into a plastic cuvette using a pipette and diluted with distilled water. The Brookhaven zeta potential software is used for the measurement. Parameters set to a temperature of 25^{o}C and refractive index (1.33). The zeta potential of the formulations is determined on day 0, 7, 14, 21 and day 28 post formulation.

(d) Micromeritic method: The stability of suspension depends on the particle size of the dispersed phase. Change in the particle size with reference to time will provide useful information regarding the stability of a suspension. A change in particle size distribution and crystal habit can be studied by microscopy and Coulter counter method.

Photo microscopy method: The microscope can be used to estimate and detect changes in particle size distribution and crystal form. Rapid processing of photo micrographs in enhanced by attaching Polaroid camera to the piece of monomolecular microscope. By using this photo micrographs we can determine the changes in physical properties and stability of suspensions.

(e) Freeze-thaw test: Freeze-thaw test conducted by placing the sample in a freezer for 18 hours followed by thawing at room temperature for 4 to 6 hours. Repeat the freeze-thaw cycle for 10 times. This test is conducted to determine the tendency to crystallize or colour.

(f) pH measurement: The measurement and maintenance pH is also very important step in the quality control testing. Generally there are two different types of methods used in the measurement of pH.

Methods for pH measurement: The simplest and cheapest is to dip a piece of pH paper into the sample.

(g) Visual inspection: With visual inspection, the ingredients and the final products are carefully examined for purity and for appearance. Physical appearance of products for patient adherence and compliance is critical so it should be:

- Good looking
- Elegance in appearance

4. Evaluation of Emulsions:

An emulsion is a system consisting of two immiscible liquid phases, one of which is dispersed throughout the other in the form of fine droplets. A third component, the emulsifying agent, is necessary to stabilize the emulsion.

Following are tests carried out for evaluation of emulsions:

(a) Determination of particle size and particle count: Determination of changes in the average particle size or the size distribution of droplet is an important parameter used for the evaluation of emulsions. It is performed by optical microscopy, sedimentation by using Andreason apparatus and coulter apparatus.

(b) Determination of viscosity: Determination of viscosity is done to assess the changes that might take place during aging. Emulsions exhibit non-Newtonian type of flow characteristics. The viscometer which should be used may be cone and plate viscometer.

(c) Determination of phase separation: This is another parameter used for assessing the stability of the formulation. Phase separation may be observed visually or by measuring the volume of the separated phases.

(d) Determination of electrophoretic properties: Determination of electrophoretic properties like zeta potential is useful for assessing flocculation since electrical charges on particles influence the rate of flocculation. Oil in water emulsion having a fine particle size will exhibit low resistance but if the particle size increase, then it indicates a sign of oil droplet aggregation and instability.

(e) Electrical conductivity: It is determined by using platinum electrodes (diameter 0.4 mm, distance 4mm) micro amperometrically to produce a current of 15 to 50 mA. Measurements are made on emulsions stored at room temperature or at 37^{o}C for short time. Stable o/w emulsion offer less resistance, but droplet aggregation increases resistance. A stable w/o emulsion does not conduct electrodes, but with droplet coagulation conductivity increases.

3.10.2 Sterile Dosage Forms

1. Evaluation of Parenterals:

Following tests are carried out for the evaluation of parenterals:

(a) Leaker test:

- Leakage occur when a discontinuity exists in the wall of a package that can allow the passage of gas under the action of a pressure or concentration differential existing across the wall.
- Presence of capillary pores or tiny cracks can cause microbes or other dangerous contaminants to enter the ampoules or may lead to the leakage of contents to outside. This may lead to contamination of the sterile contents and also spoilage of appearance of the package.
- Changes in temperature during storage can cause expansion and contraction of the ampoule and its contents, there by accentuating interchange if an opening exists.
- Leaker test for ampoules is intended to detect incompletely sealed ampoules so that they can be discarded in order to maintain the sterile conditions of the medicines.
- Tip seals are more likely to be incompletely closed than pull seals. Open capillaries or cracks at the point of seal result in leakers.

Procedure:

- Leakers are detected by this process in a visible manner. Ampoules are placed in a vacuum chamber. Completely submerged in a deeply coloured dye solution of about 0.5-1% methylene blue.
- A negative pressure is applied within the ampoule. Subsequent atmospheric pressure causes the dye to penetrate on opening thus making it visible after the ampoule has

been washed. The vacuum, about 27 inches Hg, should be sharply released after 30 minutes.

- Detection of leakers is prominent when ampoules are immersed in a bath of dye during autoclaving cycle as this has the advantage of accomplishing both leaker detection and sterilization in one operation.

Result: The colour from the dye will be visible within a leaker.

Disadvantages: Capillaries of 15 microns or smaller diameter cannot be detected by this test. Vials and bottles are not subjected to such a leaker test as the rubber closer is not rigid.

(b) Pyrogen test:

(i) LAL bacterial endotoxin test: The LAL (limulus amebocyte lysate) assay is an in-vitro assay used to detect the presence and concentration of bacterial endotoxins in drugs and biological products.

Endotoxins, which are a type of Pyrogen, are lipopolysaccharides present in the cell walls of gram-negative bacteria.

Pyrogens as a class are fever inducing substances that can be harmful or even fatal if administered to humans above certain concentrations. Water can be a source of pyrogens, so it may be important to routinely monitor water systems using the bacterial endotoxins test.

Procedure: The solution of endotoxins containing preparation is added to the lysate derive from haemolymph cells of horse shoe crab (limulus Polyphemus).

The result of the reactions is turbidity or precipitation or gelation of the mixture.

This is used as a quantitative measure to estimate the endotoxin content. The rate of reaction depends upon concentration of endotoxins, pH, temperature and presence of clotting enzyme and clottable proteins from lysate. The quantities of endotoxins are expressed in defined endotoxin units (EU). The endotoxin limit for a given test preparation is calculated from the expression k/M; where M is maximum dose administered to adult per kg/hr. The value for K is 5.0 EU/kg for parenteral preparations and it is 0.2 EU/kg for intrathecal preparations.

(ii) Pyrogen test 'fever response of rabbit':

Sham test: It is performed to select the proper animals for the main tests.

Rabbit test: The rabbit Pyrogen test in an in-vivo test to detect pyrogens qualitatively. Rabbits have a similar Pyrogen tolerance to humans, so by observing a change in body temperature in rabbits it is possible to make a determination of the presence of pyrogens. This method can detect non-bacterial endotoxin.

Procedure:

- Withheld food in the day of experiment.
- Record the initial temperature of the rabbits, any rabbit show temperature more than $39^{o}C$, should be excluded.
- Inject the sample into the ear vein of each rabbit.
- Check the temperature after 30 minutes, 1, 2 and 3 hours.

Disadvantages:

- Biological variation
- Expensive
- Laborious
- Dose dependent
- Not for antipyretic drug

Result:

- The test is positive when each rabbit show increase in temperature.
- If only two of the three rabbits show increase in temperature, repeat the test using group of five, and test will be positive if the four of the five rabbits show increase in temperature.

(c) Sterility test: Sterility testing attempts to reveal the presence or absence of viable microorganisms in a sample number of containers taken from batch of product.

Based on results obtained from testing the sample a decision is made as to the sterility of the batch.

The primary official test is performed by means of filtration but direct transfer is used if membrane filtration is unsuitable.

(i) Membrane filtration method: Media suitable for sterility tests are:

- Fluid thioglycolate medium
- Soya bean casein digest medium
- Wash the filters with fluids to remove inhibitory properties, cutting the membranes aseptically into equal parts and transferring one of the parts to each type of culture medium used.

  The media are then incubated under prescribed conditions.

(ii) Direct inoculation method: This method is only used when membrane filtration is not possible the sample is inoculated directly into the media or the device is placed directly into the media.

Result: If no growth in the media then test is positive.

(d) Particulate evaluation:

- It has been shown that particles of lint, rubber, insoluble chemicals and other foreign matter can produce emboli in the vital organs of animals and human beings.
- The USP specifies that good manufacturing practice (GMP) requires that each final container of an injection be subjected individually to a visual inspection and that containers in which visible particles can be seen should be discarded.
- Therefore, all of the product units from a production line currently are being inspected individually by human inspectors under a good light, baffled against reflection into the eye and against a black-and-white back ground.
- The USP has identified two test methods.
- The first test to be used is the light obscuration test, which uses and electronic instrument designed to count and measure the size of the particles by means of a shadow cast by the particle as it passes through a high-intensity light beam.

- If the injection formulation is not a clear, colourless solution, it exceeds the limits specified for the light obscuration test, it is to be subjected to the microscopic count test.

(e) Weight variation or uniformity of content:

- This test is intended for sterile solids used for parenteral preparations.
- The weight of 10 individual sterile units is notes and the content is removed from them and empty individual sterile unit is weighed in turn.
- Then content of active ingredient in each sterile unit is calculated by performing the assay according to the individual monographs.
- Then net weight is calculated by subtracting empty sterile unit weight form gross weight. The content in 10 sterile units is calculated by performing the assay.
- The dose uniformity is met if the amount of active ingredient is within the range of 35-115% of label claim as determine by the content uniformity method or weight variation method.
- The dose uniformity is also met if the potency value is 100% in the individual monograph or less of label claim multiplied by average of limits specified for potency in individual monograph divided by 100 provided that the relative standard deviation in both the cases is equal to or less than 60%. The fore mentioned test is carried for 20 more sterile units 14.
- The sterile units meet the requirements if not more than one unit is outside the range of 85-115%, no unit is outside the range of 75-125% and the calculated Relative standard is NMT 7.8%.

2. Evaluation of Eye Drops:

Following tests are carried out for the evaluation of eye drops:

(a) Test for sterility: All the ophthalmic preparations should be sterile i.e., free from any viable organism and its spores. Ophthalmic preparations are tested for their sterility.

The following criteria should be followed while carrying out sterility testing. Two sterile culture media are prepared for the detection of aerobic and anaerobic bacteria and fungi.

Test samples are transferred into test tubes containing clear medium. If the sample contains microorganisms, then the medium becomes turbid. If the sample is free from microorganisms, then the medium remains clear. The tests should be carried out in aseptic conditions.

Procedure:

(i) Membrane filtration method (Method A): This method is generally followed for the products which can be easily filtered and is carried out in aseptic conditions.

The apparatus consists of a sterilized filter unit with sterile membrane filter of 0.45 µ pore size. A single membrane filter is divided into two equal halves. The test solution is filtered through the membrane filer. One half of the membrane is placed in fluid thioglycollate medium at 30-35°C and other half is placed in soybean casein digest medium at 20-25°C for 7 days.

Result: If the medium shows no growth, then the sample solution passes the test. If the medium shows growth, then the test is repeated. If the growth is observed again, then the sample solution fails the test.

(ii) Direct inoculation method (Method B): Specified quantity of the solution to be tested is drawn through a sterile syringe or pipette. It is mixed with the medium and incubated for 14 days at a specific temperature. Between 3rd and 7th day of incubation, a portion of medium is transferred to a fresh medium, if it shows turbidity, then both the old and fresh media are incubated for 14 days.

Result: If the medium shows no growth, then the sample solution passes the test. If the medium shows growth, then the test is repeated. If growth is observed again, then the sample fails the test.

(b) Test for ocular toxicity and irritation: This test assesses the isotonicity of the preparation.

Procedure: Five albino rabbits are selected, the iridal vessels of whom can be easily observed for toxicity and irritation. Based on the type of dosage form, the medicament is extracted using cotton seed oil or saline. Small quantities of the extract are instilled into one eye of all the rabbits, while sterile saline solution is instilled into the other eye. After one hour all the rabbits are observed for irritation, swelling or shrinkage of the eye.

Result: No change in the eye into which the preparation is instilled indicates that the preparation under test is safe for use.

(c) Test for preservative efficacy:

- Cultures of microorganisms like *Aspergillus niger, Candida albicans, Escherichia coli* and *Pseudomonas aeruginosa*, each containing about 10,000 – 10, 00,000 organisms per ml are selected.
- Three to four samples of each preparation are taken in sterile test tubes and inoculated with few ml of each culture separately.
- They are incubated at 20 - 25°C for a period of 28 days and are observed weekly for the appearance of turbidity.
- No growth of microorganisms indicates that the preservative is totally effective.

(d) Clarity: The clarity of the formulations before and after gelling is determined by visual examination of the formulations under light alternatively against white and black backgrounds.

(e) pH: The pH of each of prepared ophthalmic formulations is determined by using pH meter (equip-tronics). The pH meter is calibrated before each use with standard pH 4, 7 and 9.2 buffer solutions.

(f) In-vitro diffusion studies: In-vitro release studies are carried out using bichambered donor receiver compartment mode (Franz diffusion cell). In-vitro release was carried out in formulations with different concentrations of gelrite using dialysis membrane. The diffusion medium 26 ml of simulated tear fluid stirred at 50 rpm at 37°C ±0.5°C. One end of the diffusion tube is covered by a dialysis membrane. The 1 ml formulation is spread on the dialysis membrane and membrane is placed such that it just touches the diffusion

medium (STF) present in receptor compartment. The drug samples are withdrawn at the interval of one hour for the period of 8 hrs. from diffusion medium and analyzed by a UV spectrophotometer at 261 nm using simulated tear fluid as blank.

(g) Determination of viscosity: The specified volume of prepared ophthalmic solution is transferred in sample cell which is placed carefully within the adaptor (Brookfield DV-II + PRO viscometer, Adapter spindle No-18). The water of 25°C is circulated through jacket of the adaptor. The viscosity values are recorded.

QUESTIONS

Long essay questions: (10 marks each)

1. Explain the factors that must be considered in the formulation of liquid orals.
2. Discuss the manufacture of liquid orals.
3. Define suspensions. Describe the different methods of evaluation of suspensions.
4. What are different types of liquid oral preparations? Describe the methods of evaluation of one in detail.
5. Define elixir. Describe different types of technology used to evaluate elixirs.

Short essay questions: (5 marks each)

1. Write a note on preservation of liquid orals.
2. Explain the filling methods used during manufacture of liquid orals.
3. How are dielectric constant and pH influence the liquid orals development?
4. Describe the importance of viscosity and clarity in the development of liquid orals.
5. Differentiate between sterile and non-sterile liquid preparations.
6. Explain evaluation of sterile liquid dosage forms.
7. Explain in detail about LAL test.

Short answer questions: (2 marks each)

1. List out the evaluation method of eye drops.
2. Define membrane filteration method.
3. Define Sham test and Rabbit test.

Multiple choice questions:

1. Which one of the following formulations is not a oral liquid?
   (a) Magnesium hydroxide suspension
   (b) Calamine suspension
   (c) Aluminium hydroxide gel
   (d) Simple linctus
2. Which one of the following ingredient is not used in oral liquid?
   (a) Water
   (b) Glycerin
   (c) Propylene glycol
   (d) Butanol

3. Match the following

(A)	(B)
(a) Viscosity	(i) Panel of experts
(b) Colour	(ii) Light scattering technique
(c) Clarity	(iii) Spectrophotometric method
(d) Taste	(iv) Viscometer

4. Match the following

(A)	(B)
(a) Preservative	(i) Apricot
(b) Antioxidant	(ii) Methyl paraben
(c) Colouring agent	(iii) Butylated hydroxyanisole
(d) Flavouring agent	(iv) Tartrazine

☆☆☆

Chapter 4 ...

CAPSULES

Upon completion of this chapter, the students will be able to understand :

- *Differences between the hard gelatin capsules and soft gelatine capsules.*
- *The various manufacturing process for the capsules.*
- *Manufacturing defect of capsules.*
- *Pelletization techniques.*

4.1 INTRODUCTION

Capsules are solid dosage forms in which the drug substance is enclosed within either a hard or soft soluble shell. Generally the shells are formed from gelatin. The capsule may be regarded as "container" drug delivery system, which provides a tasteless/odorless dosage form without the need of a secondary coating step, as may be required for tablets.

Types of Capsules:

Generally capsules are of two types:

1. Hard gelatin capsules, and
2. Soft gelatin capsules.

4.2 HARD GELATIN CAPSULES

Hard gelatin capsule consists of two parts namely 'cap' and 'body'. The diameter of cap is slightly larger than body. But the length of cap is smaller than body. The drug is filled in body and is inserted into cap to give final form capsule.

Advantages of Hard Gelatin Capsules:

- They are more elegant in appearance.
- They are easy to transport.
- They are tasteless and odourless shells.
- They are suitable for drugs possessing unpleasant taste and odour.
- Provide ready bioavailability of drug because of minimal excipients and little pressure applied during manufacturing.
- Provide enteric effect.
- They are uniquely suitable for blinded clinical trials and are widely used in preliminary drug studies.

Disadvantages of Hard Gelatin Capsules:

- They are not suitable for extremely soluble materials, such as potassium chloride, potassium bromide and ammonium chloride, because sudden release of these drugs may irritate the gastric mucosa.
- They are not suitable for efflourescent materials because they absorb moisture and cause softening of capsules.

- They are not suitable for aqueous or hydroalcoholic solutions.
- Fillling process is laborious and time consuming. Therefore production rate is slower than tableting.

4.2.1 Formulation of Gelatin Shell

Gelatin shell contains:

1. Gelatin (main ingredient),
2. Plasticizers,
3. Opacifying agents,
4. Colouring agents,
5. Flavouring agents,
6. Sweetening agents,
7. Preservatives,
8. Water, and
9. Acids.

1. Gelatin: Gelatin is a heterogenous product derived by irreversible hydrolytic extraction of treated animal collagen.

Properties of gelatin depend on:

- Parent collagen,
- Method of extraction,
- pH value,
- Thermal degradation,
- Electrolyte content.

Sources of Gelatin:

(i) Animal bones,
(ii) Frozen pork skin,
(iii) Hide portion.

Types of Gelatin:

(i) Type A: It is derived from acid treated precursor. This type of gelatin possesses an isoelectric point in region of pH 9.0.

(ii) Type B: it is derived from an alkali treated precursor of bones. This type of gelatin possesses an isoelectric point in the region of pH 4.7.

The film of capsules made from bone gelatin is tough and firm. But film tends to be hazy and brittle. Capsules made from pork skin gelatin possess plasticity and clarity, these are responsible for reducing hazy or cloudness. In practice, both the types of gelatine are used in combination to give all the desired properties to capsules.

2. Plasticizers: It increases the plasticity of the film. E.g. glycerine, sorbitol, propylene glycol.

3. Colouring Agents: These are used to impart colour to body and cap. E.g. water soluble dyes, certified lakes and vegetable colours. They are used either alone or in combination.

4 Opacifying agents: These are used to give opacity to the gelatin film. E.g. Titanium dioxide.

5. Flavouring agents: These are used in a concentration not more than 2%. E.g. ethyl vanillin, essential oils.

6. **Sweetening agents:** E.g. Sugar not more than 5%.
7. **Preservatives:** E.g. methyl paraben, potassium bisulphite.

4.2.2 Formulation of Capsule Content

Capsules mostly contain active ingredients, however the following ingredients are also used in manufacturing of capsules:

1. **Glidants:** e.g. talc, magnesium stearate, colloidal silica.
2. **Fillers (diluents):** e.g. lactose, starch, dicalcium phosphate.
3. **Disintegrants:** e.g. crosspovidone, crosscarmalose sodium.
4. **Surfactants:** e.g. sodium lauryl sulphate, sodium socusta.
5. **Hydrophilic agents:** e.g. methyl cellulose, hydroxyl ethyl cellulose.

4.2.3 Manufacturing of Hard Gelatin Capsule Shell

1. **Dipping:** Pairs of stainless steel pins are dipped into the dipping solution to simultaneously form the caps and bodies. The pins are lubricated with a proprietary mold-release agent. The pins are at ambient temperature.(about 228^{o}C), whereas the dipping solution is maintained at a temperature of about 508^{o}C in a heated, jacketed dipping pan. The length of time to cast the film has been reported to be about 12 seconds, with larger capsules requiring longer dipping times.
2. **Rotation:** After dipping, the pins are withdrawn from the dipping solution, and as they are done so, they are elevated and rotated two and a half times until they are facing upward. This rotation helps to distribute the gelatin over the pins uniformly and to avoid the formation of a bead at the capsule ends. After rotation, they are given a blast of cool air to set the film.
3. **Drying:** The racks of gelatin-coated pins then pass into a series of four drying ovens. Drying is done mainly by dehumidification by passing large volumes of dry air over the pins. Only a temperature elevation of a few degrees is permissible to prevent film melting. Drying must not be so rapid as to cause "case hardening" of the outer surface of the forming shells that would impede further moisture removal. Overdrying must be avoided as this could cause films to split on the pins due to shrinkage or at least make them too brittle for the later trimming operation. Under drying will leave the films too pliable or sticky for subsequent operations.
4. **Stripping:** A series of bronze jaws (softer than stainless steel) strip the cap and body portions of the capsules from the pins.
5. **Trimming:** The stripped cap and body portions are delivered to collets in which they are firmly held. As the collets rotate, knives are brought against the shells to trim them to the required length.
6. **Joining:** The cap and body portions are aligned concentrically in channels, and the two portions are slowly pushed together. The entire cycle takes about 45 minutes, however, about two-third of this time is required for the drying step alone.
7. **Sorting:** During sorting, the capsules passing on a lighted moving conveyor are examined visually by inspectors. Any defective capsules spotted are thus manually removed. Defects are generally classified according to their nature and potential to cause

problems in usage. The most serious of these defects are the ones that could cause stoppage of a filling machine such as imperfect cuts, dented capsules, or those with holes. Other defects may cause problems on usage, such as capsules with splits, long bodies, or grease inside. Many less important, cosmetic faults, which only detract from appearance, also may occur (small bubbles, specks in the film, marks on the cut edge, etc.).

8. **Printing:** In general, capsules are printed prior to filling. Empty capsules can be handled faster than filled capsules, and should there be any loss or damage to the capsules during printing, no active ingredients would be involved. Generally, printing is done on offset rotary presses having throughput capabilities as high as three or four million capsules per hour. Available equipment can print either axially along the length of capsules or radially around the circumference of capsules.

4.2.4 Sizes and Shapes of Hard Gelatin Capsule Shell

For human use, empty gelatin capsules are manufactured in eight sizes, ranging from 000 (the largest) to 5 (the smallest). The volumes and approximate capacities for the traditional eight sizes are listed below.

Size	Volume (ml)	Calculated fill weight (g) at powder density of 0.8 g/cm^3
000	1.37	1.096
00	0.95	0.760
0	0.68	0.544
1	0.50	0.400
2	0.37	0.296
3	0.30	0.240
4	0.21	0.168
5	0.13	0.104

Although the standard shape of capsules is the traditional, symmetrical, cylindrical shape, some manufacturers have employed distinctive proprietary shapes. Lilly's Pulvule-1 is designed with a characteristic body section that tapers to a bluntly pointed end. Glaxo Smith Kline's Spansule1 capsules exhibit a characteristic taper at both the cap and body ends.

4.2.5 Filling of Hard Gelatin Capsules

Rectification: The empty capsules are oriented so that all point to the same direction, that is, body end downward. In general, the capsules pass one at a time through a channel just wide enough to provide a frictional grip at the cap end. A specially designed blade pushes against the capsule and causes it to rotate about its cap end as a fulcrum. After two pushes (one horizontally and one vertically downward), the capsules will always be aligned body end downward, regardless of which end entered the channel first.

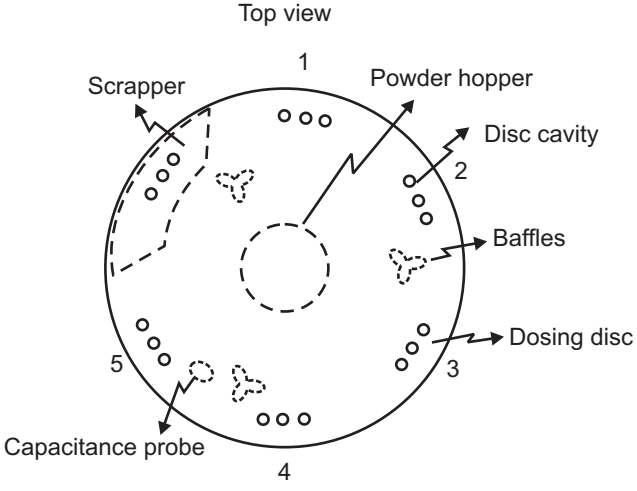
Separation of caps from bodies: This process also depends on the difference in diameters between cap and body portions. Here, the rectified capsules are delivered body end first into the upper portion of split bushings or split-filling rings. A vacuum applied from below pulls the bodies down into the lower portion of the split bushing. The diameter of the

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.

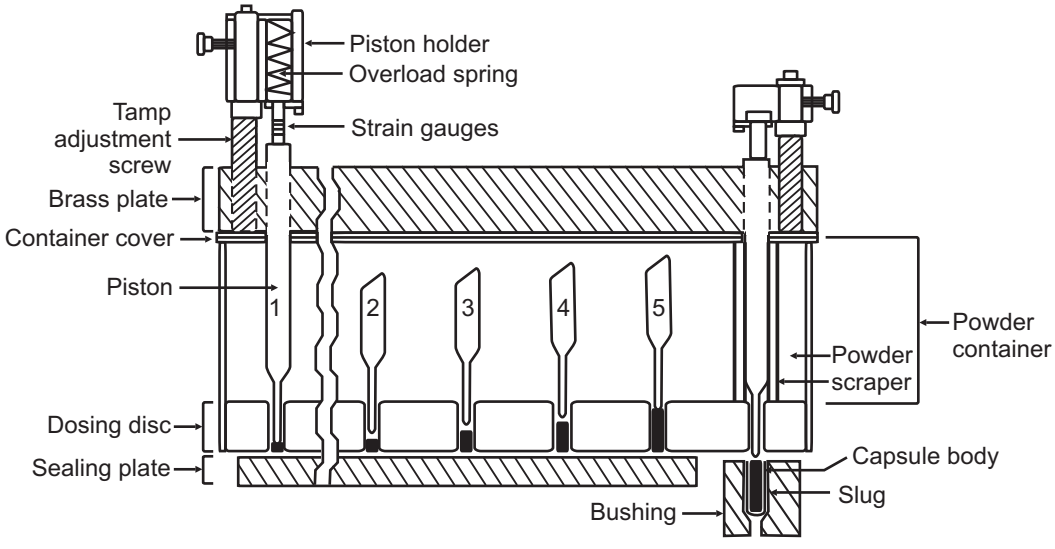
Dosing of fill material: Various methods are employed, which are described below.

Filling (dosing of material) can be done by:

1. Auger fill principle (Gravitational forces)
2. Vibratory fill principle (Overfill/Scrape-off excess)
3. Piston tamp principle (Pressured measured): Again there are two types of fillers:
   (a) Dosator machine, and
   (b) Dosing disc machine.



(a) View looking down on the dosing



(b) Side view (projected) showing progressive plug formation
Note the placement of strain gauges on the piston to measure tamping and plug ejection forces

Fig. 4.1: Dosing-disc filling principle

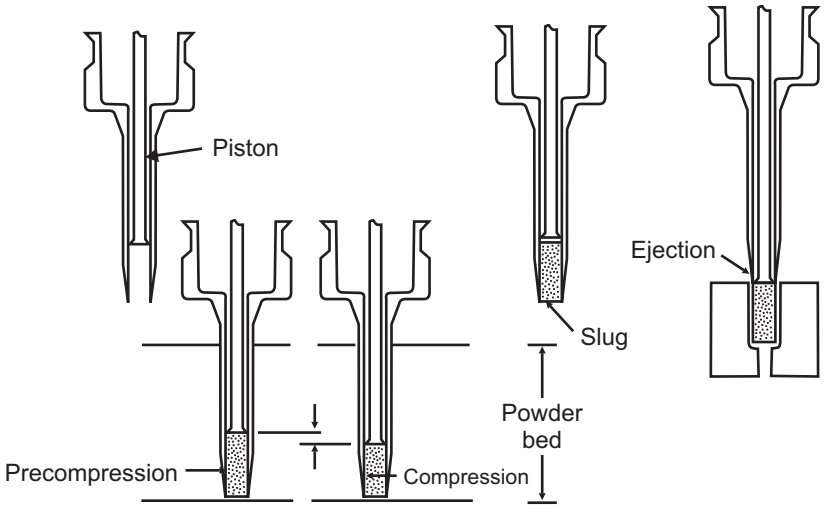


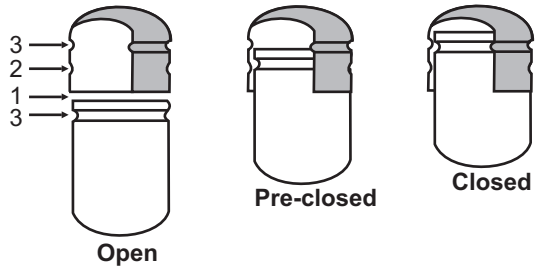
Fig. 4.2: Dosator-filling principle

Replacement of caps and ejection of filled capsules: The cap and body bushing portions are rejoined. 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 also may be used to eject the capsules.

4.2.6 Sealing and Locking of Capsules

1. Bodies are moistened with brush and painted with acacia mucilage.
2. Caps are placed on wet paper before fixing
3. Hard-gelatin capsules are made self-locking by forming indentations or grooves on the inside of the cap and body portions. Thus when they are fully engaged, a positive interlock is created between the cap and body portions.

Examples include Posilok1 (Qualicaps, Inc., Whitsett, North Carolina, U.S.) and Coni-Snap1 (Capsugel, Div. Pfizer Inc., Greenwood, South Carolina, U.S.). The rim of the body portion of Coni-Snap capsules is tapered to help guide the cap onto the body. In high-speed automatic capsule filling machines, this feature can reduce or eliminate snagging or splitting of capsules. Both brands of locking capsules are preclosed by a prelock feature based on indentations formed further down on the cap that keeps the caps and body pieces of the empty capsules together during shipping and handling, but allows their easy separation for capsule filling. The Coni-Snap principle with prelock feature is illustrated in Fig. 4.3.



1. The tapered rim prevents faulty joins
2. These indentations prevent the pre-closed capsule from opening too early.
3. These grooves lock the two halves together after filling (SNAP-FIT ™ principle)

Fig. 4.3

4.2.7 Finishing of Capsules

1. **Pan Polishing:** The accelacota tablet coating pan is issued to dust and polish capsules. A polyurethane or cheese cloth liner is placed in the pan and the liner is used to trap the removed dust as well as to impart a glossy texture to the capsules.
2. **Cloth Dusting:** In this method the filled capsules are rubbed with a cloth that may or may not be impregnated with inert oil. This method is hand operation and improves glossy to the capsules.
3. **Brushing:** In to the automatic polishing equipment capsules are fed under rotating soft brushes. Brushes remove dust from the surface of the capsule. This equipment is also connected to vaccum which removes the dust immediately. During operation scrates may develop on the capsules or sometimes deformation takes place.

4.2.8 Rotosert

It is a mechanical sorting machine that removes unfilled powder or unfilled bodies or loose caps. Rotofil is a capsule filling machine that is specifically designed to fill pellets.

4.2.9 Storage and Stability

Finished hard-gelatin capsules normally contain an equilibrium moisture content of 13% to 16%. This moisture acts as a plasticizer and thus is critical to the physical properties of the shells. At lower moisture contents (< 12%), shells become too brittle; at higher moisture contents (> 18%), they become too soft. It is best to avoid extremes of temperature and to maintain a relative humidity of 40% to 60% when handling and storing capsules.

4.2.10 Manufacturing Defects

During the manufacturing of hard gelatin capsules which involves several steps like: Dipping of stainless steel, trimming, stripping, joining of cap and body of capsule. So, during several operations few defects are formed at this stage only like:

Major defects:

1. Capsules are not specified type i.e hard shell formation.
2. It may have cracks, breaks, pinholes or splits, losing its integrity.
3. Color variation, and non uniformity of appearance.
4. Surface spots and embedded particles on capsules.
5. Body and cap are not uniform and does not fit properly.

Minor defects:

1. Capsules surface are not smooth.
2. Opacity not proper.
3. There are pits, dents, thin area, specks, spots, or blemishes.
4. Capsules not free of adhering surface spots.

4.2.11 Quality Control Test

Disintegration Test: According to B.P., which applies to both hard and soft capsules:

- Introduce one capsule in each tube and suspend the apparatus in a beaker containing 60 ml water at 37 C.
- If hard capsules float on surface of water, then disc may be added.
- Operate the apparatus for 30 minutes. Remove the assembly from the liquid.
- The capsules pass the test, if no residue remains on the screen of apparatus.

Weight variation:

- Weigh 20 capsules individually and determine average weight.
- The individual wt should be within limit of 90-110% of average weight.
- If not all of capsule fall within the limit, weigh, weigh 20 capsule individually again.
- Remove the net content of each capsule with the aid of small brush.
- Weight the empty shell individually.
  Net weight of contents individually = Weight of shell – Gross weight.
- Determine the average net content from the sum of individual net weight.
- Then determine the differences between each individual net content and average net content.

Limits: Not more than 2 of the differences are greater than 10% of the average net content.

Content Uniformity:

- 10 capsules are taken and subjected to assay.
- 9 of 10 capsules should be in the range of 15% (85 - 115%).
- 10^{th} capsule is beyond $\pm$ 15% range, the 20 capsules are assayed.
- All capsules within range of $\pm$ 25% (75 - 125%).

4.2.12 Moisture Permeation Test

- The degree and rate of moisture penetration is determined by packaging the dosage unit together with a color is revealing desiccant pellet.
- Expose the packed unit to known relative humidity over a specified time.
- Observe the desiccant pellet for colour change.
- Any change in colour indicates absorption of moisture.
- By measuring pre-test weight and protest weight of pellet, amount can be calculated.

4.2.13 Bloom Strength of Gelatin

- Gelatin is weighed into water to typically create a 6.67% solution in standard bloom bottles.
- The mix is then stirred and kept for 3 hours at room temp.
- Bottles are placed in 65^{o}C bath for 20 minutes,
- Allow the bloom jars to cool for 15 minutes at room temperature
- They are then conditioned for 16 hrs in 10^{o}C water bath.
- When conducting gelatin bloom test, the bloom jar is centered with the probe just above the sample surface.
- The probe penetrates the gelatin to a target depth of 4 mm at a speed of 0.5 mm/sec and then retracts.
- The peak force is a gel strength in grams bloom.
- Bloom may range between 150 – 250 g.

Viscosity: The viscosity for gelatin may range from 25 - 45 millipoise.

Iron content: Gelatin used in manufacturing of gelatin capsule should not be more than 15 ppm of iron.

4.3 SOFT GELATIN CAPSULES

Definition: Soft gelatin capsules are made of gelatin to which glycerin or a polyhydric alcohol such as sorbitol has been added. Soft gelatin capsules, which contain more moisture than hard capsules, may have a preservative, such as methylparaben and/or propylparaben, to retard microbial growth. These are solid dosage forms in which powder, paste, or liquid medicaments are enclosed in a soft, globular gelatin shell. They may be round, oval, or oblong in shape.

4.3.1 Nature of Shell and Capsules Contents

Typically, soft gelatin are made up of gelatin, plasticizer, and materials that impart the desired appearance (colorants and/or opacifiers), and sometimes flavours. The formulation of the capsules content for each product is individually developed to fulfill the specification and end-use requirements of the products.

1. **Gelatin:** Large number of different shell formulations are available, depending on the nature of liquid filled material. Most commonly the gelatin is alkali (base) processed (type B) and it normally constituents 40% of the wet molten gel mass. Type-A acid processed gelatin can be also used.
2. **Plasticizers:** It is used to make soft gelatin capsule shell elastic and pliable. The most commonly used plasticizer in soft gelatin is glycerol, although sorbitol and propylene glycol are also used often in combination with glycerol. The amount of plasticizer contributes to the hardness of the final product and may even affect the dissolution and disintegration characteristics, as well as it chemical and physical stability. They are selected on the basis of their compatibility with the fill formulation, ease of processing, and the desired properties of the final products, including hardness, appearance, handling and physical stability.
3. **Water:** It is the most important component of the soft gelatin capsules. It usually accounts for 30 - 40% of the wet gel formulation and its presence is important to ensure proper processing during gel preparation and soft gelatin encapsulation. The levels of water is important for good physical stability, because in harsh storage conditions soft gelatin capsules will become either too soft and fuse together, or too hard and embrittled.
4. **Colourants/Opacifiers:** Colourants (soluble dyes, or insoluble pigments or lakes) and opacifiers are typically used at low concentration in the wet formulation. They can be either synthetic or natural, and are used to impart the desired shell colour for product identification. An opacifiers, usually Titanium-dioxide, may be added to produce an opaque shell when the fill formulation is a suspension, or to prevent photo-degradation of light sensitive fill material. Titanium-dioxide used single to give white opaque shell and with combination it gives coloured opaque shell.
5. **Bloom Strength:** Bloom strength is a measurement of cohesive strength of the cross linking that occur between gelatin molecules and is proportional to the molecular weight of gelatin. And it is also known as gel strength or gel rigidity of gelatin.

Bloom strength is determined by measuring the weight in grams required to move a plastic plunger (0.5 inches diameter). 4 mm held at 10°C for 17 days. It may be range of 150 - 250.

6. **Viscosity:** Viscosity is a measure of the molecular chain length and determine the manufacturing characteristics of the gelatin film. The viscosity for gelatin can be in range of 25 -45 milipoise.
7. **Flavouring Agent:** It may be used in a concentration of not more than 2% are used. Examples are essential oil, ethyl vanillin.
8. **Sweetening Agent:** These agents like sugar can be used in a concentration of not more than 5%.
9. **Preservatives:** Gelatin is stable when it is dry. Micro-organisms attack gelatin only in presence of moisture. Hence, preservatives are essential. For example: Methyl paraben, propyl paraben, sodium met bisulphite, potassium bisulphate, etc.

4.3.2 Capsule Size

For Human use, empty capsules ranging in size from 000 the largest to 5 smallest.

Size	Volume (ml)	Size in mm
000	1.37	26.3
00	0.95	23.7
0	0.68	21.8
1	0.50	19.2
2	0.37	18.3
3	0.30	15.3
4	0.21	14.7
5	0.13	11.9

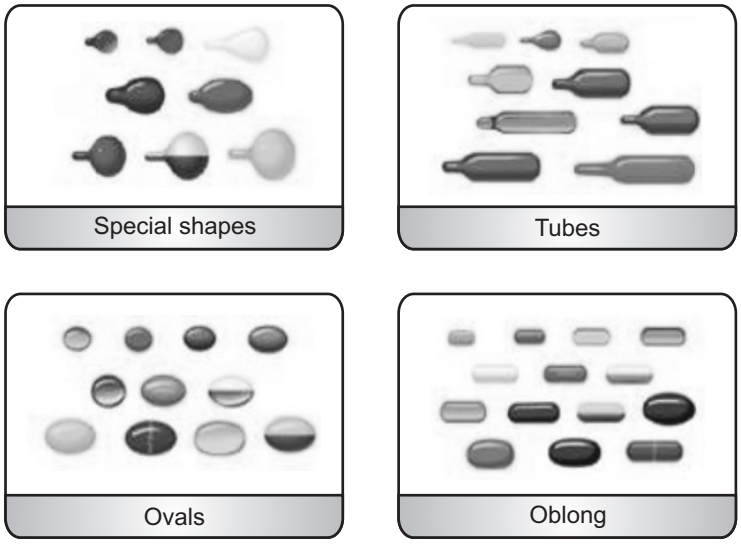


Fig. 4.4

4.3.3 Importance of Base Adsorption and Minim/gram

Based adsorption is expressed as the number of grams of liquid base required to produce a capsulatable mixture when mixed with one gram of solid. The base adsorption of solid is influenced by such factors as the solid's particle size and shape, its physical states (fibrous, amorphous, or crystalline), its density, its moisture content, and its oleophilic or hydrophilic nature.

$$\text{Base adsorption} = \frac{\text{Weight of base}}{\text{Weight of solid}}$$

The base adsorption is used to determine the "minim per gram" factor (m/g) of the solid. The minim per gram factor is the volume in minims that is occupied by one gram of the solid plus the weight of liquid base (BA) required to make 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 minims.

Importance:

- It helps to determine base adsorption and fluidity of a mixture.
- It is used to determine the minim per gram factor (M/g) of the solid.
- It is also important of establishing specification for the control of physical properties of solid.
- The convenience of using M/g factors is particularly evident in the vitamin field, where there may be many ingredients and numerous combinations.
- They are used to rapidly calculate capsules size.

BA and M/g Factors of Some Typical Solids:

Ingredients	Base	BA	M/g
Acetaminophen	Vegetable oil	0.76	25.97
Ascorbic acid	Polysorbate 80	1.10	26.92
Lactose	Vegetable oil	0.75	23.87

4.3.4 Production of Soft Gelatin Capsules

Composition of the shell:

- The basic component of soft gelatin shell is gelatin; however, the shell has been plasticized.
- The ratio of dry plasticizer to dry gelatin determines the "hardness" of the shell and can vary from 0.3 - 1.0 for very hard shell to 1.0 - 1.8 for very soft shell.
- Up to 5% of sugar may be included to give a "chewable" quality to the shell.
- The residual shell moisture content of finished capsules will be in the range of 6-10%.

Formulation:

- Formulation of soft gelatin capsules involves liquid, rather than powder technology.
- Material are generally formulated to produce the smallest possible capsules consistent with maximum stability, therapeutic effectiveness and manufacture efficiency.
- The liquid is limited to those that do not have an adverse effect on gelatin shell.
- The pH of liquid can be in the range 2.5 - 7.5.

Soft Gelatin Capsules are manufactured by following four methods:

1. Plate process,
2. Rotary die process,
3. Reciprocating die,
4. Accogel machine.

1. Plate Process:

- Place the gelatin sheet over a die plate containing numerous die pockets.
- Application of vacuum to draw the sheet in to the die pockets.
- Fill the pockets with liquid or paste.
- Place another gelatin sheet over the filled pockets, and
- Sandwich under a die press where the capsules are formed and cut out.

2. Rotary Die Process:

- In this machine the soft gelatin capsules are prepared and then filled immediately with liquid medicaments, it is having two hoppers and two rotating dies
- Liquid mixture is placed in one hopper and the liquid medicament in another Hopper.
- The two rotating dies rotate in opposite directions when the fluid gelatin mixture enters the machine from the hopper it produces two continuous ribbons.
- These half shells of the capsule are formed.
- At this stage the measured quantity of the medicament is filled in to it with the stroke of a pump with the subsequent movement of the dies, the other half capsule is formed.
- The two halves of the capsules are sealed together by the heat and pressure of the rotating dies.
- As the die rolls rotate, the convergence of the matching dies pockets seals and cuts out the filled capsules.

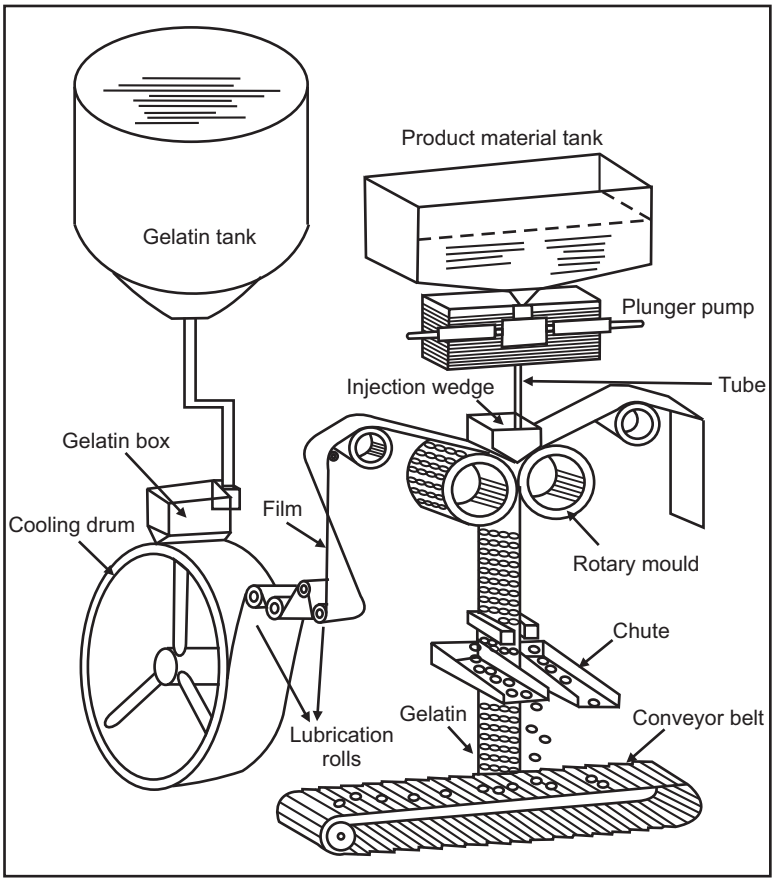


Fig. 4.5

3. Reciprocating Die Process:

- The early success of the rotary die process led others to develop continuous methods of soft gelatin capsules manufacture.
- One such method, known as the reciprocating die process, was announced in 1949 and was developed by the Nortan Company, Worchester, MA.

4.3.5 Quality Control Tests

1. Disintegration Test:

The disintegration test for hard and soft gelatin capsules follows the same procedure and uses the same apparatus described in the next chapter for uncoated tablets. The capsules are placed in the basket rack assembly, which is immersed 30 times per minute into a thermostatically controlled fluid at 37°C and observed over the time described in the individual monograph. To satisfy the test, the capsules disintegrate completely into a soft mass having no palpably firm core and only some fragments of the gelatin shell.

Weight variation: The gross weight of 10 intact capsules is determined individually. Then each capsule is cut open and the contents are removed by washing with a suitable solvent. The solvent is allowed to evaporate at room temperature over about 30 minutes, with precautions to avoid uptake or loss of moisture. The individual shells are weighed and the net contents calculated. From the results of the assay directed in the individual monograph, the content of the active ingredient in each of the capsules is determined.

Content Uniformity: Unless otherwise stated in the USP monograph for an individual capsule, the amount of active ingredient, determined by assay, is within the range of 85% to 115% of the label claim for 9 of 10 dosage units assayed, with no unit outside the range of 70% to 125% of the label claim. Additional tests are prescribed when two or three dosage units are outside of the desired range but within the stated extremes.

2. Dissolution Test:

- The dissolution test is carried out using the dissolution apparatus official in both the U.S.P and IP.
- The capsule is placed in a basket, and the basket is immersed in the dissolution medium and caused to rotate at a specified speed.
- The dissolution medium is held in a covered 1000 ml glass vessel and maintained at 370°C ± 0.5°C by means of a constant temperature suitable water bath.
- The stirrer speed and type of dissolution medium are specified in the individual monograph.

Result:

- Six capsules are tested and are accepted if each of them is not less than monograph specified i.e. +5%.
- If it fails then additional six capsules are tested. The result is accepted if the average of 12 capsules is greater than or equal to p and none of them is less than p – 15%.
- If the capsule still fails the test the additional 12 capsules are tested and are accepted if the average of 24 is greater than top, if not more than two less than p – 15% and none of them is less than p – 25%.

3. Physical Quality Control:

Finally physical control processing and packaging may be accomplished by the following in continuous operations:

- A capsule diameter sorter allows to pass to the next unit of any capsule within ± 0.020 inch of theoretical diameter.
- **A capsule colour:** The capsules are fed to it automatic from the diameter sorter by a pneumatic conveyer. In this unit, any capsule whose colour does not conform to the reference colour standard for that particular product is discarded others passes the test.

4.3.6 Packaging and Storage of Soft Gelatin Capsules

- Capsules should be packed in a well-closed glass or plastic containers and stored in a cool place.
- These types of containers have advantage over cardboard boxes that they are more convenient to handle and transport and protect the capsules from moisture and dust.
- To prevent the capsules from rattling a tuft of cotton is placed over and under the capsules in the vials.
- In vials containing very hygroscopic capsules a packet-containing desiccant like silica gel or anhydrous calcium chloride may be placed to prevent the absorption of excessive moisture by the capsules. Now-a-days capsules are strip packaged which provide sanitary handling of medicines, ease in counting and identification.
- Plastic bottle with screw cap (most popular package in USA).
- Clam shell blister (one-piece plastic that folds over and locks itself; no heating required.
- Blister pack (heat sealed blister on a cardboard).
- Plastic pail/bucket (economical bulk package).
- Plastic pouch zip locked (for sale via retail stores or route trucks must be packed in outer case for shipping).

4.3.7 Stability Testing of Soft Gelatin Capsules

1. Moisture Permeation Test:

The USP requires determination of the moisture permeation characteristics of single-unit and unit-dose containers to ensure their suitability for packaging capsules. The degree and rate of moisture penetration are determined by packaging the dosage unit together with a color-revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time interval, observing the desiccant pellet for colour change (indicating the absorption of moisture), and comparing the pretest and posttest weight of the packaged unit.

Physical Stability: Unprotected soft gelatin capsules rapidly reach equilibrium with the atmospheric conditions under which they are stored.

- This inherent characteristic warrants a brief discussion of the effects of temperature and humidity on the products.

- General statements relative to the effects of temperature and humidity on soft gelatin capsules must be confined to a control capsule that contains mineral oil with a gelatin shell having a dry glycerin to dry gelatin ratio of 0.5 - 1 and water to dry gelatin ratio of 1 - 1 and that is dried to equilibrium with 20 - 30% RH and 21 - 24°C
- The physical stability of soft gelatin capsules is associated primarily with the pick up or loss of water by the capsule shell.
- If these are prevented by proper packaging, the above controlled capsule should have satisfactory physical stability at temperature ranging from just above freezing to as high as 600°C.
- As the humidity increases the moisture content pickup of capsules increases. For example: At 30% RH at room temperature shows that gelatin retain about 12% (48 mg) of water and glycerin 7% (14 mg) of water at 60% RH the moisture content should be 17.4%. High humidity (> 60% RH at 21 - 240°C) produce more lasting effects on the capsule shell. The capsule manufacturer routinely conducts accelerated stability tests on new product as an integral part of the production development program.
- The successful results are obtained by conducing at test conditions like
  (a) 80% RH at room temperature in an open container
  (b) 400°C in open container
  (c) 400°C in closed container.
- Prior to testing, the capsule should be equilibrated to known humidity at many conditions, preferably 20 - 30% RH at 21 - 24°C.
- Evaluation of the results of the previously described heat test should be made only after the capsules have returned to equilibrium to room temperature.

Stability: 20 to 30 % RH at 21 to 24°C.

Temperature	Humidity	Effect on capsules shell
21 - 24°C	60%	Capsules becomes softer, tackier, and bloated.
Greater than 24°C	Greater than 45%	More rapid and pronounced effect

4.3.8 Applications of Soft Gelatin Tablets

- As an oral dosage form.
- As a suppository dosage form.
- As a specialty package in tube form, for human and veterinary use, single dose application for topical, ophthalmic, and rectal ointments.
- It is used in water immiscible, volatile, and non-volatile liquid such as vegetable and aromatic oils, aromatic and aliphatic hydrocarbons, ether, esters, alcohol, and organic acids.
- Solid also encapsulated into soft gelatin capsules as solution in one of the suitable liquid solvent, as suspension, or as dry powder, granules, or pelletized materials.

4.4 PELLETS

Definition: Small free flowing spherical units ranging in size, prepared by agglomeration of fine powders are called pellets.

- Their size and shape allow their administration as injections and also for oral drug delivery.
- Pellets range in size, typically, between 0.5 – 1.5 mm, though other sizes could be prepared.

4.4.1 Formulation Requirement

- **Taste masking:** Micropellets are ideal for products where perfect abatement of taste is required. Pellets provide the masking of unpleasant taste without lowering of bioavailability especially for oral products.
- **Immediate release:** Administering drugs in pellet form leads to an increased surface area as compared to traditional compressed tablets and capsules. This would considerably reduce the time required for disintegration and have the potential for use in rapidly dispersible tablets.
- **Sustained release:** Pellets are being increasingly used in the manufacture of sustained release dosage form of drugs.

Advantages of the dosage form:

- Extends day time and night time activity of the drugs.
- Reduced dosage frequency of dosage forms.
- Increased patient compliance.
- Potential lower daily cost to patient due to fewer dosage units, in contrast the whole tablet is released at once in to the small intestine as the stomach empties itself.
- Different types of polymers are utilized for coating of different drugs to enable the sustained release/controlled release rate of drugs.
- Chemically incompatible products: At times such ingredients are required to be delivered in a single dose. In the compressed tablet dosage form separate tablets would have to be administered, but the pellets can be administered in a single capsule.
- Varying dosage without reformulation
- Pellets have excellent flow properties, due to this, they can be conveniently used for filling capsules and the manufacturer can vary the dosage by varying the capsule size without reformulating the product.

4.4.2 Pelletization Process and Equipments Used

Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing semi-spherical units.

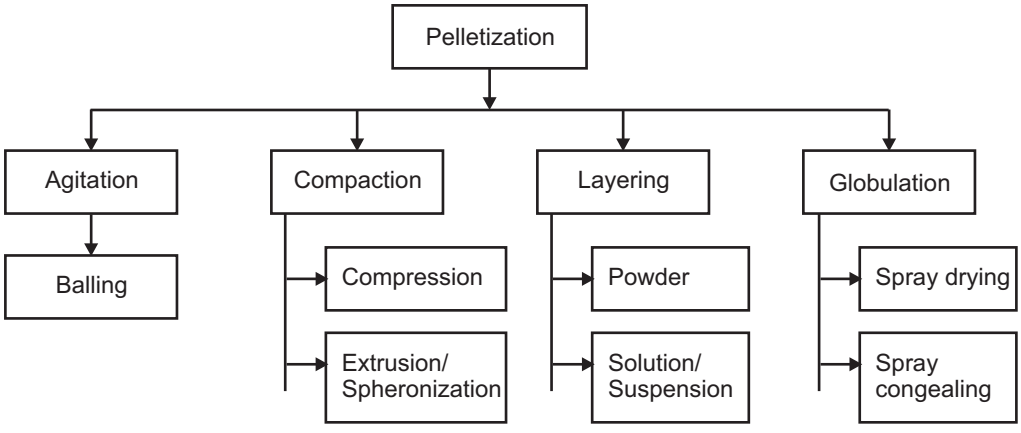


Fig. 4.6

4.4.3 Extrusion or Spheronization

- Extrusion spheronization is widely utilized in formulation of sustained release, controlled release delivery system.
- The main objective of the extrusion spheronization is to produce pellets/spheroids of uniform size with high drug loading capacity

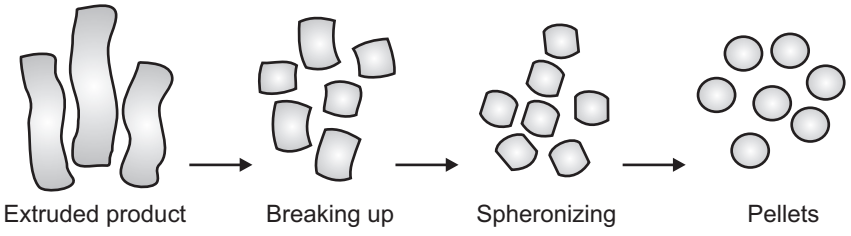


Fig. 4.7: Extrusion/Spheronization

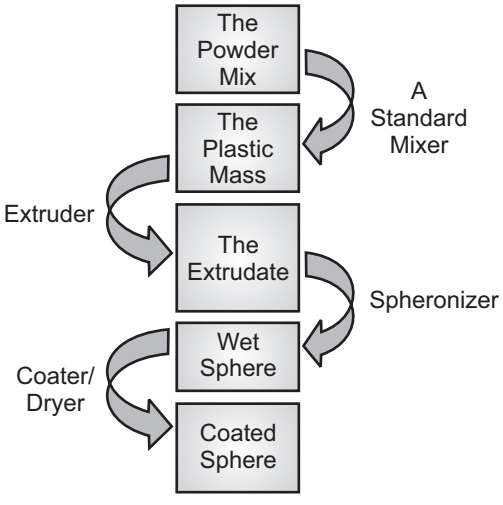


Fig. 4.8

Product Features:

- Dust free
- High spherocity
- Free flowing
- Compact structure
- Low hygroscopicity
- High bulk density
- Low abrasion
- Narrow particle size distribution
- Smooth surface

Hot melt extrusion: Hot melt extrusion is a process of converting raw material into a product of uniform shape and density by forcing it through a die under controlled condition.

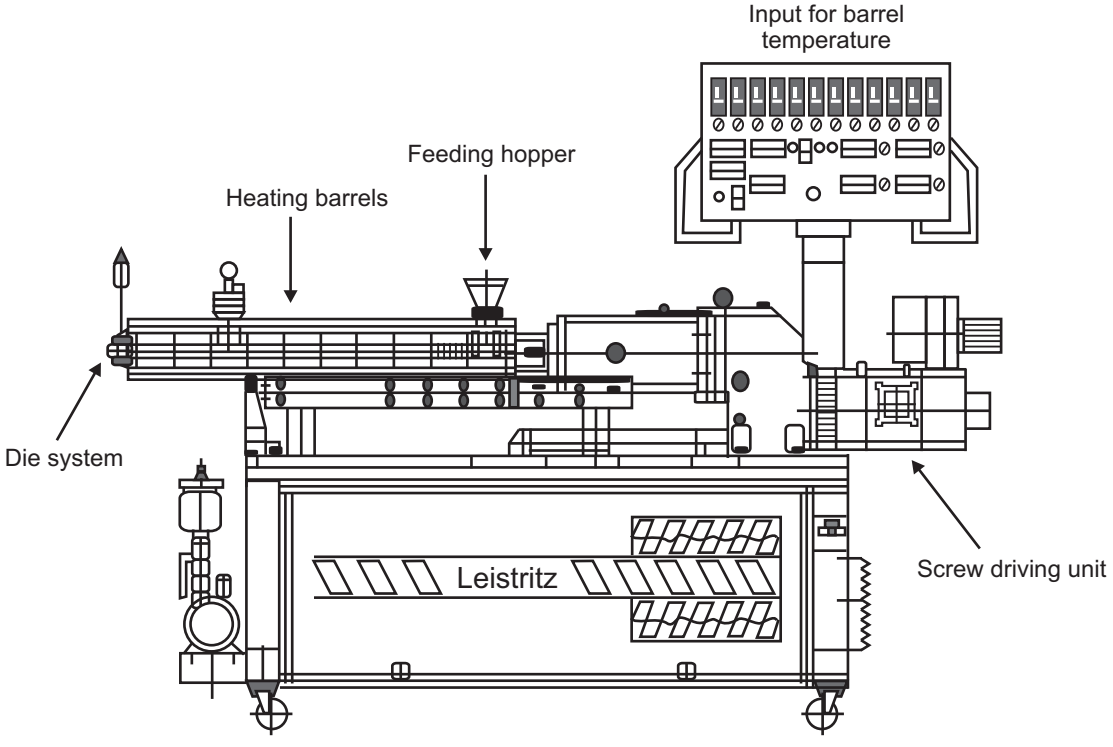


Fig. 4.9

The theoretical approach to understanding the melt extrusion process is therefore, generally presented by dividing the process of flow into four sections:

1. Feeding of the extruder.
2. Conveying of mass (mixing and reduction of particle size).
3. Flow through the die.
4. Exit from the die and down-stream processing.

Applications of Extrusion in the Pharmaceutical Industry:

In pharmaceutical industry the melt extrusion has been used for various purposes, such as

1. Improving the dissolution rate and bioavailability of the drug by forming a solid dispersion or solid solution.
2. Controlling or modifying the release of the drug.
3. Masking the bitter taste of an active drug.

4.4.4 Granulation

Wet Granulation:

- The process of adding a liquid solution to powders involves the massing of a mix of dry primary powder particles using a granulating fluid. The fluid contains a solvent that must be volatile.
- Meets all the physical requirements for compression of tablets.

Fluid-bed Granulation:

- The process is carried out continuously in a fluid-bed granulator.
- Spraying of a granulation solution onto the suspended particles, which then are dried rapidly in the hot air stream.

1. Fluid-Bed Granulation:

The fluid-bed granulation is performed following these steps: (Tangential-Spray Method)

- Pre-blending of the formulation powder, including the active ingredients, fillers, disintegrants, in a flow of air.
- Granulation of the mixture by spraying a suitable liquid binder onto the fluidized (suspended) powder bed.
- Drying of the granulated product to the desired moisture content.

Parameters:

- Equipment parameters
- Product parameters
- Process parameters

Advantages over Traditional Wet Granulation:

- Automated, performed in one unit, thus saving costs, transfer losses and time.
- Fluid bed granulation process improves the dissolution efficiency of both nimodipine and spironolactone tablets.

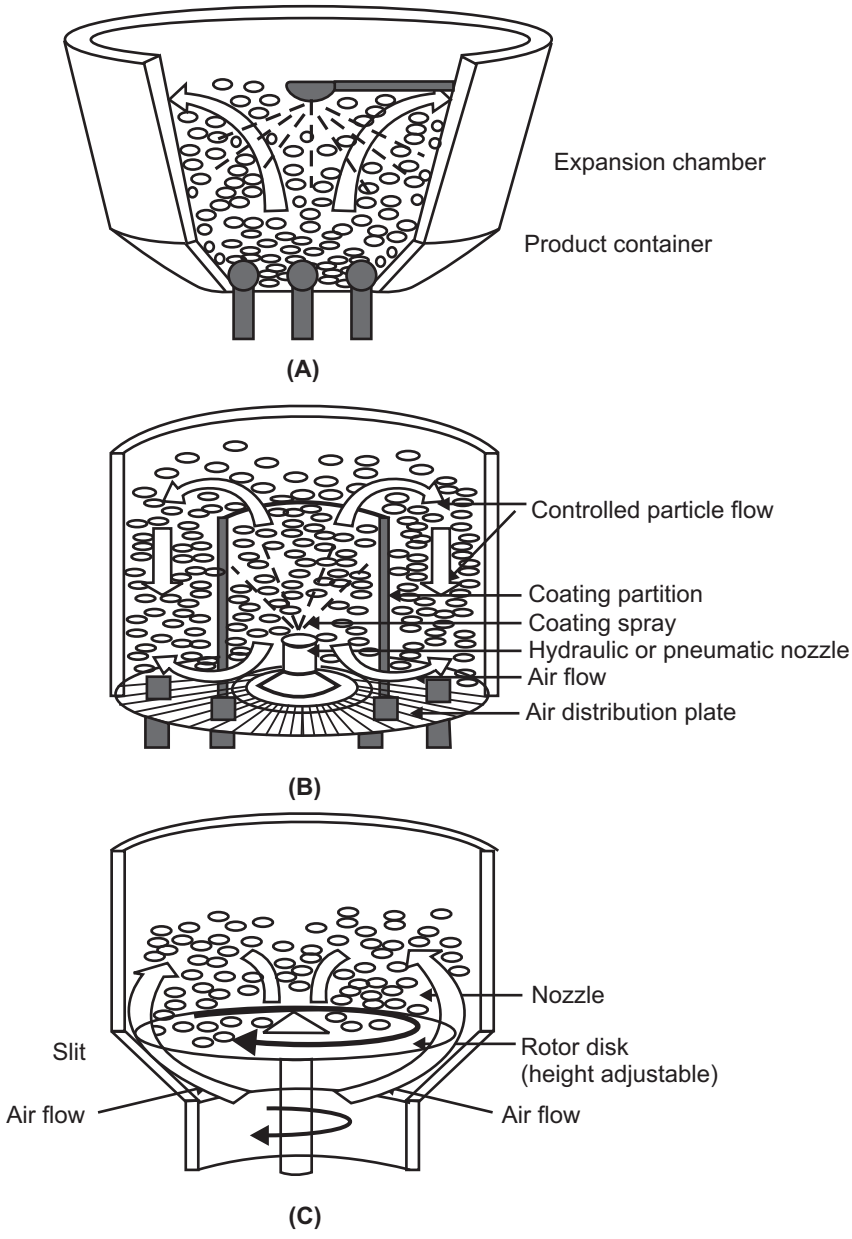


Fig. 4.10: Three versions of fluidized bed granulator

2. Melt Granulation:

Granulation is achieved by the addition of meltable binder.

Binder is in solid state at room temperature, but melts in the temperature range of 50 - 80˚C. e.g. Polyethylene Glycol (PEG) 2000, 4000, 6000, 8000 (40 - 60°C).

- Melted binder then acts like a binding liquid.
- No need of drying phase, since dried granules are obtained by cooling it to room temperature.

4.4.5 Spray Drying

A drug solution or suspension is sprayed, with or without excipients, into a hot-air stream, generating dry and highly spherical particles.

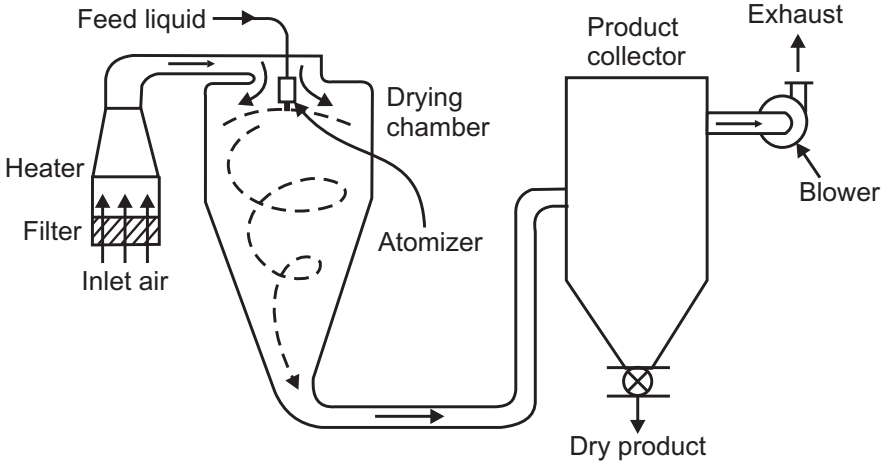


Fig. 4.11

4.4.6 Spray Congealing

Also called spray-chilling, a technique similar to spray-drying, but no source of heat is required.

- Drugs can be suspended in molten wax and can give sustain release effect.
- Monoglycerides and similar components are spray-congealed.

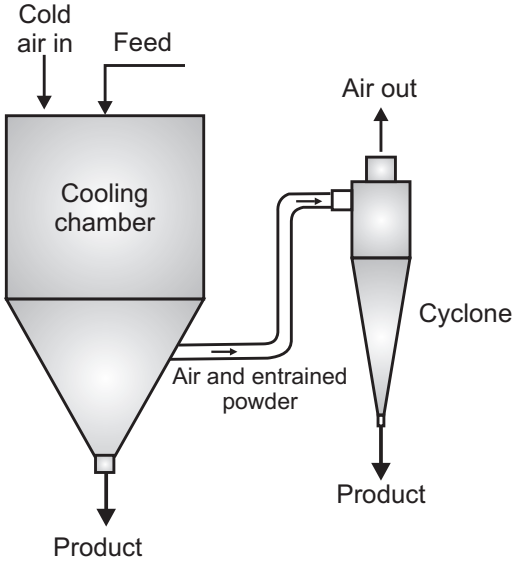


Fig. 4.12: Spray-congealing

QUESTIONS

Long essay questions: (10 marks each)

1. Explain the quality control test for the hard and soft gelatin capsule.
2. Explain briefly about the formulation and manufacturing process of hard gelatin capsule shell.
3. Explain briefly about pelletization process.

Short essay questions: (5 marks each)

1. What are the processes for the filling of hard gelatin capsules?
2. Outline manufacturing defects of capsules.
3. Explain spheronization process for pelletization.

Short answer questions: (2 marks each)

1. Write the size of capsules.
2. What is Base Adsorption? Write its importance.
3. Define Rotosort. Write its advantages in pharmaceutical companies.

☆☆☆

Chapter 5 ...

PARENTERAL PRODUCTS

Upon completion of the chapter students will be able to understand :

- *Parenteral (Sterile Products) and production of sterile products.*
- *A range of types of parenteral dosage forms.*
- *The applications and rationale of different parenteral dosage forms.*
- *Advantages / disadvantages of different parenteral dosage forms.*
- *Factors affecting parenteral preparations.*
- *Formulation aspects of parenterals.*
- *Preparation of different parenteral dosage forms.*

5.1 PARENTERALS

Definition:

- Parenteral preparations are sterile, pyrogen-free liquids (solutions, emulsions, or suspensions) or solid dosage forms packaged in either single-dose or multidose containers.
- These preparations are administered through the skin or mucus membranes into internal body compartments.
- These include any method of administration that does not involve passage through the digestive tract.

The term parenteral is derived from the Greek word Para – outside and Enterone – Intestine. It denotes the route other than oral.

History:

In 1492, Pope Innocent had received a transfusion from young boys. In 1656, Christopher Wren used sharpened hollow quill of a feather to inject crude extract of opium into the vein of a dog. J. D. Major and Johannes Elsholtz were first who successfully injected humans in 1662 using solutions of opium. In 1850s Alexander Wood was credited to give subcutaneous injections using a true hypodermic syringe. Today, parenteral dosage forms are available with high standards.

Parenteral Advantages:

- If drug is not absorbed orally it can be given parenterally.
- Drug which is unstable in GIT can be given parenterally.
- Drugs which are undergoing extensive first pass metabolism are given parentally which avoid the first pass metabolism.
- When patients need rapid drug action in emergency situations as onset of action of parenterals is rapid.
- Patient is uncooperative/unconscious (accident, surgery etc.).

- Complete drug bioavailability (upto 100%) is possible.
- Prolonged drug action is possible.
- Parenteral therapy provides the means of correcting serious disturbances of fluid and electronic balances.
- When food cannot be taken by mouth, total nutritional requirement can be supplied by the parenteral route.
- Patient compliance problems are largely avoided.

Parenteral Disadvantages:

- Most inconvenient route of administration /pain upon injection.
- Generally need medical expert for administration (like physician or nurse usually in hospital or clinic).
- If administered by patients themselves, need good training.
- It requires strict adherence to aseptic procedures.
- It requires more time than those administered by other routes.
- Chances of improper dosing are more.
- Chances of adverse effects are more.
- Danger of blood clot formation is there.
- Drug cannot be recovered in adverse conditions as it is irreversible.
- The manufacturing and packaging requirements of parenteral dosage forms are more costly than other dosage forms.

5.1.1 Types of Parenterals

1. Based on route of administration, the types of parenterals are:

• Intravenous (IV)	• Vein
• Intramuscular (IM)	• Muscle
• Subcutaneous (SC)	• Under the skin
• Intradermal (ID)	• Into the skin
• Intraarticular	• Joints
• Intrasynovial	• Joint-fluid area
• Intraosseous	• Bones
• Intracerebral	• Brain
• Intraspinal	• Spinal column
• Intrathecal	• Spinal fluid
• Intra-arterial	• Arteries
• Intracardiac	• Heart
• Endotracheal	• Down the trachea

2. Based on volume, parenterals are of Two Types:

(i) Small volume parenterals (SVP): These are sterile, pyrogen free injected products that are usually packed in volumes up to 100 ml.

These are aqueous preparations, usually administered by IV because of local irritation.

These SVP's are packed into Ampoules or Vials.

(ii) Large volume parenterals (LVP): These are sterile, pyrogen free injected products that are usually packed in volumes more than 100 mL(ranging from 101 ml to 1000 ml).

3. Based on the composition:

These products can be administered by Intra or Extra vascular routes.

These LVP's are packed into either glass or plastic container of 1 lit capacity.

Difference between SVP and LVP

Parameter	SVP	LVP
Volume	100 ml or less	101 – 1000 ml
Routes	IV, IM and SC	IV – LVP and non IV-LVP
Dosage unit	Single or multiple	Single
Preservative	Used	Not used
Buffers	Used	Not used
Formulation	Solution, emulsion, suspension	Solution and o/w nutrient emulsion
Isotonicity	Not essential	Must
Pyrogenicity	Not essential	Must
Use	Therapeutic and diagnostic	Nutrition, detoxification and during surgery

5.1.2 Basic Criteria for a Parenteral Preparation

- It should be sterile (free from living and detectable microorganisms).
- It should be free from pyrogens which cause the body temperature rise.
- It should be free from visible particulate matters (may cause the embolism means blocking the blood capillaries).
- It should be isotonic (which protect the RBC).

5.1.3 Parenteral Products: Routes of Administration

1. Intramuscular (IM) Route:

- **Administration**: deep skeletal muscle far from nerves & blood vessels.
- **Adults:** administered into the upper outer quadrant of the gluteus maximus.
- **Infants:** lower portion of deltoid muscle of the upper arm or midlateral muscle of the thigh.
- **Site of injection:** May vary with multiple injections.
- **Note:** during administration plunger of the syringe withdrawn back to assure absence of blood.
- 0.5 - 5 ml syringe \ 20-25 gauge \ 5/8-3" length needle.
- **Volume:** maximum 5 ml in gluteus region and 2 ml in deltoid.
- **Vehicle:** aqueous, oleaginous or suspension – influence duration of action.
- **Advantage:** suspensions can be administered.
- Less rapid than IV but has longer duration of action.

Intramuscular (IM) Injections:

- Intramuscular injections are given at 90 degree to the skin, penetrate deep, aspirate to check whether you have puncture an artery, vein or nerve, if blood comes, withdraw the needle, change position.
- Less rapid than IV but has longer duration of action.
- In general the injection of drugs into the muscle or the adipose tissue beneath the skin allows a deposit or 'depot' of drug to become established that will be released gradually into the systemic circulation over a period of time.
- By changing the formulation of the drug, the period over which it is released can be influenced. For example, the formulation of antipsychotic agents such as flupentixol in oil allows them to be administered once a month or every three months.
- **Danger of IM injections:** It may cause paralysis, abscess, cysts, embolism, hematoma, scar formation etc.

2. Subcutaneous (SC) Route:

- Injections in fatty subcutaneous tissues below the skin.
- Small volume injections up to maximum 2 ml.
- 1-3 ml syringe \ 25-32 gauge \ 1/2-5/8" length needle.
- **Site of Administration:** Abdomen, upper-outer arms, upper-outer thighs, and upper back.
- At least 1 inch (2.5 cm) pinched fold of skin and tissue is necessary for administering SC injections.

Subcutaneous Injections:

- These are given by holding the needle at 45 degree angle while piercing the skin, skin is pinched tight.
- Put in needle so that hub of needle shaft touches the skin, aspirate to check the location of needle. If blood is aspirated, withdraw the needle and try at other site, if not gently push the medication into subcutaneous tissue, withdraw needle and gently massage the area to help in absorption.

3. Intradermal (ID) Route:

- Drug is administered into the dermal layer of the skin.
- Generally interior surface of the forearm.
- 1mL syringe \ 25-29 gauge \ 1/4-5/8" (upto 1 inch).
- Usual dose is about 0.1ml.
- The needle injected horizontally into the skin with bevel facing upward. Injection made when the bevel just disappear.
- 5-15 degree angle with bevel up, no aspiration or massage.

Intradermal Injections:

- Intradermal injections are given by pulling the skin tight, insert the needle, bevel up, holding it an angle of 10 degrees as it penetrate skin, turn the needle bevel down

and inject a small amount of medication into the skin at junction of epidermis and dermis, until a wheel appears.

- **Uses:** for diagnostic determination, desensitization or immunization

Physicochemical Properties of the Drug:

- Unstable in moisture
  - Dry
  - Suspension
  - Replace water by other solvent
- Insoluble in water
  - Non-aqueous solvent
  - Derivative (salt)
- Route of drug administration
  - IV Aqueous
  - Others may not be aqueous
- Desired onset of drug action
  - Physical state of the drug (suspension)
  - Vehicle (aqueous or not)
- Duration Oleaginous > suspension > aqueous

5.2 CONSIDERATIONS IN PARENTERAL PREPARATION

- Solvents and vehicles must meet special purity and other standard to assure safety.
- Added substances (buffer, stabilizers preservatives) should be approved for parenteral products.
- Prepared in controlled areas under strict sanitation standards & personnel specially trained, clothed to maintain sanitation.
- Packing hermetically sealed container of specific & high purity.
- Volume slightly excess of the labeled size to help administration.
- Volume is limited depending on route and type (single or multiple).
- Dry parenteral should reconstitute fast with ease (lyophilized).
- The finished product must meet sterility standard.
- Must be pyrogen free.
- No particulate matter should be present.
- Solvents and vehicles must meet special purity & other standard to assure sterility, stability and safety.

5.2.1 Vehicles

Vehicles used should be

- Pharmacologically inert, non toxic and compatible with blood, maintain solubility of the, drug,
- Be physically and chemically stable.
- Does not affect the pH.

- Must be pyrogen free.
- No particulate matter.
- The finished product must meet sterility standard.
- Water is the ideal vehicle for most injections since aqueous preparations are well tolerated by the body.
- Easy visual inspection for particulate contamination, chemical precipitation and colour change.
- It may accelerate drug hydrolysis resulting in inert or toxic products.
- Solvents and vehicles must meet special purity and other standard to reassure sterility, stability and safety.

Ideal properties of vehicle used should be:

- The vehicle should be pharmacologically inert.
- It should be non toxic and compatible with blood.
- It should maintain solubility of the, drug (Active Pharmaceutical Ingredient, API).
- It should be physically and chemically stable.
- It does not affect the pH of the dosage form.
- It must be free from pyrogen.
- It should not contain particulate matter.
- The finished product must meet sterility standard.
- Water is the ideal vehicle for most injections since aqueous preparations are well tolerated by the body.
- Easy visual inspection for particulate contamination, chemical precipitation and colour change.
- It may accelerate drug hydrolysis resulting in inert or toxic products.
- Vehicle can be water, water-miscible co-solvents or non-aqueous solvents.
- Aqueous is preferred.

Non-aqueous may be used due:

- Drug of limited water solubility.
- Drug susceptible to hydrolysis.
- Desired physicochemical factors (extended release).
- Intramuscular.
- Must be safe in the amount administered.
- Do not interfere with therapeutic activity of the drug.
- Selection depends on the formulation.
- Fixed vegetable oils like corn oil, cotton seed oil, peanut oil, sesame oil, castor oil, olive oil.
- Should be properly characterized: purity, iodine number, saponification number.
- Glycerin.
- PEG.

- Propylene glycol.
- Alcohol.
- Less common ethyl oleate, isopropyl myristate, dimethylacetamide.
- Fixed oils should not be administered by IV route and injected only by IM route to produce sustained release effect. Full information about the physico-chemical characteristics of the active drug can greatly help in developing a stable and safe parenteral dosage form.
- Crystallinity, polymorphism, particle size, solubility, dissolution, microscopic examination, thermal stability etc.
- Chemical form of active drug, chemical and/or microbial potency,, partition coefficient, spectra, dissociation constant, pH profile (Profile of pH versus solubility and versus stability help in predicting the chemical and physical stability of the drug in solutions or suspension as a result of pH changes due to storage or admixing the drug with an infusion fluid.
- Exceptional physical and chemical purity.
- Free of microbes and pyrogen.
- Stable on storage.
- Properly packed and stored to prevent contamination.
- The use of whole pack during manufacturing.

5.2.2 Preservatives

Definition: They are substances that are incorporated into the parenteral dosage form to maintain stability, ensure sterility and minimize pain and tissue irritation and aid in parenteral administration.

1. Antimicrobial preservatives
2. Anti-oxidants
3. Buffer
4. Chelating Agents / Sequestering Agents
5. Cryoprotectants and lyoprotectants
6. Inert Gas
7. Solubilizing Agents and Surfactants
8. Tonicity modifiers
9. Viscosity modifiers

- Usually added in multiple dose vials to protect the product from contamination due to repeated dose withdrawal.
- Also added to most unit-dose parenterals which are not terminally sterilized.

Types of Preservatives:

1. **Acidic:** Phenols and parabens (Butyl-P-hydroxybenzoate, Methyl-P-hydroxybenzoate).
2. **Neutral:** Alcohols e.g. Benzyl alcohol
3. **Mercurial:** Thimerosal
4. **Quaternary ammonium compounds:** benzalkonium chloride.

5.2.3 Antioxidants

Antioxidants prevent oxidation of drug during sterilization.

Mechanism of action:

- Preferentially oxidized: Ascorbic acid and Na bisulfite, metabisulfite or sulfite.
- Blocking an oxidation chain reaction: Ascorbic acid, BHT &Tocopherols.
- Complexing agent with catalyst: EDTA
- Synergistic action: acids (citric, phosphoric, tartaric, ascorbic).
- Added to maintain pH for Solubility, Stability and Pain reduction.

pH	Buffer system	Concentration (%)
3.5 - 5.7	Acetic Acid/Acetate	1 - 2
2.5 - 6.0	Citric Acid/Citrate	1 - 5
6.0 - 8.2	Phosphoric Acid/Phosphate	0.8 - 2
8.2 - 10.2	Glutamic Acid/Glutamate	1 - 2
> 8.0	Carbonic Acid/Carbonate	> 1

- Other systems used in parenterals: Glycine (pH 6.5 - 7.5), Lactate (pH 3-6), Maleate (pH 2.5 - 5.0), Tartarate (pH 3 - 5)
- Trace quantities of heavy metal ions often catalyze destructive changes in medicaments.
- For example the breakdown of the sulfur containing rings of benzyl penicillin (copper, lead, mercury and zinc).
- Oxidation of adrenaline (copper, iron and chromium).
- Decomposition of oxytetracyclin (copper).
- Sources of metal contamination are raw material impurities, solvent such as H_2O, rubber stopper, container or equipment employed in the manufacturing process.
- The most widely used chelating agents are ethylenediamine tetra acetate (EDTA) derivatives and salts of citric acid and tartaric acids.

5.2.4 Cryoprotectants

- Stabilize and prevent denaturation of proteins from effect of freezing.
- A hydration shell is maintained around the protein molecules which reduces the denaturing effect of freezing.
  - **Sugars:** Sucrose, Lactose, Glucose, Trehalose
  - **Polyols:** Glycerol, Mannitol, Sorbitol
  - **Amino Acids:** Glycine, Alanine, Lysine
  - **Polymers:** PEG, Dextran, PVP

5.2.5 Lyoprotectants

- Substance which protect drugs especially proteins from degradation during drying (dehydration).
  - **Sugars:** Mannitol, Lactose, Maltose, Maltodextrin, Trehalose, Sucrose
  - **Amino Acids:** Glycin, Histadine, Arginine.

- In injections in which oxygen is a serious cause of decomposition, improved stability may be obtained by replacing the air in the final container with an inert gas such as nitrogen or carbon dioxide.
- For best result, the water must be boiled to remove air and purging the container with the used inert gas, prior to filling.

5.2.6 Solubilizing Agents and Surfactants

- Surfactants are used extensively in parenteral suspension for wetting powders and provide acceptable syringe ability (e.g. steroids and fat-soluble vitamins).
- Solvents and vehicles must meet special purity and other standard to assure safety.
- Added substances (buffer, stabilizers preservatives) should be approved for parenteral products.
- Prepared in controlled areas under strict sanitation standards and personnel specially trained, clothed to maintain sanitation.
- Packing hermetically sealed container of specific and high purity.
- Volume slightly excess of the labeled size to help administration.
- Volume is limited depending on route and type (single or multiple).
- Dry parenteral should reconstitute fast with ease (Lyophilized).
- The finished product must meet sterility standard.
- Must be pyrogen free.
- No particulate matter.
- Solvents and vehicles must meet special purity and other standard to assure sterility, stability and safety.
- **Natural water:** is not used for drinking or any pharmaceutical formulation. It is highly contaminated.
- **Drinking water:** may be used in the early stage of chemical synthesis and in the early stages of the cleaning of pharmaceutical manufacturing equipments.
- **Purified water**: (USP monograph), is used in the preparation of some bulk pharmaceutical chemicals, do not use purified water in preparations intended for parenteral administration.
- Must be protected from microbial proliferation.
- **Sterile purified water:** It is purified water which is packaged and rendered sterile, contains no antimicrobial agent.
- It is not for parenteral administration.
- Water For Injection, USP.
- **Most Frequently used for Parenteral Formulations:**
  - Purified water underwent distillation or reverse osmosis.
  - Clear, colourless, odourless and having a pH of 5 -7.
  - Total dissolved solids not more than 1 mg in 100 ml.
  - No added substances.
  - May not be sterile.

- Pyrogen free.
- Collected in sterile and pyrogen free container (glass or glass lined).
- Must store in tight container at suitable temperature.
- Must be used within 24 hour.

- **For products to be sterilized after preparation:**
  - Sterile water for injection with suitable antimicrobial agent(s).
  - Filled in vials/syringe in volume not more than 30 ml.
  - Name and concentration of preservative must be stated.(benzyl alcohol).
  - Intended for small volume injectable (multidose vials).
  - Not to be used with large volume parenteral (usually with 5mL or less).
  - Concern chemical compatibilities.
  - Suitable vehicle properties.
  - No irritation, sensitization, toxicity or pharmacological activity.
  - Should not affect the activity of the drug.
  - Should have suitable physicochemical properties for intended use (stability, viscosity, fluidity with temperature, boiling point, miscible with body fluid, low vapor pressure).
  - Purity (eases of purification & standardized).
  - Must remain clear at $10^{o}C$.
  - Intramuscular.
  - Must be safe in the amount administered.
  - Do not interfere with therapeutic activity of the drug.
  - Selection depend on the formulation.
  - Fixed vegetable oils.
  - Corn oil, cotton seed oil, peanut oil, sesame oil, castor oil, olive oil.
  - Should be properly characterized: purity, iodine number, saponification number.
  - Glycerin.
  - PEG.
  - Propylene glycol.
  - Alcohol.
  - Less common Ethyl oleate, isopropyl myristate, dimethylacetamide.
  - Fixed oils must never be administered by IV route and injected only by IM route to produce sustained release effect.
- Sterile products are dosage forms of therapeutic agents that are free of viable microorganism. These includes parenteral, ophthalmic and irrigation preparations.
- Parenterals are unique as they are injected through the skin or mucous membranes into internal body compartments. So, they must be free from microbial contamination and toxic components as well as possess and exceptionally high level of purity.
- Parenteral may be given by various routes: Intravenous, intramuscular, subcutaneous, intradermal and intraperitoneal.

When given through intravascular route, complete drug bioavailabilty occurs immediately. Similarly for other routes atleast blood vessel wall or tissue cell wall must be permeated before the drug enters the circulation. Most of permeation often occurs by passive diffusion mechanism. It is favourable when drug has both lipophilic and hydrophilic properties. Especially lipophilic drug are being major permeation through the passive diffusion. Once in circulating the blood, the physiological effect of drug is affected by the degree of binding to the plasma proteins and by its rate of elimination by hepatic metabolism and / renal excretion.

Intravenous and intraspinal preparations are most of times given in the form aqueous solutions and non-aqueous are rarely given.The danger of blockage of fine capillaries embolism, particularly in the brain precludes the use of form other than solutions for IV administration, although emulsions have been given in which the particle size of dispersed phase is carefully controlled less than 5 μm. Preparation given intramuscularly, subcutaneously or intradermally can be administered as solution, suspension or emulsion.

The nature of preparation can influence significantly the rapidity of onset of therapeutic effect from drug. Then the duration of effect and the form of the absorption pattern achieved. Therefore the formulation for parenteral product must be integrated carefully with its intended administration in a patient. The chemical and physical properties of drug must be determined, its interaction with any desired excipients must be studied and the effect of each step of the process must be studied.

Irrigating solutions: These are also required to meet the same standards as parenteral preparations because during an irrigating procedure, considerable amounts of these solutions can enter the blood stream directly through open blood vessels of wounds or abraded mucous membranes.

Effect of Route of Administration:

The intended route of administration has a marked effect on the formulation of a parenteral product. The volume in which a dose of the drug must be encompassed is one factor to consider.

- For intracutaneous injections a volume of more than 0.2 ml rarely is used because tissue volume is small and compact; also, absorption is quite slow owing to the lack of blood vessels.
- Volumes of 1 ml or less may be injected subcutaneously and only.
- Occasionally volumes of more than 2 ml are given intramuscularly.
- Volumes of 10 ml or less may be given intraspinally, but only by the IV route may large volumes be given safely, provided careful control of the rate of administration is undertaken.

Isotonicity (same osmotic pressure) is a characteristic that is probably of greatest significance for intraspinal injections because the circulation of the cerebrospinal fluid is slow, and disturbances of osmotic pressure quickly cause headache and vomiting. Isotonicity is preferable for the comfort of the patient, but is not essential for SC and IM injections. Generally IV solution should be isotonic, although slow administration of a paratonic solution

may be performed safely if rapid dilution with the blood occurs. Suspension should not be given intravenously because of the danger of the blockage of small blood vessels (embolism). Aqueous or oleaginous suspension cannot be given subcutaneously because of the pain and irritation.

Ophthalmic preparations: These are formulated in much the same way as parenteral solutions. Eye being sensitive to irritation, so formulation should be directed towards minimizing irritation. Suspension of solids has been used in the eye when the therapeutic need superseded the need to avoid irritating effects for example corticosteroids.

Sterile products are mostly

- Frequently solutions or
- Suspensions or
- Solid pellets for tissue implantation.

The control of a process to minimize contamination for a small quantity of such product can be achieved with relative ease. As the quantity of product increases, the problems of controlling the process to prevent contamination multiply. Therefore, the preparation of sterile products has become a highly specialized area in pharmaceutical processing. The standards well-known, the attitude of personnel and the process control must be of a superior level.

5.3 FORMULATIONS

1. Ophthalmic Preparations:

Products to be instilled into the eye, while not parenteral by definition have many similar, and often identical, characteristics. The formulation of stable, therapeutically-active ophthalmic preparations requires high purity of ingredients as well as freedom from chemical, physical (particles), and microbial contaminants. These preparations usually require buffers to stabilize the pH of the product, additives to render it isotonic or nearly so, and stabilizers such as antioxidants when appropriate for the particular ingredients. Those ophthalmic used in larger quantities, such as eye irrigants, or in the case of devices such as contact lenses, are usually relatively uncomplicated solutions similar to large-volume parenterals.

One feature not as critical for ophthalmics is freedom from pyrogens since pyrogens are not absorbed systemically from the eye; however, in so far as pyrogens are indicative of a microbiologically clean process, they should not be present.

2. Freeze-dried Products:

Solution intended to be freeze-dried must be aqueous, for the drying process involves the removal of water by sublimation. Since the solution is in existence for only a brief period during processing, stability problems related to the aqueous system are practically non-existent. However, the formulation must reflect the characteristics to be imparted to the solid residue (cake) after drying, and those required of the solution after reconstitution at the time of use. Often, the drug alone does not give sufficient solid residue or the characteristics appropriate for the product; therefore, substances often must be added to provide the characteristics desired.

Among the characteristics required of a good cake are

- Uniform colour and texture.
- A supporting matrix of solids sufficient to maintain essentially the original volume after drying.
- Sufficient strength to prevent crumbling during storage.

In addition, the nature and amount of solids in the solution largely determine

- The eutectic temperature of the frozen solution, the subzero temperature at which the frozen material will melt, which determines the temperature below which the product must be held during freeze-drying.
- The rate of thermal and vapour transfer through the product during the process of drying.
- The rate of solution of the product during reconstitution. The percentage of solids in the frozen plug should be between approximately 2 and 25%. Among the best salts for providing uniformity.

3. Long-acting Formulations:

Long acting parenteral formula is ideally designed to provide slow and sustained release of a drug over prolonged period of time, essentially to simulate and replace the more hazardous, continuous i.v. infusion of a drug.

5.3.1 Types of Depot Formulation

1. Dissolution controlled
2. Binding of drug molecules to adsorbents
3. Encapsulation type
4. Esterification type

1. **Dissolution-controlled**: The rate of drug absorption is controlled by the slow dissolution of drug particles, with subsequent release to tissue fluid surrounding the bolus of product in the tissue. The formation of drug salts with very low aqueous solubility is one of the most common approaches to this type of formulation. Further the suspension of the drug particles in the vegetable oils, and especially if gelled with the substances such as aluminium monostearate produces prolonged absorption rates.
2. **Binding of drug molecules to adsorbents:** Only the free portion, in equilibrium with that which is bound can be absorbed. As drug is absorbed, a shift in the equilibrium is established, and the drug is released from the bound state to the Free State. Ex: Binding of vaccine to aluminium hydroxide gel to provide sustained release.
3. **Encapsulation type:** In this type biodegradable or bioabsorbable macromolecules are used which serve as a diffusion matrix for the drug. Here the release is controlled by the rate of permeation out of the barrier and the rate of biodegradation of the barrier macromolecules.
4. **Esterification type:** In which the rate of absorption is controlled by the partitioning of the drug esters from the reservoir to the tissue fluid and by the rate at which the drug ester regenerates the active drug molecules.

Biphasic (Suspension):

The solid content of the parenteral suspension usually ranges between 0.5 and 5%, but may go as high as 30% in some antibiotic preparations. The amount of solids and the nature of the vehicle determine the viscosity of the product, and sometimes the property of thixotropy is also utilized particularly with oleaginous suspensions, to provide the sedimentation stability of the gelled preparation during storage and the syringeability of a fluid at the time of administration. Probably the most important requirement for parenteral suspension is a small and uniform particle size. These factors gives slow, uniform rates of sedimentation, predictable rates of dissolution, drug release and also reduces the tendency for larger crystal growth during storage.

The stabilization of the suspension for the period between manufacturer and use presents number of problems. As indicated, solids gradually settle and may cake, causing difficulty in redispersion prior to the use. Surface active agents may aid in the preparation and stabilization of the suspension by reducing the interfacial tension between the particles and the vehicle.

Similarly the addition of hydrocolloids such as sodium carboxymethylcellulose, enhances the effect of surfactant and cause loss of surface charge of the dispersed particles, water repellency and the tendency to agglomerate.

5.3.2 Emulsions

The principal problem in the formulation of parenteral emulsions is the accomplishment and maintenance of the uniform oil droplets of 1 to 5 μm in size as the internal phase. In case of emulsion separation of the phase does not occur compared to the suspension because of the difference in density between the oil and water is relatively small. The dispersed phase should have droplet sizes of less than 1μm. The emulsion must be stable to autoclaving. However elevated temperature produces coalescence of the dispersed phase and excessive shaking causes have been found to aid in stabilizing but are adversely affected by the elevated temperatures.

Difficulty:

- Preparation is troublesome.
- Its more complicated because of the rigid requirement of the particle size control to prevent embolism in blood vessels
- Also the limited choice of the emulsifiers and stabilizers of low toxicity, and by the preservation of the oil phase against the development of rancidity.

5.3.3 Formulation Development

The main objective is the elicitation of a therapeutic effect in the patient. The formulation of sterile products involves the combination of one or more ingredients with medicinal agent to enhance the convenience, acceptability or effectiveness of the product.

Therapeutic Agent:

- It is a chemical compound subject to the physical and chemical reaction characteristics of the class of the compound to which it belongs.

- Therefore careful evaluation must be made for every combination to ascertain whether adverse interaction occurs.
- Information concerning basic properties must be obtained including molecular weight, solubility, purity, colligative properties and chemical properties.

5.3.4 Vehicle or Solvent System

Aqueous System:

- The most commonly employed vehicle is water, since it is the vehicle for all natural body fluids.
- **The most tests for the quality of water are:** total solids content, gravimetric evaluation of the dissociated and undissociated organic and inorganic substances present in water.
- Electrolytic measurement of conductivity of water is most frequently used method. Measurement can be achieved by immersing electrode in water and measuring the specific conductance.
- **Additional tests:** Quality of water for injection with permitted limits is described in the USP monographs. The 10 ppm (parts per million) total solids officially permitted for Water for injection may be much too high when used as vehicle for many products. Water shall retain a minimal amount of organic compounds. Such compounds are undesirable for two main reasons: they may be toxic, and they may serve as sources of nutrition for microorganisms.
- Water for Injection normally should not have a conductivity of more than 1 micromho (1 megohm, approximately 0.1 ppm NaCl) and total organic carbon (TOC) not more than 500 ppb.

Non-aqueous and Mixed Solvents:

- In the formulation of sterile pharmaceutical products, it is sometimes necessary to eliminate water entirely or in part from the vehicle, because of solubility factors or hydrolytic reactions.
- A non-aqueous solvent must be selected with great care for it must not be irritating, toxic, or sensitizing, and it must not exert an adverse effect on the ingredients of the formulation.
- The screening of such solvent must therefore include an evaluation of its physical properties such as density, viscosity, miscibility and polarity, as well as its stability, solvent activity, and toxicity.
- Solvents that are miscible with water and that are usually used in combination include dioxolanes, dimethylacetamide, N-(6-hydroxyediy1)-lactamide, butylene glycol, polyethylene glycol 400 and 600, propylene glycol, glycerin, and ethyl alcohol.
- Water-immiscible solvents like fixed oils, edible oleate, isopropyl myristate, and benzyl benzoate. The most frequently used non-aqueous solvents are polyethylene glycol, propylene glycol, and fixed oils.

Solvent Selection:

- If aqueous, the solution is physiologically compatible with body tissues and the biologic response elicited should be reasonably predictable.

- The high dielectric constant of water makes it possible to dissolve ionizable electrolytes, and its hydrogen bonding potential brings about the solution of such organic substances as alcohols, aldehydes, ketones, and amines.
- Since therapeutically active compounds given by injection range in property from highly polar to non-polar, solvents having complementary properties must be employed if a solution is to be achieved.
- Solvents to be injected must be of low toxicity to the body tissue.
- The use of mixed solvents often reduces degradative reactions. Ex: Barbituric acid derivatives hydrolyze readily in water, particularly at a low pH.

Solutes:

- The physical and chemical purity of solutes used for sterile preparations must also be exceptional. Obviously, the contaminants entering a product with a solute have the same effect as if they entered via the vehicle. Even small traces of contaminants may be detrimental to products, necessitating purification of the solute. For a few substances (for example, ascorbic acid and calcium gluconate), special parenteral grades are commercially available.
- Solutes should be free from microbial and pyrogenic contamination. This entails not only proper quality of the chemical as procured, but also storage conditions designed to prevent contamination, particularly after a container has been opened.

5.3.5 Additives

- Substances added to a product to enhance its stability are essential for almost every product. Such substances include solubilizers, antioxidants, chelating agents, buffers, tonicity contributors, antibacterial agents, antifungal agents, hydrolysis inhibitors, antifoaming agents, and numerous other substances for specialized purposes.
- These agents must be prevented from adversely affecting the product. Added substances must be non-toxic in the quantity administered to the patient. They should not interfere with the therapeutic efficacy or with the assay of the active therapeutic compound.
- They must also be present and active when needed throughout the useful life of the product. Therefore, these agents must be selected with great care, and must be evaluated as to their effect upon the entire formulation.

Antibacterial Agent:

Antibacterial agents in bacteriostatic concentration must be included in the formulation of products packaged in multiple-dose vials, and are often included in formulations to be sterilized by marginal processes or made by aseptic manipulation.

Antioxidants:

In many formulations antioxidants are added to protect a therapeutic agent susceptible to oxidation, particularly under the accelerated conditions of thermal sterilization, may function in at least two ways:

1. By being preferentially oxidized (reducing agents), and thereby gradually used up.
2. By blocking an oxidative chain reaction in which they are not usually consumed.

In addition, certain compounds have been found to act as synergists, increasing the effectiveness of antioxidants, particularly those blocking oxidative reactions. A fourth group of compounds are useful in this connection in that they complex with catalysts that otherwise would accelerate the oxidative reaction.

Buffers:

- These are added to maintain the required pH for many products, as change in pH may cause significant alterations in the rate of degradative reactions.
- Changes in pH may occur during storage as a result of the dissolution of glass constituents in the product, release of constituents from rubber closures or plastic components in contact with the product, dissolution of gases and vapours from the airspace in the container and diffusion through the rubber or plastic component, or reactions within the product.
- Buffers must have the capacity to maintain the pH of the product against these influences, but not enough to prevent the body fluids from overwhelming the buffer following administration.
- Acetates, citrates and phosphates are the principal buffer systems used. Buffer systems must be selected with consideration of their effective range, concentration, and chemical effect on the total product.

Tonicity Contributors:

- Compounds contributing to the isotonicity of a product reduce the pain of injection in areas with nerve endings.
- Various agents used to adjust tonicity are such as sodium chloride or other sodium salts and non-electrolytes such as glycerin and lactose are most commonly used for this purpose.
- Tonicity adjusters are usually the last ingredients added to the formulation and the osmolality of the formulation measured. Although the freezing point depression of the solution is most frequently used to determine whether a solution is isotonic, isotonicity actually depends on the permeability of a living semipermeable membrane that separates the solution from a biologic cell system.
- Most frequently for sterile pharmaceutical preparations, the membrane concerned is the one enclosing the red blood cells.
- A preparation cannot be considered to be isotonic until it has been tested in biological system. This has been described by hemolytic method. If the formulation is still isotonic (< 280 mOsm/ kg as measured by an osmometer), tonicity adjuster are added until formulation is isotonic. If the formulation is hypertonic, the degree of hypotonicity and the intended route of drug administration need to be considered.

Chelating Agents:

- These may be added to bind, in non ionizable form, trace amounts of heavy metals, which if free would catalyze degradative changes.
- The most commonly used chelating agents are: trisodium/calcium disodium salt of ethylene diamine tetra-acetic acid in the range of 0.05% (w/v) E.g. Stabilization of thimerosal in poliomyelitis vaccine.

Inert Gases:

- Theses have been used to displace oxygen from a solution and reduce the possibility of oxidative changes in the formulation. E.g. Sodium bicarbonate injection decomposes, particularly during autoclaving to produce sodium carbonate, carbon dioxide and water.
- Saturation of the solution with carbon dioxide inhibits this reaction and stabilizes the solution.

Protein Stabilizers:

- A number of ingredients have been shown to stabilize proteins both in the dry and solution state.
- Serum albumin competes with therapeutic proteins for binding sites in glass and other surfaces and minimizes the loss of the protein caused by surface binding.
- A number of different types of substances are used as cryoprotectants and lyoprotectants to minimize protein denaturation during freeze-drying.
- Primary examples include polyhydric alcohols (sorbitol, glycerol, polyethylene glycol); amino acids (glycine, lysine, glutamine); non-reducing sugars (trehalose, sucrose); and polymers such as dextran, polyvinylpyrolidone, and methyl-cellulose. Surface active agents, such as Poloxamer 188 (Pluronic 68), polysorbate 80, and polysorbate 20 are widely used to minimize protein aggregation at air/water and water / solid interfaces.
- Antioxidants, buffers and chelating agents are also used to stabilize proteins in solution when necessary.

5.4 CONTAINERS

- Containers are in close contact with the product. Both the chemical and physical characteristics affect the stability of the product, but the physical characteristics are given primary consideration in the selection of a protective container.
- Glass containers traditionally have been used for sterile products, many of which are closed with rubber stoppers. Interest in plastic containers for parenterals is increasing, and such containers are being used for commercial ophthalmic preparations and IV solutions.

5.4.1 Plastic Containers

- The principal ingredient of the various plastic materials used for containers is the thermoplastic polymer.
- Although most of the plastic materials used in the medical field have a relatively low amount of added ingredients, some contain a substantial amount of plasticizers, fillers, antistatic agents, antioxidants, and other ingredients added for special purposes.
- These ingredients are not usually chemically bound therefore, may migrate out of the plastic and into the product under the conditions of production and storage.
- Plastic containers are used mainly because:
  - Light in weight
  - Non-breakable
  - When low in additives have low toxicity and low reactivity with products.

Drawbacks:

- Tissue toxicity can occur from certain polymers, but additives are a more common cause.
- Reactivity due to sorption (absorption and/or adsorption) has been found to occur most frequently with the polyamide polymers, but additives leached from any of the plastic materials may interact with ingredients of the product.
- Most polymers are adversely affected by the elevated temperatures required for thermal sterilization and have a relatively high permeability for water vapour.
- Significant permeation of gases including oxygen may occur with some materials. Ex: polystyrene

Polypropylene:

- It is the most widely used.
- It is a linear polymer that can be produced to be highly crystalline. Because of its crystallinity, it has a high tensile strength, a high m.p. of 165°C and relatively low permeability to gases and water vapours.
- It is translucent, abrasion-resistant, and has high surface gloss.
- Withstands normal autoclaving temperatures.
- Flexible polyethylene containers are used for ophthalmic solutions to be administered in drops and flexible polyvinyl chloride bags for IV solutions.
- The newer group of polymers, the polyolefins has made possible the development of bottles that are rigid enough to hold their shape during processing but can collapse under atmospheric pressure as outflow of a solution occurs during IV administration to the patient.

USP Procedure for Evaluating the Toxicity of Plastic Materials:

1. Implanting small pieces of plastic materials intramuscularly in rabbits
2. Injecting eluates using sodium chloride injection with an without alcohol intravenously in mice and injecting eluatesusing PEG400 and sesame oil intraperitoneally in mice
3. Injecting all four eluates subcutaneously in rabbits. The reaction from the test samples must not be significantly greater than non-reactive control samples.

5.4.2 Glass Containers

- It is the preferred material for injectable products.
- Is composed principally of silicon dioxide tetrahedron, modified physico-chemically by such oxides as those of sodium, potassium, calcium, magnesium, aluminium, boron and iron.
- The two types of glass commonly used are: soda lime and borosilicate glass.

Chemical Resistance:

- The USP provides the powdered glass and the water attack test for evaluating the chemical resistance of glass.
- The test results are the measurement of the amount of alkaline constituents leached from the glass by purified water controlled elevated temperature conditions.

- Similarly powdered glass test is performed on ground, sized glass particles and water attack test is performed on whole containers.
- Water attack test is used only with containers that have been exposed to sulfur dioxide fumes under controlled humidity conditions.

On the basis of results from the official test glass are classified as:

- Type I
- Type II
- Type III
- NP (Non parenteral)
- Type I is preferred most for the sterile products.
- Type II and III may be used when the product has non-aqueous vehicle or the period of contact with aqueous vehicle is brief, as with dry powders reconstituted just prior to use/ if the non reactivity between the glass and product has been established.

5.4.3 Physical Characteristics

Containers use considerations:

1. Rubber closures
2. Composition and reactivity
3. Physical characteristics
4. Testing
5. Devices

5.5 PRODUCTION

- Production process includes all the steps from accumulation and combining of the ingredients of the formula to the enclosing of the product in the individual container for distribution. Intimately associated with these processes are the personnel who carry them out and the facilities in which they are performed.
- To enhance the assurance of successful manufacturing operations, SOP is very essential.
- Extensive records must be kept to give assurance at the end of the production process that all steps have been performed as prescribed, an aspect emphasized in the FDA's Good Manufacturing Practice.
- In-process control is essential for assuring the quality of the product, since these assurances are even more significant than those from product release testing.
- In the initial step, the formula ingredients, container components and processing equipments that have been released for use are drawn from their respective storage areas. The ingredients are compounded according to the master formula in an environment designed to maintain high level of cleanliness. And if the product is solution, it is filtered during transfer to the asceptic filling room.
- Process equipments and container components are cleaned thoroughly, assembled in a clean environment, sterilized and depyrogenated prior to the use.

- It is then packaged. Outer wrapping of the packages should be loosened. All supplies must be introduced into the aseptic filling rooms.
- After this the containers are sealed.
- It is then transferred to the packaging area. This room must be clean. Packaged products are kept in quarantine storage until all tests have been completed and inprocess control records have been evaluated.
- Then the product is released for distribution.

1. Facilities
2. Environmental control
   - Traffic control
   - House keeping
   - Surface disinfectant
   - Air control
3. Personnel
4. Processing
5. Water for injection
6. Storage and distribution
7. Cleaning equipment and containers
   - Rinsing new containers
   - Cleaning rubber and plastic components
   - Sterilization of equipment
8. Compounding the product
9. Filtration of solutions
10. Filling procedures
    - Filling equipment for liquids
    - Filling equipment for solids
11. Sealing
    - Sealing ampoules
    - Sealing bottles, cartridges and vials
12. Automation of processing
13. Sterilization of the product
    - Freeze drying
14. Packaging
15. Stability
16. Quality control
    - Leak test
    - Clarity test
17. Pyrogens and pyrogen test

5.5.1 Facilities

- Should be designed for the control of cleanliness environment appropriate for each step.
- Surrounding area should provide a buffer area in which standards of cleanliness are only slightly lower than those for the asceptic rooms.

- The prevention of contamination must be the primary objective.
- The ceiling, walls, and floors should be constructed of material that is easy to clean and non porous, to prevent the accumulation of debris and moisture.
- Spray-on-tile is a ceramic epoxy finish applied by spraying or painting to form continuous, smooth, seal coating on the ceiling and walls.
- Ceramic-plastic cement is the best materials for floors.
- Glass is used in partition to permit supervisory view of operation as well as to provide more pleasant, better lighted, less confining surroundings for the operators.
- Furniture should be of non-porous, hard surfaced materials, preferably stainless steel.
- The basic designs and construction features have been continued with the HEPA filtered laminar airflow capabilities. Laminar airflow is most frequently added to a clean room to achieve greater environmental control in local areas.

5.5.2 Environmental Control

- For environmental control both the physical and chemical is essentials.
- Allowance must be made for variations in control associated with the seasonal conditions.
- The standards of environmental control varies depending upon the area involved and the type of product prepared asceptically maintained under the most rigid control that the existing technology permits.
- High standards of cleanliness, excluding daily use of the disinfecting procedures are usually acceptable for clean up and pacakaging areas.

Traffic Control:

- Carefully designed arrangement to control and minimize traffic particularly in and out of the aseptic area is essential.
- Access by personnel to the aseptic corridor and aseptic compounding and filling rooms is only through an airlock.
- Personnel should be permitted to enter aseptic areas only after following rigidly prescribed procedures.
- Unauthorized personnel should never be permitted to enter the aseptic area.

Housekeeping:

- Cleaning personnel must be imbued with the philosophy that not one remaining particle of debris is acceptable.
- All equipments and surrounding work area must be cleaned thoroughly at the end of the working day.
- The ceiling, walls and other structural surfaces must be cleaned with a frequency commensurate with the design of the facility.
- All cleaning equipments should be selected for its effectiveness and freedom from lint-producing tendencies.

Surface Disinfectant:

- After thorough cleaning, all surfaces should be disinfected, in the asceptic areas.
- An effective liquid disinfectant should be sprayed or wiped on all surfaces
- UV rays may be particularly useful to irradiate the inside, exposed surfaces of processing tanks, surface under hoods, surface of conveyor belts, underside of conveyors and the inside of containers.
- Ultraviolet lamps must be kept clean and care must be taken to check for decrease in effective emission, natural occurrence due to a change in the glass structure with aging.

Air Control:

- A spun glass, cloth or shredded polyethylene filter may be used for preliminary cleaning operation.
- To remove finer debris down to the sub- micron range including microorganism, a High efficiency particulate air (HEPA) filter, as defined as 99.7% efficient in removing particles of 0.3 µm size.
- Air passing through these units can be rendered virtually free from foreign matter. Another air cleaning system washes the air with a disinfectant and controls the humidity at same time.
- Blowers should be installed in the air ventilation system upstream to the filters so that all dirt-producing devices are ahead of the filters. The clean air is distributed to the required areas by means of metal ducts.
- The two types of rooms employed are:
  - Class 100
  - Class 10,000
- Class 100 clean room is defined as a room in which the particle count in the air is not more than 100 per cubic foot of 0.5µm and larger in size. The airflow must be uniform in velocity and direction throughout any given cross section of the area. The air velocity employed should be 100±20 ft/ min.
- This class is mostly specified for critical aspects/ clean operations.
- This is expensive and requires effective maintenance and monitoring.
- Class 10,000 rooms are defined as one in which the particle count is no more than 10,000 per cubic foot of 0.5µm and larger in size.

Personnel:

- The people who produce sterile products are usually non-professional persons, supervised by those with professional training.
- All employees should be in good health and should be subjected to periodic physical examinations.
- The attire worn by personnel in the asceptic areas usually consists of sterile coveralls, hood, face masks, rubber gloves and shoe covers.
- Personnel working in equipment wash rooms, sterilizing rooms and packaging areas are normally required to don clean uniforms daily and to be conscious of cleanliness.

5.6 FORMULATIONS FOR INJECTIONS

Example: Diazepam for 5 mg/ml injection.

Ingredient	Quantity
Diazepam	500 mg
Propylene glycol	40 ml
Ethyl alcohol	10 ml
Sodium benzoate	4.9 mg
Benzoic acid	100 mg
Benzyl alcohol	1.5 ml
Sterile water for injection	q.s. 100 ml
Sodium hydroxide or hydrochloric acid	q.s. pH 6.2 - 6.9

Example: Amikacin for 250 mg/ml injection.

Ingredients	Quantity
Amikacin sulfate (equivalent to 25 g amikacin)	33.375 g
Sodium bisulfite	660 mg
Sodium citrate, anhydrous	2.19
Sulfuric acid	q.s. pH 4.5
Sterile water for injection	q.s. 100 ml

5.7 STERILE POWDERS

Due to instability in water, many drugs are formulated as drug powders to be reconstituted prior to administration. E.g. Penicillins, barbiturates, benzocain. Sterile water for injection is supplied with dry powders to make "solutions / or suspensions for injections". The obtained solution / suspension will meet with all the requirements of solution /suspension for parenteral. Reconstituted solutions can be given by IV or IM route, however suspension is forbidden for IV administration.

5.7.1 Methods of Preparing a Sterile Drug Powder

There are three methods. They are:-

- Sterile recrystallization
- Lyophilization
- Spray drying

1. Sterile Recrystallization:

The drug is dissolved in a solvent and the obtained solution is sterilized through 0.22 µm membrane filter. A sterile anti-solvent is then added to crystallize the drug particles, which is filtered and dried aseptically.

Advantage: Flexible and economic.

Disadvantage: Variations from batch to batch and contamination.

2. Lyophilization:

It is a process of separating a solid substance from solution by freezing the solvent and evaporating the ice under vacuum. Drug solution is sterile filtered into sterile trays which are 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: Removal of water at low temperatures.

Disadvantage: Biological molecules are damaged by the stress associated with freezing, and drying. It is costly and time consuming.

3. Spray Drying:

The solution of the drug is sprayed into a dry chamber where it comes in contact with a hot steam of a sterile gas (80-100°C).

Advantage: Simple, Economical, scalable, faster. Coating of particles during drying prolonged release.

Disadvantages: High processing temperatures and high shear forces can easily damage drugs.

- Higher level of drug losses than freeze drying.
- Limited solvent choice for a given drug.
- Cannot prepare product directly in vials or plates.

Procedure of Reconstitution:

1. Clean the rubber diaphragm of the medication vial and the diluents vial with an alcohol swab.
2. Unpack the desired syringe; pull the plunger to fill the barrel with air equal to the desired amount of diluents.
3. Inject the air into the vial of WFI to create positive pressure and to ease withdrawal.
4. Invert vial and withdraw the desired amount of WFI.
5. Inject the WFI into the medication vial and withdraw the syringe and needle.
6. Invert and shake the vial to mix well.
7. Positive pressure may be created in the freshly mixed medication vial for easy withdrawal (step 3).

5.8 STORATE AND DISTRIBUTION

- The storage and distribution of WFI is as important as production.
- A closed system with air exchange through a filter that removes microorganism, dirt and vapours from the air as the tank is filled and emptied.
- WFI should not be held for more than 24 hr at room temperature before it is used, but if held at 80°C.
- The distribution may be by direct withdrawal from the tank, or in large plants through a pipe system.
- When a pipe system is used precaution must be followed to prevent the contamination/ construction with welded stainless steel pipe, elimination of elbows/ pockets in which water can stagnate for long periods and thorough cleaning/ sanitation at frequent intervals.

Cleaning Equipment and Containers:

- Equipments and containers to be used should be scrupulously cleaned.
- Debris should be removed by hot detergents. Live steam can sometimes be used to loosen debris effectively, particularly in area where it is not accessible.
- After cleaning, it should be rinsed with WFI.
- A new method for large tanks, pipelines and associated equipments that can be isolated and contained within a process unit has been developed and identified as a CIP (Clean in place) system. Cleaning is accomplished with high pressure rinsing treatments delivered automatically within the equipment which is followed by steam sterilization.
- The glasswares and metalwares is automatically conveyed, usually in an inverted position through a series of rigorous, high pressure treatment including hot detergent, hot tap water and final rinses with distilled water.

Compounding of the Product:

- The product should be compounded under clean environment conditions.
- The accuracy of compounding should meet the rigid standards accepted in pharmaceutical procedures, regardless of the batch size, recognizing that small multiple errors may be additive.
- Similarly in large batch particular attention must be given to achieve and maintain homogeneity of solutions, suspension and mixtures maintaining a given temperature and accelerating cooling.

Filtration of Solutions:

- The primary objective of filtration is clarification/ sterilization of solution. Clarification is termed "polishing" and a highly polished solution requires the removal of particulate matter down to at least 0.3 μm size.
- A solution having a high polish conveys the impression of exceptional quality and purity, a highly desirable characteristic for sterile solution.
- After filtration the solution must be protected from environmental contamination until it is sealed in the final container. The filtrate is fed directly from the collecting vessel to the filling machine through sterile hose connections.
- A secondary "in-line" filter is often included as close to the outlet of the filter as possible to collect any lint or other matter picked up from the lines/ equipments.

5.9 FILLING AND SEALING

Filling Equipments for Liquids:

- For filling, a means is provided for repetitively forcing a measured volume of the liquid through the orifice of the delivery tube designed to enter the constricted opening of a container.
- The tube must freely enter the neck of the container and deliver the liquid deep enough to permit air to escape without sweeping the entering liquid into the neck of the container.

- The delivery of relatively small volume of liquid is usually obtained from the stroke of the plunger of syringe.
- A drop of liquid normally hangs at the tip of the tube after a delivery. Thus, a retraction device is designed as a part of the most filling machines.
- Filling machines should be designed so that the parts through which the liquid flows can be easily demounted for cleaning and sterilization. It should be constructed of non-reactive materials such as borosilicate glass or stainless steel.
- The pressure pump filler often is operated semi-automatically and differs from the gravity filler principally in that the liquid is under pressure.
- Vacuum filling is commonly used in faster filling lines for large liquid volumes because it is more adaptable to automation. The vacuum draws the liquid from the reservoir through the delivery tube into the bottle. When the liquid level reaches the level of an adjustable overflow tube, seal is mechanically loosened and the vacuum is released.
- Emulsion and suspension often requires specially designed filling equipments because of their viscosity. To obtain a reasonable flow rate, high pressure must be applied/ containers with large opening must be used. It is necessary to keep suspension and emulsion instantly agitated during filling so that the product remains homogenous.

Filling Equipments for Solids:

- The rate of flow of solid materials tends to be slow and irregular whereas small, granular particles flow most evenly. Containers with large openings must be used even the filling rate is slow and the risk of spillage is present.
- When the solid is obtained in relatively free-flowing form, machine methods of filling may be employed. This method involves the measurement and delivery of volume of solid material which has been calibrated in terms of weight desired.
- Another filling machine consists of an adjustable cavity in the rim of the filling wheel which is filled by vacuum as the wheel passes under the hopper.The contents are held by vacuum until the cavity is inverted over the container when a jet of sterile air discharges the dry solids.

Sealing Ampoules:

- Ampoules may be closed by melting a portion of the glass of the neck to form either bead-seals (tip seals) or pull seals. Tip seals are made by melting sufficient glass at the tip of the ampoule neck to form a bead of glass and close the opening.
- Pull seals are made by heating the neck of a rotating ampoule below the tip, then pulling the tip away to form a small, twisted capillary just prior to being melted closed. It is a slower process but the seals are more reliable than that form tip-sealing.
- The heating with high temperature gas-oxygen flame must be even and carefully controlled to avoid distortion of the seal.

Sealing Bottles, Cartridges and Vials:

- Rubber closures must fit the opening of the container snugly enough to produce a seal.
- A faster hand method involves picking up the closure and inserting it into a vial by means of a tool connected to a vacuum line.
- When closures are inserted by machine, the surface of the closure is usually halogenated or coated with silicone to reduce the friction.
- Aluminum caps are used to hold rubber closures in place. Single caps contains hole/ center that is torn away at the time of use to expose the rubber closures. Whereas the double aluminum caps usually have an inner cap with permanent center hole, which in use is exposed when the entire outer cap is torn off. The triple aluminum caps are used for large bottles with rubber closures having permanent holes for attachment to administration sets.

Automation of Processing:

- When machines are designed/ used so that the constant attention of human operator is required, the operation is identified as being semi-automatic.
- For automatic operation, machines are usually linked together by conveyor belts in an arrangement that requires little attention from an operator.
- The belts carry each vial in sequence to the filling wheel, to the stoppering machine and then out to the collecting turntable. A crimping machine should be inserted after stoppering machine.
- Automation of the entire process would convey an empty dose container from its supply carton through the entire process until it is filled with a product, labeled and placed in the shipping carton.

5.10 STERILIZATION AND PACKAGING

5.10.1 Sterilization of Product

Freeze-drying:

- It is a drying process applicable to the manufacture of certain pharmaceuticals and biological that is thermolabile or otherwise unstable in an aqueous solution for prolonged storage periods, but is stable in dry state.
- The rate of drying depend on the thermal conductance of the frozen product, rate at which the vapour can diffuse through the progressively thicker layer of dried porous material and the rate of transfer of vapour through the system to the condenser surface.
- In production, large freeze driers are usually operated by an automatic control system. The product is usually processed until there is less than 1% moisture in the dried material.
- Freeze driers also may be equipped for stoppering vials within the drying chamber.
- Numerous biologic preparations, tissue sections and viable microorganism are being preserved in the freeze dried state. Multiple vitamin combinations, antibiotics, hormones are other examples.

5.10.2 Packaging

- The package is an extremely important part of the product, for it presents the product to the user.
- It must be particularly dignified, neat and attractive appearance if it is to convey to the user the quality, purity and reliability.
- The labeling should be legible and the identity and strength of the drug should be distinguishable.
- The packaging should protect the product against physical damage during shipping, handling and storage and should protect light-sensitive substances from ultraviolet radiation.

5.11 QUALITY CONTROL

- The three general areas of quality control are incoming stock, manufacturing and the finished product.
- For sterile products, incoming stock control encompasses routine tests on all ingredients as well as special evaluations such as pyrogen test on WFI, glass test on containers and identity test on rubber closures.
- It is also may be necessary to perform microbial load tests to determine the number and type of microorganism presents.
- The production control includes all of the final assays and tests to which the product is subjected.
- In addition to the chemical and biological tests, a sterile product is subjected to leak test, clarity test, pyrogen test and sterility test.

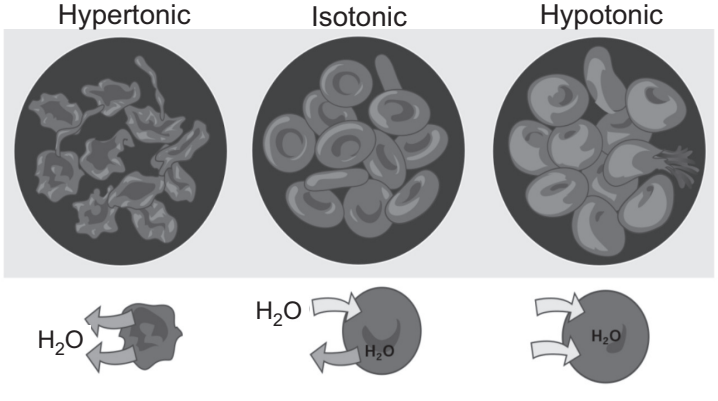


Fig. 5.1

- Quality of the product should be ensured at 3 stages of product life cycle:
  - After procuring raw material
  - Processing
  - Final product

5.11.1 Pyrogen Test

The Detection of Endotoxins via the LAL Test, the Gel Clot Method:

Fig. 5.2

- The Limulus Amebocyte Lysate test is recommended in international pharmacopoeias as the method for detecting bacterial toxins both in the raw materials used for the production of medicines and for the final products.
- Also useful for the cosmetics industry and in food production as it is the method recommended by the FDA (Food and Drug Administration) for the detection of pyrogens.
- One of the main advantages of the LAL test that the crabs, from which the hemolymph is extracted to prepare the LAL reagent, remain alive.

Bacterial Endotoxins:

The Gram-negative bacteria have an external membrane formed by lipopolysaccharides. This structure is toxic to other superior organisms, such as animals and humans. These lipopolysaccharides are known as endotoxins in order to differentiate them from the other toxins that could be secreted by the bacteria, but do not form a part of their structure, called exotoxins. When the bacteria multiply or are destroyed, part of these endotoxins passes into the environment, thus performing their pathogenic function.

The myths and facts regarding bacterial endotoxins:

The toxicity mechanism that the endotoxins trigger is caused by the lipid fraction of the lipopolysaccharides. For example, when the lysis of the bacteria within an organism takes place, the response in the presence of the lipids that go into the bloodstream can be through the activation of the complement system. This lipid fraction leads to the release of different cytokines, such as interleukins 1 and 8. The production of the tumour necrosis factor is probably also activated. The infection produced is associated with inflammatory processes and can pose a great danger for the infested organism. Interleukins 1 are a series of cytokines that the organism releases as an immune response and against the inflammation. This signal leads to the migration of neutrophils towards the place where the infection has occurred, producing chemotaxis. This facilitates the occurrence of phagocytosis; however, in some cases, depending on the state of the immune system of the individual and the level of infection, the bacteria could lead to a generalized sepsis, along with the risks that are brought about by the sepsis. It is known that there are many cases where the Gram-negative bacteria have caused death by systemic infection in higher mammals. Ex of Gram-negative bacteria: Salmonella, Escherichia coli, Shigella and Neisseira.

The Limulus Amebocyte Lysate Test:

The Limulus Polyphemus crab is one of the animals that have survived on land since prehistoric time with origins that date back more than 200 million years. This resistant animal experiences coagulation in its haemolymph due to the presence of bacterial endotoxins. Upon the discovery of this fact in the 60s, research was continued until managing to take advantage of this reaction to conduct in vitro detection tests for endotoxins in different environments. The Limulus Polyphemus belongs to a group of Horseshoe Crabs, which live in the Atlantic coast in the northern part of the American continent, including the Gulf of Mexico.

Applications of the LAL method:

- In invertebrates, the amebocytes fulfil the function of white blood cells in vertebrates. They defend the organism against pathogens; therefore, they respond to the influx of endotoxins from the bacteria by releasing a series of enzymes. Scientists studied this phenomenon until ascertaining that, if a lysate of the amebocytes extracted from the Horseshoe Crab in a watery environment is diluted, this could serve to detect very small quantities of endotoxins.
- The amebocytes contain procoagulant enzymes that trigger a chain of reactions. The final product of these chain reactions is a gel comprised by coagulated proteins. The enzymatic response is produced when the amebocytes enter into contact with the endotoxins. This mechanism is often compared to the trypsin that also triggers a chain of reactions to finally form the thrombin, the agent responsible for the coagulation of blood in humans.
- The LAL test is only valid for detecting endotoxins and not any other type of pyrogen (a name that is given to any compound that could cause fever). In many occasions, this test is used with the goal of detecting other pyrogens, which is wrong.
- While bacterial endotoxins, as they are highly resistant to heat and to different chemical reagents used for sterilization, are one of the most common pyrogens left present after the common measures of sanitation in industries, a negative LAL test only indicates the absence of endotoxins and not the absence of other pyrogen micro-organisms.
- Conducting this test can only lead to the confirmation of an environment free of pyrogens when this test is accompanied by other analyses and specific sanitary measures to eradicate the rest of the contaminating micro-organisms.

Applications of the LAL test in the pharmaceutical industry

Gel-Clot Method to quantify endotoxins via the LAL test

- The LAL test can be conducted by using different methods to measure the process of gelation that occurs as a response from the amebocytes against the endotoxins. These methods are the so-called Gel-Clot method, turbidimetric and chromogenic methods.

- The Gel-Clot method is based on the presence or absence of a gel clot. The gelation occurs when proteins are coagulated due to the presence of endotoxins. The detection limit of the tests depends on the manufacturer of the kit that contains the LAL reagent. Using the Gel-Clot method, the detection limit is normally between 0.01 and 0.03 endotoxin units per one millilitre of the solution used in the test. This means that a solid gel does not come to be formed below this concentration of endotoxins when moving the test tube. A criterion used in the method of gelation is to turn the test tube 180° and ascertain that the gel remains intact. The Gel-Clot method can be used in a qualitative manner, yielding positive results or negative ones if the gel is not formed. The method can also be used in a semi-quantitative fashion.
- In addition to PYROSTAR™ ES-F, Wako provides investigators with a complete line of accessories and reagents for the purpose of LAL testing. Among the offered products, you can find control standard endotoxins, a solution for the extraction of endotoxins on medical devices and the Toxinometer® ET-6000 measurement system. You can also find other tests designed for endotoxin determination via chromogenic methods.

5.11.2 Leakage Test

Ampoules are the containers which are hermetically sealed (Air tight containers) thereby the product in it is protected from external environment.

Leakage test is performed to ensure proper packing of the container therefore the contents may not be leaked.

5.11.3 Sterility Test

- The main purpose of steriity test is to detect the presence of viable form of microbes in the product.
- Sterility test can be done in two ways either by :

1. Membrane filtration method
2. Direct Inoculation method

- To perform the sterility test, initially the culture media should be prepared which supports the growth of microbes- both aerobic and anaerobic, fungi.
- The medium may be Fluid thioglycollate medium (Anarobic bacteria), soybean – casein digest (Aerobic bacteria and Fungi)

Method (A) : Membrane Filtration Method:

- A membrane suitable for sterility test has a nominal pore size not greater than 0.45 µm, diameter of approximately 47 mm.
- Cellulose nitrate filtrate is used for: aqueous, oily and weakly alcoholic solutions and cellulose acetate filters are used for strongly alcoholic solutions.
- At first the membrane is rinsed with diluting or rinsing fluid.
- Fluid products in pressurized aerosol form are freezed in an alcohol-dry ice mixture at least at – 20°C and added prior to transfer of the contents.

- After filtration of the contents, the membrane is aseptically cut into two equal parts, and each one half is transferred to both the culture medium.
- Fluid thioglycolate medium is incubated at 32.5 ± 2.5°C, whereas soyabean-casein digest medium is incubated at 22.5 ± 2.5°C, for not less than 14 days.
- And the medium is examined for any microbial growth at intervals. If no evidence of microbial growth is found, the product to be examined complies with the test for sterility.
- Similarly if evidence of microbial growth is found, the product to be examined doesn't comply with the test for sterility. The test may be considered invalid if one of the following conditions are fulfilled:
  (i) The data of the microbial monitoring of sterility testing facility, the testing procedure used during the test reveals a fault.
  (ii) Negative controls also show microbial growth. If the test is declared to be invalid, it is repeated with the same number of units as in the original test.If no evidence of microbial growth is found in the repeat test , the product examined complies with the test for sterility. And if microbial growth is found in repeat test, the product examined does not comply with the test for sterility.

Method B: Direct Inoculation:

- It is utilized particularly for surgical devices, sterile devices, surgical dressings and sutures.
- Particular quantity of the preparation is transferred into the culture medium so that the volume is not more than 10%.
- Neutralize with suitable substances or by dilution in a sufficient quantity of culture medium.
- Inoculated media is then incubated for not less than 14 days.
- Observe the cultures at particular interval.
- When thioglycolate medium is used for detection of anerobic organism, keep shaking/mixing to a minimum to maintain anaerobic condition.
- After 14 days, transfer to fresh vessels of the same medium, and then incubate the original and then transfer vessels for not less than 4 days.
- The results are interpreted as incase of membrane filtration method.

QUESTIONS

Long essay questions: (10 marks each)

1. Draw schematic of aseptic area. Give classification of clean area.
2. Explain processing of sterile products.
3. Discuss various zones specified for environmental control in manufacturing area of parenterals.
4. Comment of facilities and procedures followed in change room of parenteral production.
5. Discuss in detail about aseptic processing of parenteral formulations.
6. Elaborate upon formulation of injections.

Short essay questions: (5 marks each)

1. Discuss formulation of lyophilized parenteral products.
2. Discuss various types of containers and closures used in packaging of parenteral formulations.
3. Discuss quality control testing of plastic containers.
4. Discuss quality control testing of glass containers.
5. What is dye bath test? What is its objective? How it is performed?
6. Discuss filling and sealing of ampoules, vials and infusion fluids.
7. Enlist various in-process quality control tests for parenteral formulations.
8. Enlist various quality control tests for finished parenteral products.
9. Comment on sterility testing of parenteral products.
10. What are pyrogens? Discuss tests used to detect the presence of pyrogen in sterile parenteral products.
11. Write notes on:
    (a) Clarity test for parenteral products
    (b) Leaker test for parenteral products
    (c) Content uniformity and weight
    (d) Extractable volume test
    (e) Stability testing of parenteral products

Short answer questions: (2 marks each)

1. Why antimicrobials are not added in SVP?
2. Classify parenterals based on various parameters.
3. Give ideal requisites of parenteral products.
4. Enlist and explain various routes of parenteral drug delivery.
5. What are advantages and limitations of parenteral products?
6. Discuss in detail preformulation parameters of parenteral formulations.
7. What are essential requirements of parenteral products?
8. Write about vehicles used in SVP and LVP.

Chapter 6 ...

OPHTHALMIC PREPARATIONS

Upon the completion of this chapter, the students will be able to understand:

- *The key building of ophthalmic preparation.*
- *The role and responsibilities of ophthalmic preparation.*
- *The different technologies used in evaluation of ophthalmic preparations.*

6.1 INTRODUCTION

Ophthalmic formulations are sterile products meant for instillation into the eye in the space between the eyelids and the eyeballs.

Criteria for Selection of a Drug for Ophthalmic Use:

1. The drug must be bio-chemically and pharmacologically potent.
2. The drug must be non toxic to both ocular and systemic tissues.
3. The drug must be sufficiently stable that neither significant loss in potency from diminished availability nor little increase in toxicity from byproducts of degradation arises.
4. The drug can be either targetable to tissues and location of primary disease state etiology or to sites responsible for symptomatic response.
5. The drug must be sufficiently compatible with the dosage form, and with the tissues exposed to it, to achieve an effective pharmaco-kinetic tissue profile.

6.2 FACTORS AFFECTING ABSORPTION OF THE DRUG IN THE EYE

1. **Loss of drug due to spillage**: This takes place by spillage of drug from the eye and its removal by the nasolacrimal drainage. The normal volume of tears in the human eye is approximately 7-10 µl (if blinking occurs). The human eye can accommodate a volume of up to 30 µl without spillage from the palpebral fissure. With an estimated drop volume of 50 µl, 70% of the administered volume of 2 drops can be seen to be expelled from the eye by overflow. If blinking occurs, the residual volume of 10 µl indicates that 90% of the administered volume of 2 drops will be expelled within a few minutes.
2. **Drainage:** Drainage of the drop through the nasolacrimal system into the gastrointestinal tract begins immediately on instillation. This takes place when either reflex tearing or the dosage form causes the volume of fluid in the palpebral tissue to exceed the normal lacrimal volume of 7-10 µl. The excess fluid volume enters the superior and inferior lacrimal puncta, moves down the canalicula into the lacrimal sac, (as shown in fig) and continues into the gastrointestinal tract. This also is the mechanism by which a patient may often sense a bitter or salty taste, for example ammonium salts.
3. **Superficial absorption:** Superficial absorption of drug into the palpebral and bulbar conjunctiva, with generally concomitant rapid removal from ocular tissues by the peripheral blood flow also is an influencing factor.

4. **Transcorneal absorption:** Often this route is most effective in bringing drug to the anterior portion of the eye. Although transport of hydrophilic and macromolecular drugs has been reported to occur by limbal or scleral routes, often this is at rates significantly reduced from those expected for transcorneal transport of conventional, modestly lipophilic agents of low molecular weight. Even here, transmembrane transport is a significant requirement for availability.

6.3 REQUIREMENTS OF OPTHALMIC PREPARATIONS

1. Sterility and preservation
2. Tonicity
3. pH/Buffering
4. Surface activity
5. Clarity/foreign particles
6. Viscosity/thickening agents (15 cps to 25 cps)

1. Sterility:

Ophthalmic solutions should be sterile when prepared, and care must be taken to prevent contamination during use.

Ophthalmic solutions used during surgery or in the traumatized eye generally do not contain preservative agents, because these are irritating to the eye. These solutions are usually packaged in single-dose containers and any unused solution is discarded.

Ophthalmic solutions are most frequently contaminated by the organism *Pseudomonas aeruginosa*. This is a very dangerous micro organism. It can cause complete loss of sight within 24 - 48 hours. Contamination with a variety of other micro organisms is also frequent.

A sterile multiple-dose ophthalmic solution can be contaminated in a number of ways if precautions are not taken.

(a) If a dropper bottle is used, the tip of the dropper may touch the surface of a table or shelf.

(b) The tip can touch the eyelid or eye lash of the patient during administration.

Even though ophthalmic preparations are sterile, they must contain an effective, topically non-irritating anti bacterial agent or a mixture of such agents. Preservatives prevent the growth of, or destroy, micro organisms accidentally introduced in the preparation when the container is opened during use. The preservative should be non-toxic, non-irritant, and should be compatible with medicament.

Examples:

- Benzalkonium chloride : 0.013 %
- Benzethonium chloride : 0.01 %
- Chlorobutanol : 0.5 %
- Phenyl mercuric acetate : 0.004 %
- Phenyl mercuric nitrate : 0.004 %
- Thiomersal : 0.01 %

Ophthalmic preparations are sterilized by any of the following techniques:

(a) Autoclaving
(b) Filtration
(c) Chemical sterilization

(a) Autoclaving: The most preferable method of sterilization is autoclaving of the final containers. This method can be preferred if the ingredients of the preparation are thermostable. Steam under pressure is commonly stated to kill all living organisms, including spores and viruses. Following sterilization, pressure must be reduced slowly to prevent bursting of bottles.

(b) Filtration: The advantage of the filtration is that, it is carried at room temperature and does not cause or accelerate decomposition by heating. Buffering certain drugs near the physiological range makes them quite unstable at high temperature. But the disadvantage is that it does not remove or destroy viruses. Another advantage of the filtration is the retention of all particulate matter, the removal of which is important in the manufacture and use of ophthalmic solutions.

The filtration method involves transfer of solution into final containers after passage through the filter. Filtration uses positive or negative pressure. It is essential to note that unless great care is taken small amounts of drug can be trapped in the filtration assembly.

(c) Chemical sterilization: Disadvantages are: (a) This method does not destroy viruses. (b) This method often requires considerable time to destroy bacteria and sometimes may be quite ineffective. Antibacterial agents added in the preparation enhance the sterilizing capacity of chemicals during sterilization.

For this method to use: (i) The glassware should be as nearly sterile as possible. (ii) All solutions should be made with sterile distilled water. (iii) The solution should be dispensed in a sterile container.

2. Tonicity:

Ophthalmic preparation must be isotonic with lachrymal secretions to avoid discomfort and irritation. If hyper tonic solution is instilled into the eye, then the solution could cause the drawing of water toward the site of the topical application. Conversely, a hypotonic solution might induce the hemolysis of red blood cells, or the passage of water from the site of an ophthalmic application through the tissues of the eye.

Active ingredient and other solutes added in the preparation contribute to the osmotic pressure of the solution. If quantity of solution instilled is small, eyes can tolerate a certain range of hypo/hyper tonicity. When quantity of solution instilled is large, adjustment of tonicity is absolutely essential.

The freezing point of lachrymal fluid is $-0.052^{o}C$. 1g molecular weight of non electrolyte is dissolved in 1000g of water to observe change in freezing point and thereby tonicity. Therefore 61.8 g of boric acid (molecular weight of boric acid is 61.8 g) is dissolved in 1000 g of water. The freezing point of this solution is $-1.86^{o}C$. To calculate the quantity of boric acid required to prepare isotonic solution, the following formula is used:

$$\text{Weight of boric acid required} = \frac{\left(\begin{array}{c}\text{1 g molecular weight}\\ \text{of boric acid}\end{array}\right) \times \left(\begin{array}{c}\text{Freezing point of}\\ \text{Lachrymal secretions}\end{array}\right)}{\text{Freezing point of boric acid solution}}$$

$$= \frac{61.8 \times 0.52^{\circ}C}{1.86^{\circ}C} = 17.3 \text{ g}$$

Hence, 17.3 g of boric acid dissolved in 1000 g of water should produce a solution isotonic with tears or blood.

For electrolytes, calculation is slightly different. E.g. sodium chloride solution. Assume that sodium chloride in weak solutions dissociates up to about 80%. The 100 molecules yield 180 particles. (80 particles of sodium + 80 particles of chloride + 20 particles of undissociated sodium chloride).

To calculate the quantity of sodium chloride required to prepare isotonic solution, the following formula is used;

$$\text{Weight of sodium chloride required} = \frac{\left(\begin{array}{c}\text{1 g molecular weight}\\ \text{of sodium chloride}\end{array}\right) \times \left(\begin{array}{c}\text{Freezing point of}\\ \text{Lachrymal secretions}\end{array}\right)}{1.86^{\circ}C \times \text{Dissociation value}}$$

$$= \frac{58.5 \times 0.52^{\circ}C}{1.86^{\circ}C \times 1.8} = 9.09 \text{ g}$$

Hence, 9.09 g of sodium chloride in 1000 g of water should make a solution isosmotic with tears or blood.

The dissociation values of substances can be used for calculations are :

Name of the substance	Dissociation constant
Non electrolytes	1.0
Substances that dissociates into 2 ions	1.8
Substances that dissociates into 3 ions	2.6
Substances that dissociates into 4 ions	3.4
Substances that dissociates into 5 ions	4.2

Since 0.9% sodium chloride solution is considered to be isotonic, other drugs are compared with regard to their "sodium chloride equivalents".

For example,

Molecular weight of sodium chloride = 58.5

Dissociation value (i) of Sodium chloride = 1.8

Molecular weight of Atropine sulphate = 695

Dissociation value (i) of Atropine sulphate = 2.6

$$\frac{695 \times 1.8}{58.5 \times 2.6} = \frac{1 \text{ g}}{\text{x g}}$$

$$\therefore \quad \text{x g} = \frac{58.5 \times 2.6}{695 \times 1.8} = 0.12$$

$\therefore$ 0.12 g of sodium chloride represents 1 g of atropine sulphate.

When combination of drugs is used in prescription, then each drug contribution must be taken into consideration.

Ingredient	Given formula	Working formula
Atropine sulphate	1%	300 mg
Sodium chloride	QS to isotonicity	234 mg
Sterile water to	30 ml	30 ml

For 30 ml solution of sodium chloride solution,

30 × 0.9 % = 0.27 g = 270 mg of sodium chloride

Concentration of Atropine sulphate present in the formulation is 1%

i.e. 1 g in 100 ml or 300 mg in 30 ml

0.12 × 300 mg = 36 mg

Thus, 270 – 36 = 234 mg of sodium chloride

3. pH and Buffers:

Buffers are used in an ophthalmic solution for the following reasons;

(a) to reduce discomfort to the patient.

(b) to ensure drug stability and safety.

(c) to control the therapeutic activity of the drug substance.

Normal tears have the pH of about 7.4. Tears possess some buffer capacity. The introduction of an unbuffered medicated solution may cause irritation. This leads to increased secretion of tears in an attempt to restore normal physiological condition.

Most drugs used ophthalmically are weakly acidic (alkaloidal salts) and have only weak buffer capacity. Therefore, the buffering action of the tears is sufficient to neutralize the ophthalmic solution and is thereby able to prevent marked discomfort. For maximum comfort, an ophthalmic solution should have the same pH as the lachrymal fluid (7.4). However, this is not possible, because at this pH, many drugs are insoluble in water. For example, alkaloidal salts are likely to precipitate as the free alkaloidal base at pH 7.4.

Many drugs are most active therapeutically at pH levels which favour the unionized molecule. Sometimes, the pH at which the drug is therapeutically active may be the pH at which the drug is unstable. For this reason, a compromise pH is generally selected for a solution and maintained by buffers to permit the greatest activity while maintaining stability.

The buffer system of an ophthalmic solution contributes to stability in another way by preventing an increase in the pH of the solution due to the normal leaching by the solution of alkali from the glass container.

The pH values of ophthalmic solutions are adjusted to a range at which an acceptable shelf life stability of at least 2 years can be achieved.

4. Surface Activity:

The vehicles used in ophthalmic preparations must have good wetting property. Satisfactory wetting leads to increased penetration of the drug into the cornea and other tissues. In order to achieve good wetting property, wetting agents or surfactants are added.

These agents must be suitable for ophthalmic use and should not interact with any of the ingredients of the ophthalmic preparation.

Benzalkonium chloride is most commonly used wetting agent. Because it also possesses antimicrobial property.

Other surfactants are polysorbate 80, polysorbate 20, dioctyl sodium sulfosuccinate, benzethonium chloride etc.

5. Clarity:

The ophthalmic solutions must be clear and free from foreign particles such as fibres and filaments. The ophthalmic solutions are subjected to filtration to obtain desired clarity. Bacteria proof filters such as membrane filters are used for filtration. These filters such as membrane filters are used for filtration. These filters neither absorb any solution nor furnish any fibres or particles to the filtrate. In case of ophthalmic suspensions, a separate filter should be used for different ophthalmic products in order to avoid the contamination.

6. Viscosity:

To increase the time of contact of the drug with the eye, the viscosity of the preparation is increased. Viscosity can be increased by using thickening agents. Examples include PVA, PEG, MC, CMC etc. These should possess the following ideal properties:

(i) These should be easy to filter

(ii) These should be easy to sterilize.

(iii) These should be compatible with other ingredients.

(iv) These should possess requisite refractive index and clarity.

The thickening agents are not added in the formulation of eye drops and eye lotions that are required to be used during or after surgery. Because these may cause some adverse effects on the interior of the eye. Viscosity can be increased upto 15-50 cps. owever viscosity values higher than this offer no significant advantages. Such high viscosities tend to leave a residue on the lid margins.

6.4 MANUFACTURING FACILITIES

Environment: Environmentally controlled areas are used for the manufacture. Class 100 space is the area where not more than 100 particles are present per cubic foot of air of a diameter of 0.5 micrometer or larger. Similarly class 1,00,000 space is defined. Class 100 space is required for filling and capping operations. For the purpose HEPA filtered laminar airflow sources are used. Class 1,00,000 space is required for the storage of raw materials, finished products.

Walls, ceilings, and floors should be constructed of materials that are hard, non-chipping or non-flaking, smooth and unaffected by surface cleaning agents and disinfectants.

All lights and windows should be flush mounted in walls and ceilings for ease of cleaning and disinfection. Ultra Violet lamps may be provided in recessed, flush-mounted fixtures to maintain surface disinfection.

Separate entrances for personnel and equipment should be provided through specially designed air locks that are maintained at a negative pressure relative to the aseptic manufacturing area and at a positive pressure relative to environmentally controlled area.

Equipment should be designed for simplicity of operation and should be constructed for ease of disassembly, cleaning and sterilization.

Personnel must be trained in the proper mode of gowning with sterile, non shedding garments, and also in the proper techniques and conduct for aseptic manufacturing. Cool working environment should be maintained, with relative humidities controlled to between 40 and 60% RH.

Raw Materials: All raw materials used in the compounding of ophthalmic pharmaceutical products must be of the highest quality available. Complete raw material specifications for each component must be established and verified for each lot purchased.

Equipments: All tanks, valves, pumps, and piping must be of the best available grade of corrosion-resistant stainless steel. All product-contact surfaces should be finished either mechanically or by electro-polishing to provide a surface as free as possible from scratches or defects that could cause corrosion. Care should be taken in the design of such equipment to provide adequate means of cleaning and sanitization.

Types:

1. Ophthalmic drops
2. Ophthalmic suspensions
3. Ophthalmic lotions
4. Ophthalmic ointments
5. Ophthalmic inserts

6.4.1 Opthalmic Drops

Ophthalmic drops (solutions) are sterile aqueous/oily solutions, essentially free from foreign particles, suitably compounded and packaged for instillation into the eye. The ophthalmic drops must be protected from contamination during use and must be used within 2 weeks after first opening of the container. For this reason, they should be prescribed in small amount i.e. 5 to 10 ml.

Requirements:

(i) **Sterility:** They should be sterile.

(ii) **Tonicity:** They should be isotonic with lachrymal secretions

(iii) **Clarity:** They should be free from foreign particles, fibres and filaments.

(iv) **pH:** They should have almost neutral pH.

(v) **Preservation:** They should be preserved with a suitable preservative.

(vi) **Buffer action:** They should have buffering capacity.

(vii) **Storage:** They should remain stable during its storage.

(viii) **Package:** They should be packaged in dropper containers so that it must be easy to instill into the eyes.

Types of drugs supplied in the eye drops form are:

Antiseptics, Anesthetics, Anti-inflammatories, Mydriatics, Miotics and Diagnostic aids.

Formulation:

Ingredient	Examples
Vehicle	Water / non aqueous vehicle
Thickening agent	Methyl cellulose, CMC, Polyvinyl alcohol, PEG
Buffers	Borate buffer (Boric acid/borax) Phosphate buffer (Sodium acid phosphate/sodium phosphate) Citrate buffer (citric acid/sodium citrate)
Tonicity modifiers	Sodium chloride, boric acid
Antioxidants	Sodium metabisulphite and sodium thiosulphate
Preservatives	Phenyl mercuric nitrate/acetate, benzalkonium chloride, chlorohexidine acetate, chlorobutol, thiomersal
Chelating agents	Disodium edentate
Wetting agents	Polysorbate 20 and Polysorbate 80

Method of Preparation of Eye Drops:

(i) Dissolution: Dissolve the drug and excipients (all or part) in the water (all or part).

(ii) Sterilisation: Sterilise the solution by heat or by filtration through sterile depth or membrane filter media into a sterile receiver.

(iii) Addition of excipients: If the procedure is incomplete, the sterile solution is then mixed with the additional required sterile excipients such as sterile viscosity imparting agents, preservatives etc.

(iv) Make up the volume: Finally the volume is made up with sterile water.

(v) Filling and packaging: The solution after filtration is filled into borosilicate glass containers or plastic containers in aseptic condition. The containers are immediately closed using suitable closures.

(vi) Sterilization: A few drugs are dissolved in simple aqueous vehicles that are stable to normal autoclaving temperatures and times (121^{o}C for 20-30 minutes). Such drug products must be packaged in glass or heat resistant package which are terminally sterilized by autoclaving.

Most ophthalmic products are not stable to heat either physically or chemically.

Because of the product sensitivities, most ophthalmic products are aseptically manufactured and filled into previously sterilized containers in aseptic environments using aseptic filling and capping techniques. Such products are not terminally sterilized.

(vii) Labeling: The lable should contain the following directions :

"Not for injection."

"If irritation persists, discontinue the use and consult physician."

"Discard the preparation, if any particles are seen."

"Don't touch the tip of dropper to any surface."

6.4.2 Ophthalmic Suspensions

Ophthalmic suspensions are sterile biphasic liquid dosage forms containing solid particles dispersed in a liquid vehicle intended for application to the eye. These are not commonly used as compared to eye drops. These are preferred to formulate under the following conditions:

(i) When the drug is insoluble in the desired vehicle.
(ii) When the drug is unstable in solution form.
(iii) When sustained action is desired.

Requirements:

(i) Sterility: They should be sterile.
(ii) Tonicity: They should be isotonic.
(iii) Viscosity: They should possess desired viscosity.
(iv) Buffer action: They should have buffering capacity.
(v) Particle size: The particle size should be non-irritating and non-scratching to the cornea. The drug used is in a microfine form, usually 95% or more of the particles have a diameter of 10 micrometers or less.
(vi) Distribution of particles: The suspended particles must get distributed uniformly throughout the vehicle.
(vii) Storage: The suspended particles must not agglomerate into larger ones on storage.
(viii) Package: They should be packaged in dropper containers so that it must be easy to instill into the eyes.
(ix) Auxiliary lable: *S*hake well before use.

Examples of drugs used in the form of suspensions are:

(a) Tetracycline hydrochloride
(b) Oxytetracycline HCl and Hydrocortisone acetate
(c) Tobramycin and Dexamethasone
(d) Prednisolone phosphate

6.4.3 Opthalmic Lotions

Eye lotions are sterile aqueous liquids used for washing of the eyes.

Requirements:

(i) Sterility: They should be sterile.
(ii) Tonicity: They should be isotonic .
(iii) pH: The should have almost neutral pH.
Tonicity and pH in eye lotions is more important than in eye drops because of the large volumes administered. Additives such as buffers and isotonic salts are used for this purpose.
(iv) Preservation: These are generally used for single time and do not contain any preservative. If they are formulated for multiple use, these should contain a suitable preservative.

(v) Shelf life: They should be freshly prepared and should not be stored for more than 2 – 3 days.

(vi) Direction to use: These are usually supplied in concentrated form and are required to be diluted with an equal volume of warm water before use.

(vii) Mode of administration: These are usually applied with a clean eye bath or sterile fabric dressing and a large volume of solution is allowed to flow quickly over the eye.

(viii) Use: These are applied in relatively large volumes to remove foreign materials and to relieve irritation.

(ix) Labeling conditions: The lable should bear the same directions as that of eye drops.

The *examples of drugs* used for preparation of eye lotions are sodium chloride, sodium bicarbonate, boric acid, borax and zinc sulphate.

6.4.4 Ophthalmic Ointments

Ophthalmic ointments are sterile semisolid dosage forms meant for administration into the eye.

Requirements of ophthalmic ointment bases:

(i) Base must be non-irritating to the eye.

(ii) Base must permit the diffusion of the medicinal substance throughout the secretions bathing the eye.

(iii) Base must have melting or softening point close to body temperature.

(iv) Base must be able to sterilize and retain its sterility.

Examples of ophthalmic ointment base: The principal semisolid dosage form used in ophthalmology is an anhydrous ointment with a petrolatum base. Most commonly used base is

Yellow soft paraffin :	80 g
Liquid paraffin :	10 g
Wool fat :	10 g

Method of preparation: Melt wool fat, yellow soft paraffin on a water bath. Add liquid paraffin. Filter through coarse filter paper placed in a heated funnel. It is sterilized by dry heat method (160^{o} C for 2 hours). The drug is added to the ointment base either as a solution or as a finely micronized powder. The drug is then intimately mixed with the base, usually by milling.

White soft paraffin is not used in the preparation of ointment base because it is prepared by bleaching the yellow soft paraffin. Some of the bleaching agent may remain adhered to the base even after careful washing which when used in the eye may lead to irritation. Wool fat is used in order to ensure satisfactory emulsification of the solution and helps in the absorption of active ingredients. Liquid paraffin is incorporated to reduce the melting pint and viscosity of the base, so that it can be easily expelled from the collapsible tube and apply to the eye.

Filling: After preparation the ophthalmic ointments are filled into previously sterilized tin or plastic tubes. These tubes are typically small, holding approximately 3.5g of ointment and fitted with narrow gauge tips which permit the extrusion of narrow bands of ointment. The container components and the exterior surface of the final packages are sterilized by heat, ethylene oxide gas or ioning radiation.

General Method of Manufacturing Ointments:

(i) All raw materials used must be sterile or if possible ingredients are dissolved in water and is then sterilized by heat, filtration or radiation.

(ii) The ointment base is sterilized by heat and filtered while molten to remove extraneous foreign particulate matter.

(iii) The molten state of sterilized base is placed into a sterile steam jacketed kettle to maintain the ointment in a molten state under aseptic conditions.

(iv) Previously sterilized active ingredients and excipients are added aseptically.

(v) While still molten, the entire ointment may be passed through a previously sterilized colloid mill for adequate dispersion of the insoluble components.

Labelling: In addition to the general labelling requirements, the label on the container or on the sealed outer package enclosing an eye ointment, should indicate that the contents are sterile provided that the container has not been opened.

Advantage:

- The primary advantage of an ophthalmic ointment over an ophthalmic solution is the increased ocular contact time of the drug to increase drug bioavailability.

Disadvantages:

- Greasy nature
- Blurred vision which occurs as the ointment base melts and is spread across the lens.

Examples:

- Atropine sulphate eye ointment
- Hyoscine eye ointment
- Chloramphenicol eye ointment
- Hydrocortisone eye ointment
- Chlorotetracycline eye ointment
- Neomycin sulphate eye ointment
- Mercuric oxide eye ointment
- Tetracycline HCl eye ointment
- Gentamicin sulphate eye ointment

6.4.5 Opthalmic Inserts (Ocusert)

Ophthalmic insert is a dosage form that administers a drug or drugs at programmed rates, at a specific body site, for a prescribed time period to provide continuous control of drug therapy and to maintain this control over extended periods.

Shape and structure of the Ocusert: The Ocusert is a soft, flat, flexible, sterile and elliptical device with dimensions of 13.4 x 5.7 x 0.3 mm. The elements of Pilocarpine Ocusert system is shown in Fig. 6.1. Ocusert consists of (a) pilocarpine reservoir in alginate base, (b) rate controlling membranes of EVA (ethylene vinyl acetate) and (c) annular ring.

The platform component for the Pilocarpine Ocusert consists of the EVA copolymer membranes, which serve as the housing. An annular ring of the membrane impregnated with titanium dioxide forms a white border for visibility. The free-base form of pilocarpine is used, since it exhibits both hydrophilic and lipophilic characteristics. Drug diffuses through these membranes at a constant rate.

It is designed to be placed in the inferior cul-de-sac between the sclera and the eye lid and to release pilocarpine at constant rate of 20 or 40 µg per hour around the clock for 7 days. The rate of drug diffusion is controlled by the polymer composition, the membrane thickness, and the solubility of the drug. The devices are sterile and do not contain preservatives.

Advantages:

- The Ocusert exposes a patient to only one-fourth to one-eighth the amount of pilocarpine, compared with drop therapy.
- This could lead to reduced local side effects and toxicity.
- It provides precise controlled rate of delivery and therefore around-the-clock control of intra ocular pressure, where as drops used four times a day can permit periods where the intra ocular pressure might rise.
- The Ocusert provides for more patient convenience and improved compliance, as the dose needs to be administered only once per week.
- It is designed to provide for the release of medication at predetermined and predictable rates.
- It permits the elimination of frequent dosing by the patient.
- It ensures nighttime medication.

Disadvantages:

- The clinical experience seems to indicate that the Ocusert has a compliance problem of its own (i.e. retention in the eye for the full 7 days).
- The patient must check periodically to see that the unit is still in place, particularly in the morning on rising.
- Replacement of a contaminated unit with a fresh one can increase the price differential of the already expensive Ocusert therapy compared with inexpensive drop or once-a-day gel therapy.

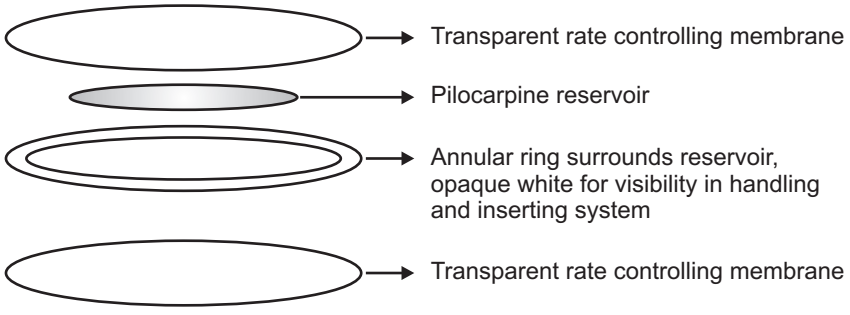


Fig. 6.1

6.5 PACKAGING OF OPHTHALMIC PREPARATIONS

Ophthalmic solutions, lotions and suspensions have been packed almost entirely in plastic bottles since the introduction of droptainer plastic dispenser. A few products still remain in glass dropper bottles because of special stability considerations.

1. Plastic Droptainer Bottles:

Advantages :

- Convenience of usage by patient.
- Decreased contamination potential.
- Lower weight and cost.
- Dispensing tip can be designed to deliver only one drop or a stream of fluid for irrigation, depending on pressure applied.
- If used properly solution remaining in bottle is only minimally exposed to air born contaminants during administration and thus will maintain very low to non-existent microbial content.

Disadvantage:

- The major disadvantage of plastic is opaqueness due to which it is difficult for inspecting clarity and precipitate formation or any other change in the solution.

Properties:

- The plastic bottle and dispensing tip is made up of low density polyethylene resin, which provides flexibility and inertness but the major problem being sterilization aspect i.e they cannot be autoclaved. The method of sterilization applicable is radiation sterilization (gamma-irradiation) or gaseous sterilization (ethylene oxide).
- A high density polyethylene resins can be utilized to overcome the problem of autoclaving, but it has its own disadvantage i.e. it is less flexible. The statement that they can be autoclaved may refer only to lack of visible change, however autoclaving may alter the physical properties of plastic and thereby affect the permeation, leaching and sorption of the container. Volatile components may also be lost. Radiation sterilization may also affect the physical properties of the plastic.
- Plastics used in containers for ophthalmics frequently contain residues from the polymerization processes, plasticizers, stabilizers, antioxidants, pigments, and

lubricants. Factors such as plastic composition, processing and cleaning operations, contacting media, inks, adhesives, absorption, adsorption and permeability of preservatives, and conditions of storage may also affect the suitability of a plastic for specific use.

2. Glass Dropper Bottles:

- These are used for products, which are extremely sensitive to oxygen or contain permeable components that are not sufficiently stable in plastic. The glass should be type-I for maximum compatibility with sterilization process and product. The glass container is made sterile by dry heat or moist heat.
- The use of colourants for caps attains a special importance. Red colour is used to denote mydriatic drug such as atropine, and green colour for mitotic drug like pilocarpine.

3. Metal Collapsible Tubes:

(a) Tin tubes: Ointments are packed in small collapsible tin tubes usually holding 3.5 g.

Advantages:

- It is compatible with wide range of drugs in petrolatum based ointments.
- Lower cost.

(b) Aluminium tubes:

Advantage: Aluminium tubes are used because of their lower cost.

Disadvantage: Internal coating is essential to impart the resistance.

4. Plastic Collapsible Tubes:

- The plastic tubes made form flexible low density polyethylene resins have been considered as an alternative material but they do not collapse and tend to suck back the ointment.
- A tube can be designed by selection of the laminate materials and their arrangement and thickness to provide the necessary compatibility, stability, and barrier properties. Laminated tubes are usually heat-sealed. The crimp usually contains the lot code and expiration date.
- The screw cap is made up of polyethylene or polypropylene. Poly propylene must be used for autoclave sterilization. Poly ethylene must be used for gaseous sterilization.

6.6 OPHTHALMIC POWDERS FOR RECONSTITUTION

Several drugs are prepared as sterile powders for reconstitution. Pharmacist reconstitute the preparation using diluent provided with the products before dispensing to the patient. To maintain the optimum potency and preservation of the reconstituted solution the diluent supplied must only be used.

The sterile powder is usually manufactured by freeze drying. Sterile dropper assembly is provided along with the container. This form is preferred over solution form when longer shelf life of certain drugs is required.

Examples: Alpha chymotrypsin, Echothiophate iodide

6.7 CONTACT LENS SOLUTIONS

Contact lenses are therapeutic ophthalmic devices meant for use in the eye. Contact lenses are divided into the following types:

1. Rigid, hydrophobic called 'hard lenses' made of poymethyl methacrylate (PMMA).
2. Rigid, semihydrophobic.
3. Flexible, hydrophilic called 'soft lenses'.
4. Flexible, hydrophobic and rigid gas permeable.

Each lens class is accompanied by its support solution products and devices.

1. Hard Contact Lenses:

They provide durability and clear crisp vision to the patient. These are made of a rigid plastic resin PMMA & hence called hard contact lenses. Therefore many people found them extremely uncomfortable to wear and tolerate. These are practically impermeable to O_2 and moisture, another disadvantage to corneal epithelial respiration and to patient comfort. Care must be taken to prevent the hard lens from resting directly on the corneal surface to protect the epithelial tissue from physical damage. To prevent such direct contact, solutions are used that wet the surface of the lens to provide a cushioning layer between the corneal epithelium and the inner surface of the lens.

Wearers of hard contact lenses generally use two solutions for the routine maintenance program:-

(a) Wetting solution: It is used primarily for treating the lenses before insertion. Due to its hydrophobic nature, polymethyl methacrylate is poorly wetted by the lachrymal fluid of the eye. Hence, the contact lenses require moistening with a wetting agent to make the insertion easy and comfortable. Since the contact lens solutions are required to be used daily for years together, they should be prepared carefully and all the ingredients used should be of good quality.

The formulation of contact lens solution

Wetting agent	Polyvinyl alcohols, polysorbate 80
Antimicrobial agent	Benzalkonium chloride, chlorobutol,
Isotonicity adjuster	Sodium chloride
Buffering agent	Boric acid/borax
Thickening agent	Polyvinyl alcohols, cellulose derivatives

(b) Storage solution: It is used for overnight cleansing, soaking and storage. The contact lenses after its removal from the eye are cleaned with wetting solution and rinsed with purified water. Then they are stored in a storage solution to prevent dehydration.

The formulation of storage solution contains a non-ionic surface active agent which will help in cleaning the contact lenses. It also contains preservatives to prevent the microbial growth. The solution should be changed after every few days because the preservatives may be practically inactivated by the organic materials present in the form of debris.

Contact lens solutions should be sterile. The lable should warn against contamination during use and encourage frequent changes of storage solution.

2. Soft Contact Lenses:

These are soft flexible type lenses made of a hydrophilic transparent plastic, hydroxyethyl methacrylate (HEMA) that contains 30-80% water. This increased water content of the lens improves its permeability to oxygen. These are of 2 types.

(a) Daily wear lenses: These must be removed at night before to sleep.

(b) Extended-wear lenses: These are designed to be worn for more than 24 hours upto 30 days. But it is advised not to leave them in the eye for more than 4-7 days, and remove for cleaning and disinfection.

Certain medicaments from eye drops and preservatives from wetting and storage solutions are strongly absorbed by the soft contact lenses. Due to this reason patients wearing soft contact lenses should be advised to remove them before instilling eye drops. For cleaning, soft contact lenses are heated in 0.9% sodium chloride solution. The wetting and storage solution used for hard contact lenses should not be used. Special proprietary storage solutions are available. The wetting of soft contact lenses is not a problem because of the hydrophilic nature of the lens. The storage solution should be sterile.

3. Rigid Gas Permeable Contact Lenses:

They take the advantage features of the soft and hard contact lenses. These are constructed of material that is oxygen permeable but hydrophobic. Thus they permit the transmission of oxygen through the lens more than hard lenses, while providing the durability and ease of handling as that of hard lenses. These may be either daily wear/extended wear.

6.8 EVALUATION OF OPHTHALMIC PREPARATIONS

6.8.1 Evaluation of Ophthalmic Suspension

Tests for Physical Stability (include the General Test):

(a) Sedimentation rate:

- The rate at which the suspension particles settle in the vehicle is called sedimentation rate.
- Ratio of the sedimentation volume to time gives the sedimentation rate.
- Different samples of the suspension are taken and sedimentation volumes are determined graph plotted between the sedimentation volume (on y-axis).
- Time (on x axis)-horizontal curve and slope of graph gives the sedimentation rate.
- Sedimentation rate should be low to facilitate installation of uniform dose each time.

(b) Redispersibility:

- The sediment formed during storage of the suspension should be easily redispersible by normal shaking to provide uniform dose at all time.
- Redispersibility depends on the surface tension of a suspension.
- Different samples are collected and surface tension of each is determined.
- Lesser the surface tension of a sample, more redispersible it is.

(c) Viscosity:

- Using Brookfield viscometer, the viscosity of different samples is determined.
- More is the viscosity of a sample, less is the rate of setting of particles and more is the stability.

(d) Particle size:

- Smaller particles settle at a slow rate and implicate the stability of a suspension
- Using coulter counter apparatus or photomicroscopy.
- The particle size of different sample is determined.
- Out of the 50 particles tested, 20 are not more than 25 μ, 10 are not more than 50 μ and no particle is more than 100 μ in size.

6.8.2 Evaluation of Ophthalmic Ointment

(A) Test for Minimum Fall:

- Nearly five ointment tubes are selected at random.
- Net weight of the ointment in each tube is determined.
- The result should match with the quantity specified on the label of the tubes.
- This test is to be as certain that each tube is filled with the minimum specified quantity.

(B) Test for Metal Particles:

- This test is to be as certain that the ointment is not contaminated by the particles of the packaging material which can irritate the ocular tissue.
- Different sample are collected from ten ointment tube.
- Each sample is melted using heat.
- Than examined under microscope for metal particles.
- The particles identified are counted and their size is measured with the help of eyepiece micrometer.
- For the total samples, the total number of metal particles (sized 10 μm or more) is more than 50 and only one sample contains more than 8 particles.

(C) Squeesability:

- Represent the product output and the minimum amount to be expelled out.

6.8.3 Evaluation of Ophthalmic Emulsion

The quality of the emulsion can be determined by:

- Globule size
- Globule size distribution
- Physical appearance
- Spreadability

6.8.4 Evaluation of Ophthalmic Gels

- Viscosity
- Clarity
- Spreadability
- Residence time

6.8.5 Evaluation of Ophthalmic In-situ Gel

(i) Gelling time:

- The time taken by the gel forming solution to transform into gel phase is called gelling time.
- The gelling time should be less so that the onset of action will be fast.

(ii) Viscosity:

- It is check at both room temperature and body temperature.

6.8.6 Evaluation of Ophthalmic Injection

1. Test for Pyrogens:

Ophthalmic injections are tested for the presence of pyrogen.

- Pyrogens are endotoxins which are produced by gram negative bacteria.
- The test for pyrogens is carried out on aqueous preparation also.
- Rabbits are the test animals which are considered for test for pyrogen of quick response and it should be around 1.5 kg.

(a) Selection of rabbit /animal: condition:

- The weight of the rabbit is 1.5 kg - 2.5 kg and it should be constant.
- It should be free from disease.
- Wash out period should be minimum of 2 weeks to be considered.

Procedure:

- The rabbit should have a normal temperature (body temperature of 38.3^{o}C- 39.4^{o}C (101^{o}F -103^{o}F).
- The body temperature greater than 49.8 ^{o}C should not be selected for the test.
- If any rabbit has been used for positive test during last 2 weeks or negative test during 2 days should not be selected again for the test.
- Syringes or needles or glass was used in this procedure should be free from pyrogen
- It can be sterilized by heat.
- The animal have to be fasted for 12 hours before the test and then injected to the ear vein.
- Observe the changes.
- Once after injection, the temperature has to be observed after 1-2 hours.
- The different initial and final temperature readings should not excess 1-4^{o}C (for average animal) and should not exceed 0.6^{o}C (for individual animal).

(b) LAL test (limulus amoebocyte lysate test):

- For identification of gram positive bacteria.
- Enzyme is produced by horse shoe crab.
- Test for particulate matter

To identify particulate matter, four different methods are used:

- Visual method
- Light blockage method
- Filtration method
- Coulter counter method

(i) Visual methods: The sample is filled in the container and is carried out to identified the foreign particles against black and white background in presence of light.

In case of colourless solution, white background is used and for coloured solution, black background is used.

(ii) Light blockage method: Instrument consists of bright white light source and photodiode sensor.

- The sample to be tested is allowed to pass through the instrument.
- The stream of the sample solution passes between the light source and photodiode sensor.
- The instrument measures the cross sectional area of the particles and size of the particles can be easily determined the method is employed for hydraulic oils.

(iii) Filtration method: The samples are filtered through membranes filter with pore size of 0.02 μm.

- The particle should be microscopy (to know the particle size and weight) if the particle is higher it has to be discard.

(iv) Coulter counter method: The coulter counter is an electrical method to determine the particle size.

- It consists of two electrodes and orifice.
- Electrodes are connected to an amplifier.
- When a particle passes through the orifice, increased electrical retention is observed.
- This is because, the particle displaces its own volume of the electrolyte, hence particle size is determined.
- Determined particle size of diameter below 0.1 mm.

2. Packaging Test /Test for Packaging:

(i) Leakage test: The test is carried out in ampoules.

- This method is employed to see whether the ampoules which are sealed by the fusion method are intact or not.
- In the vacuum chamber, vacuum is applied and ampoules are dipped in 1% sodium methylene blue solution.
- After releasing vacuum, the ampoules are checked for leakage if any evaluation are done by examining whether the dye enter the ampoules or not.
- If the preparation becomes coloured it indicates there is leakage in the container, hence the particular batch will be rejected.

(ii) Spark detector method: This is also a method determination of leakage in the container carried out if the pot present in the ampoules are thermobile (e.g. vaccine).

- Ampoule contains an inert gas and sample is introduced into the spark detector, the gas inside the ampulse gloves.
- Indicates that container is intact and free from any leakage.

QUESTIONS

Long essay Questions: (10 marks each)

1. Explain about the manufacturing facilities in ophthalmic preparation.
2. Describe in detail the factor affecting absorption of the drug in the eye.
3. Briefly explain the evaluation of ophthalmic preparation.

Short essay questions: (5 marks each)

1. Explain the manufacture of ophthalmic ointments.
2. Requirements for the ophthalmic preparation.
3. What are ocuserts? Explain briefly.

Short answer questions: (2 marks each)

1. What are the standards for ophthalmic preparation?
2. What are the preservative for ophthalmic preparation?
3. What are contact lenses? Classify them.

Chapter 7 ...

COSMETICS

Upon completion of the course the student shall be able to:

- *Know the manufacturing technique of different cosmetics preparations.*
- *Know various formulation and development of cosmetic preparations.*
- *Evaluate different preparations and evaluate their quality.*
- *Explore a vast knowledge regarding skin, hair, oral hygiene and bath preparations used as cosmetics.*

7.1 INTRODUCTION

Cosmetic is a greek word which means adorn. It may be defined as a substance which comes in contact with the various part of human body like skin, hair, nail, lips, mucous membrane etc. Cosmectic substance helps in changing the appearance of the body and also makes the odour of the body, it protects the skin and keep it in a good condition. In general, cosmetic are external preparation which is applied in the external part of the body.

Examples of cosmetics: Skin-care creams, powder, lotion, lipstick, nail-polish, eye and face make-up, deoderants, baby-makeup hair colourants and spray.

Uses of Cosmetics:

1. They are used as cleansing, moisturing and beautifying agent.
2. They help in enhancing the attractiveness of the body.
3. They help in altering the appearance of the body.
4. Sunscream helps the body to protect from the UV.
5. Acne, wrinkles, dark-circles can be treated by the beauty products.
6. Cosmetics can treat the skin infection.

7.2 LIPSTICKS

Definition: Lipsticks can be defined as dispersion of the colouring matter in which a base consisting of a suitable blend of oils, fats and waxes with suitable perfumes and flavours moulded in the form of sticks to impart attractive gloss and colour, when applied on lips.

Lipsticks impart moist appearance to the lips by disguising their defects.

Ideal Characteristics of Good Lipsticks:

The ideal requirements for a good lipstick may be as follows:

1. It should effectively cover lips with colour and impart a gloss which would last long.
2. It should not alter in the degree of its shade and maintain intensity of colour.
3. It should adhere firmly to the lips and should not provide any grease, appearance.
4. It should possess good shear thinning property so as to deposit the colour with minimum pressure.

5. It should show a smear proof colouring effect.
6. It should possess required plasticity and be able to maintain all the properties throughout the storage period.
7. It should not be grainy.
8. It should be easily dried.
9. The stick should possess even firmness and should maintain its strength at varying temperatures upto 55°C.
10. The stick should not dry or break easily.
11. The lipstick should possess a nice aroma and a good flavour.
12. It should be safe and non-irritating to the lips.
13. It should not result in blooming or sweating of the lips.

7.2.1 Formulation of Lipstick

Composition:

Ingredients	Examples
1. The solid components waxes: (a) Hydrocarbon waxes (b) The mineral waxes (c) Hard waxes (d) Microcrystalline waxes	 White bees waxes Ozokerite wax, ceresin wax Carnauba wax, candellila wax
2. The liquid component	Mineral oil, vegetable oil, castor oil
3. The softening agent	Anhydrous lanolin, lecithin
4. The colouring agent	Carmine, pigmented stain
5. Pearlescent pigment	Guanine crystal
6. Opacifying agent	Titanium dioxide
7. Perfumes	Rose oil, cinnamon oil
8. Miscellaneous agents: (a) Preservative (b) Antioxidant (c) Flavouring agent	 Prabeans BHA, BHT Cinnamon oil, spearmint oil etc.

1. The Solid Components/Waxes:

The solid components are responsible for the final structure of the product by solidifying liquid matrix.

(a) Hydrocarbon waxes: White bees wax: It is also known as common wax and forms the oily base in the formulation of the lipstick.

Uses:

- It forms important base to entrap the castor oil.
- It has good plastic property and can be readily deformed.
- It is used as traditional stiffing agent.

Advantages:

- It is compatible with vegetable mineral and animal waxes.
- It can be moulded to the required form.

Disadvantage:

If concentration is more than 20% then it forms dull film.

(b) Mineral waxes: Microcrystalline waxes have replaced the mineral waxes but still used as the same name.

(i) Ozokerite wax:

Uses:

- It increases the melting point of the base.
- It can be easily transferred to the required base.

Advantage: It is available in different bases.

Disadvantage: It may be subjected to adulteration.

(c) The hard waxes: These are mainly responsible for the shape and hardness of the lipstick.

Uses:

- Provide rigidity to the stick
- Helps in modifying by shrinking the stick

Disadvantage:

It is not miscible with the other waxes and remain as separate solid phase

(d) Microcrystalline waxes: These are hydrocarbon containing long carbon chain.

Uses: Maintains crystal structure of the lipstick.

Disadvantage: Possess low solubility in the castor oil.

2. The Liquid Components:

These are mostly constituted by oil such as mineral oil, vegetable oil, castor oil, alcohol, etc.

(a) Minerals oils :

- Contain blend of hydrocarbon from the petroleum source.
- Available as light mineral or heavy mineral oil.

(b) Vegetable oil: sesame oil and olive oil may be used.

(c) Castor oil: Obtained from the castor plant, Ricinuscommunis.

- Forms valuable lipstick base.
- High viscosity and good dissolving power.
- Posses stability towards oxidation.
- Easily compatible with other ingredients.

7.2.2 Preparation of Lipstick

Successful preparation of lipstick shades depend upon the adequate dispersion of the lake colours in the lipstick mass. It is advisable to prepare the dispersion of lake colours in castor oil. Dispersions arc generally prepared by milling about 25% concentration of lakes in castor oil.

Method of Preparation:

1. If the solvent is used for the dissolution of bromo acid, the solution is first prepared and set aside.

2. If commercial colour pastes are not used, then lake colours are first dispersed by mixing.
3. The colour paste is passed through the triple roller mill until it become soft and free from grittle particle.
4. The colour acid is now mixed with bromo acid mixture.
5. All ingredients are then arranged in increasing order of their melting point.
6. This mixture is remilled until it is perfectly smooth.
7. Preservative and anti-oxidant are mixed in the remaining oil.
8. Finally perfume is added and mass is stirred.
9. Automatic ejection mould is preferred for the large scale production.
10. The mould is lubricated with liquid paraffin or isopropyl myristate before pouring mass into mould.
11. It is important to prevent settling down of colouring mass when moulds are cooled.
12. Lubrication facilitates the easy removal of the stick.

7.2.3 Evaluation of Lipsticks

The efficiency, stability and the consistency of the finished product can be determine by the evaluation studies

The evaluation tests for the lipsticks are as follows:

1. **Melting point determination test:** The determination of melting point is done in order to determine the storage characteristics of the product.
   The melting point of lipstick base should be between 60-65^{o}C which will avoid the sensation of friction or dryness during application.
   The method of determination is known as capillary tube method :

(a) Here in this method, about 50 mg of lipstick is taken and is inserted into a glass capillary tube open at both ends.

(b) The capillary tube is ice cooled for about 2 hours and then placed in a beaker containing hot water and a magnetic stirrer.

(c) The temperature at which material starts moving through the capillary is said to be the melting point temperature.

(d) Another important parameter is the droop point which determines the temperature at which the product starts oozing out the oil and becomes flattened out.

2. **Microbiological test:** The test is carried out in order to determine the extent of contamination either from the raw materials or mould. The test involves the plating of known mass of sample on two different culture media for the growth of microorganism and incubating them for a specific period of time. The extent of contamination can be estimated by counting the number of colonies.
3. **Test for rancidity:** The oxidation of oil such as castor oil and many other ingredients may result in bad odour and taste and also result in a sticky product. The test for rancidity can be done by using hydrogen peroxide and determining its peroxide number.

4. **Test for the application force:** This is a test to determine the force to be applied during application. In this method, two lipsticks are cut to obtain flat surfaces which are placed one above the other. A smooth paper is placed between them which is attached to a dynamometer to determine force required to pull the paper. The pressure reading indicates the force of application.
5. **Storage stability:** This test is done in order to determine the stability of product during storage.
6. **Stability to oxidation:** The oxidative characteristics of the finished product are determined in order to check the stability of the product to oxidation. The extent of oxidation can be determined by peroxide number of product after exposure of substance to oxygen for a specific period of time.
7. **Determination of surface characteristics:** The study of surface property of the product is carried out in order to check the formation of crystals on the surface or the contamination by microorganisms or formation of wrinkles or the exudation of liquids.
8. **Determination of colour dispersion:** The test is done in order to determine the unit or in dispersion of the colour particles.

7.3 SHAMPOO

Simple procedure is involved in the preparation of shampoo. Initially only one method available for the preparation of shampoo, but later the basic method was modified in order to obtain different type of shampoo like cream, gel, aerosol etc.

Formulation of Liquid Shampoo:

Formula	Quantity for 100 g
Triethanolamine lauryl sulphate (surfactant)	50 g
Lauricisopropanolamine (foam booster)	2 g
Perfume, colour, preservative	q. s.
Water	48 g

7.3.1 General Method for Preparation of Shampoo

Liquid shampoo is usually prepared by this method which involves the following steps:

1. Initially the detergent is converted into a solution form or a detergent solution may be directly obtained from the manufacturer.
2. Take about half of the detergent solution into a separate container. To it, add the total amount of secondary surfactant i.e., alkanolamide.
3. Dissolve the alkanolamide along with stirring. Sometimes, gentle heat is also applied.
4. To the remaining half of the detergent solution add suitable amount of perfuming agent and dissolve it.
5. The perfume solution is then added to the alkanolamide solution.
6. Colour and preservatives are dissolved separately in sufficient volume of water and then added to the main solution.

7. The whole solution is mixed well by gentle stirring. Excessive stirring may lead to bubble formation.
8. Final volume of the preparation is usually adjusted by the addition of clear sterile water. This gives clear liquid shampoo.
9. However, when the preparation contains lauryl alcohol ether sulphate. It is required to adjust the viscosity of the shampoo.
10. Viscosity adjustment is done by using an electrolyte solution. Usually, a solution of sodium chloride is added subsequently with constant stirring. Care must be taken to prevent the excess addition of sodium chloride.

7.3.2 Methods of Preparation

The methods of preparation of various types of shampoos are modification of the above mentioned general method of preparation of shampoos.

Formulation of Cream Shampoo:

Formula	Quantity for 100 g
Sodium lauryl sulphate (surfactant)	38 g
Cetyl alcohol (builder)	7 g
Perfume, colour, preservative	q. s.
Water	55 g

Preparation of Cream Shampoo:

Certain formulae of cream shampoo may include glycol stearate or waxes. Usually, glycol stearate is used as an opacifier and preparation method for such formulae is similar as discussed above. But when wax is included in the formula, the process involves the following steps.

(a) Initially, a solution of detergent and water are heated to about 80°C.
(b) The wax is heated separately in a container at 80°C which facilitates the melting of wax.
(c) Both the solution are kept at 80°C and mixed. Uniform mixing is achieved by constant and gentle stirring.
(d) The solution is allowed to cool about 40 to 45°C
(e) Finally under warm condition mixture is transferred to suitable condition.

Formulation of Gel Shampoo:

Formula	Quantity for 100 g
Alkyl dimethyl benzyl ammonium chloride	15 g
Triethanolamine lauryl sulphate (surfactant)	28 g
Coconut diethanolamide	7 g
Hydroxyl propyl methyl cellulose	1 g
Perfume, colour, preservative	q. s.
Water	49 g

Preparation of Gel Shampoo:

The method involved in the preparation of gel shampoo is similar to the clear liquid shampoo. After preparation the liquid shampoo is usually treated with suitable thickening agent and gelling agent such as hydroxyl propyl-methyl cellulose, this gives the gel consistency.

7.3.3 Evaluation of Shampoo

Shampoos are evaluated for the following aspects.

1. Evaluation of safety
2. Evaluation of anti-microbial property

1. Evaluation of Safety:

Safety is an important aspect which must be considered as first and foremost parameter of evaluation. As stated earlier, the shampoos are made from synthetic detergent which irritate the skin scalp and eyed.

(a) Draize test : Safety is determined by using Draise test which suggests two separate methods for testing skin and eye toxicity. The following steps are involved in the test:

(i) Six albino rabbits were selected weighing 2 kg.
(ii) Round patch is made on each of the rabbit skin by removing hair.
(iii) Apply dilute preparation of shampoo on each patch.
(iv) Shampoo will react for 2-3 hr and then it is removed.
(v) After washing the skin is examined for any irritation
(vi) Based on result obtained shampoo is evaluated as safe or toxic.

(b) Eye-toxicity test : The following steps are involved in the test:

(i) Six adult albino rabbit are selected
(ii) One eye is considered as test and another as control eye.
(iii) To each eye the product is applied.
(iv) Washing is done with tap water for 20 seconds.
(v) Eye are rewashed after 5 minutes and then after 24 hours.
(vi) The control eye is also washed on first day and then after 24 hours.
(vii) The test eyes are observed at 1, 24, 48 and 72 hours respectively.
(viii) The product is considered to be toxic if there is development of iris and corneal lesions which remain for more than 7 days.

2. Evaluation of Anti-microbial Activity:

Shampoo is liable to microbial growth because they are liquid or viscous preparation. So preservative is usually added to stop such growth.

Evaluation of preservative usually involves the study of anti-microbial activity. This is usually done by method called “challenge study”.

Procedure for Challenge Study:

(a) Species like *pseudomonas* are selected.
(b) A culture of any one of the test organism is prepared.

(c) The product is inoculated in culture media for a period of 10-12 weeks.
(d) Inoculums usually contain 5 lakhs to 1 crore microorganisms.
(e) Two types of samples are prepared, one with preservative and one without preservative.
(f) The test come to the conclusion only when it has been proven that product has not supported the microbial growth.

7.4 COLD CREAM

These types of emulsions are water-in-oil type of emulsions. They produce cooling sensation by the evaporation of water, after application of cream to the skin. Hence, they are known as creams. They should produce emollient action by the layer left on the skin after application, should be non-occlusive.

Formula	Quantity for 100 g
Beeswax	8 g
Mineral oil (light liquid paraffin)	20 ml
Borax	0.5 g
Distilled water	10 ml
Perfume	q.s.

Method of Preparation of Cold Cream:

1. Beeswax is melted in a container by using water bath to temperature of about 70°C.
2. The mineral oil is added to the melted beeswax. This is mixture A.
3. In another container water is heated to the temperature of about 70°C and borax is dissolved in it. This is mixture B.
4. Mixture B is added slowly to the mixture A along with stirring.
5. Finally perfume is added to the formulation.

7.5 VANISHING CREAMS

They are oil in type of emulsion. When applied on the surface of the skin, they spread as thin oil less film which is not visible to the naked eye. Hence, they are called as vanishing creams. They are used to hold powder on the skin as well as well as to improve adhesion.

7.5.1 Properties of Vanishing Creams

1. It should have high melting point.
2. It should be pure white in colour.
3. It should posses very little odour.
4. It should have less number of iodine.

7.5.2 Use of Glycerin in Vanishing Cream

1. Helps to soften and protect the skin and prevent chaps.

7.5.3 Ingredients of Vanishing Creams

Ingredients	Uses
1. Main Ingredient: Example: Stearic acid	It governs the consistency of the cream and imparts pearlescent property to the cream by forming crystals.
2. Humectants: Examples: Glycerin, sorbitol	It prevents excessive drying of the cream.
3. Alkalies: Examples: (a) Potassium hydroxide	It imparts fine texture and consistency without providing harshness.
(b) Sodium hydroxide	It is used in combination with potassium hydroxide because it forms hard cream, when used alone.
(c) Carbonate i.e., potassium and sodium carbonate	Due to the creams become spongy.
(d) Ammonia	It is effective but difficult to handle and it makes cream yellow in colour.
4. Emulsifying agent Examples: Triethanolamine soap	These provide cream with less luster.
5. Purified water (Distilled and deionized)	Provides stability to the cream because hard water leads to the formation of the magnesium causing inversion of emulsion
6. Preservatives	Prevents deterioration caused by the bacteria.
7. Perfume Examples: Sandal wood, lavender oil	Imparts odour to the preparation.

7.5.4 Method of Preparation of Vanishing Creams

1. Stearic acid melted in container by using water bath.
2. Potassium hydroxide dissolved in water and glycerine is added and heated to the temperature of 75°C.this is called aqueous phase.
3. Slowly aqueous phase is added to the melted stearic acid
4. Perfume is added to the preparation when it attains 40°C.

7.5.5 Evaluation of Vanishing Creams

Evaluation of Vanishing creams is carried out by the following methods:

1. In-vitro method, and
2. In-vivo method.

1. In-Vitro Method of Evaluation:

Tests are carried out to know the performance of the product. Various instruments have been used by the investigator to evaluate the effect of temperature and humidity.

Various instruments used in in-vitro method are as follows:

(a) Tensile strength tester
(b) Hargen's Gas Bearing Electron dynamometer (GBE)
(c) Occlusive potential of ingredient
(d) Gravimetric analytical method
(e) Thermal analytical method
(f) Electrical methods.

(a) Tensile strength tester: This method is useful for determining the tensile property of the exercised stratum corneum of the skin. The stress or strain characteristics of stratum corneum obtained from various sources can be studied by using this instrument.

(b) Hargen's gas bearing electro dynamometer: It determines the visco-elastic behavior of the skin. It also determines the effect on the skin. It is used both in-vitro and in-vivo test.

(c) Occlusive potential of ingredient: The occlusive potential of raw materials or ingredients used in formulation of the creams, are determined by knowing the water diffusion rate.

(d) Gravimetric analytical method: This method is helpful in establishing relationship between water content present in strarum corneum and relative humidity. This is done by suspending bits of callus.

Water content = Dry weight of the tissue – Equilibrium value.

(e) Thermal analytical methods: Various thermal analytical methods are used in order to provide information about the effect of temperature which cause change in stratum corneum.

(f) Electrical methods: Various electrical properties such as capacitance, impedance and dielectric constant are measured by electrical methods provide information about the variation in the water content present in the stratum corneum of the skin.

2. In-Vivo Method of Evaluation:

(a) Transpirometry
(b) Scanning Electron Microscopy (SEM)
(c) Optical Microscopy and Macrophotography
(d) Skin friction
(e) Sensitivity test.

7.6 TOOTH PASTES

Dentrifrices such as toothpaste, toothpowder, and tooth gel are meant for cleaning the surface of the teeth by removing the food debris and plaque adhered to the surface of the teeth which is the main cause for tooth problem.

7.6.1 Formulation of Tooth Pastes

Ingredients	Examples
1. Agents responsible for cleansing action: (a) Polishing agents/ Abrasive agents (b) Foaming agents/ Surfactants	(a) Precipitated calcium carbonate (b) Phosphates of calcium (c) Dental graded silica (d) Trihydrated alumina (i) Sodium lauryl sulphate (ii) Sodium lauryl sarcosinate
2. Agents responsible for formation of toothpaste: (a) Humectants (b) Gelling agents/ Binding agents	(a) Sorbitol 70 (b) Glycerine (c) Propylene glycol (i) SCMC (ii) Cellulose ethers
3. Agents for improving palatability: (a) Sweetening agent (b) Flavouring agents	(a) Sodium saccharin (b) Chloroform (c) Cinnamol oil (d) Spearmint oil
4. Miscellaneous ingredients: (a) Colouring agent (b) Whitening agent (c) Preservative (d) Therapeutic agents	 (a) Titanium dioxide (b) Hydrogen peroxide (c) Sodium benzoate (d) Xanthum gums

1. Polishing Agents/ Abrasive Agents:

(a) Precipitated calcium carbonate: Also known as precipitated chalk and is available in a number of grades.

Advantages:

- It is of very low cost.
- Available in different grades in white or off-white colour.

Disadvantage

- It is incompatible with sodium fluoride which is used as anticaries agent.

(b) Phosphates of calcium: A large variety of insoluble calcium phosphate are used as abrasive agents.

Advantages:

- It provide good flavor stability.
- It has less abrasive effect on dentine.

Disadvantage:

- It is incompatible with sodium fluoride.

(c) Dental grade silica: These are polymers of silica which are used as abrasive agent in formulation of toothpaste in large quantities. These are available in two forms:

(i) Abrasive form of silica.

(ii) Thickening form of silica.

Advantages:

- Mostly used as abrasive in gels.
- They are inert and easily compatible with other ingredients.

Disadvantage:

- Abrasive property is not consistent.

(d) Trihydrated alumina: It is available as suspension or crystalline powder.

Advantages:

- It is less costly.
- It possesses stability with fluorides.

Disadvantage:

- It has poor thickening property.

2. Foaming Agents/ Surfactants:

These are also known as wetting agents. The mechanism of cleansing action is by reducing the surface tension at the interface of the adhered material and enamel of the teeth.

The properties of the surfactant are as follows:

- Should be compatible with other ingredients of the formulation.
- Should possess good surface active property.

The most commonly used surfactants are:

(a) Sodium lauryl sulphate.

(b) Sodium lauryl sarcosinate.

3. Humectants:

Humectants are used in order to prevent the rapid drying of dentifrices. They prevent excessive moisture loss from product. They may additionally impart plasticity to the final product.

The most commonly used humectants in the formulation of dentifrices are as follows:

(a) Sorbitol 70

(b) Glycerin

(c) Propylene glycol

7.6.2 Preparation of Toothpaste

Toothpastes are prepared by following methods:

1. Dry gum method
2. Wet gum method

1. Dry Gum Method:

(a) All solid components except surfactants are mixed together in a dry mixer.

(b) The liquid components such as humectants and water are gradually added to the dry mix.
(c) The mixing is carried out till smooth paste is formed.
(d) The remaining ingredient such as surfactant and flavouring agents are added to paste under vacuum.

2. Wet Gum Method:

(a) All liquid components are mixed to form liquid phase.
(b) The binding agent is the mixed with liquid phase with uniform stirring.
(c) The solid ingredients excluding the surfactants are the gradually added to the mucilage with uniform mixing in an agitation mixer, in order to form homogeneous paste.
(d) The remaining ingredients i.e. surfactants, flavouring agent, colouring agents are added under vacuum to the homogeneous paste.

7.6.3 Evaluation of Toothpaste

1. Tests for Abrasive Character:

The cleansing action of dentifrices mainly depends on their abrasive property. The abrasion should not lead to any damage to the enamel and hence the test for checking abrasion has been done on the extracted teeth.

2. **Determination of particle size:** The particle size is determined by the microscopical techniques or by involving the method of sieving.
3. **Test for cleansing property:** In this the tooth cleanser such as powder, paste are brushed onto polyester film and the change in reflectance character of lacquer coating is measured.
4. **Determination of the consistency of the product:** For the maintenance of the flow property all throughout the storage period, determination of the consistency is done.
5. **Determination of pH of the product:** 10% solution of the paste in water is made and pH of the dispersion is measured using pH meter the pH should be in the range of 4.4 to 6.8 in order to maintain the consistency of the product.

7.7 HAIR DYES

Hair dyes (colourants) are the cosmetic preparations which are used by men and women either to change the natural hair colour or to mask grey hair. The properties of typical hair colourants are:

- The formulation of the hair colourant should be stable.
- They should colour the hair evenly.
- They should not lead to loss of the natural shine of hair.
- The shaft of the hair must not be damaged.
- The natural moisture of the hair must not be lost.
- Must possess properties like non-irritant and non-sensitizing.
- Must be non-toxic in nature. Must impart stable colour to the hair.
- The coloured hair must be unaffected by air, water, sunlight, sweat, friction, shampoos, lotions, gels, oils etc.

7.7.1 Classification of Hair Colourants

The major classification is listed as follows:

1. Temporary hair colourants.
2. Semi-permanent hair colourants/Direct dyes
3. Oxidative dyeing systems: It includes:
   (a) Semi-permanent hair colourants.
   (b) Permanent hair colourants.
4. Gradual hair colourants.
5. Natural dyes.

1. Temporary Hair Colourants:

They are leave-in preparations. The hair is not rinsed after the application of the colourant. The colourant is easily removed with one wash using a shampoo because they are absorbed in to the cuticle and cannot enter into the cortex of the hair. They are rarely called as water rinses.

Basically temporary hair colourants consist of dye stuffs and acid. The different dye stuffs are acid dyes, basic dyes, metalized dyes and disperse dyes. Chemically the dye stuffs are azo dyes, anthraquinone dyes, benzoquinoneimine dyes, triphenyl methane dyes, phenazanic dyes and xanthenic dyes. The hair colourants are available in different formulations like powders, crayons, liquids and shampoos.

2. Semi-permanent Hair Colourants / Direct Dyes:

These colourants have a long lasting. colour retaining ability when compared to colour shampoos. The colour produced is stronger as well. Dark colours are obtained with the colourants though they do not contain H_2O_2. This offers an advantage that the melanin of the hair doesn't get bleached but is only masked with the colourant. The colour obtained on the grey hair is different than the black (pigmented) hair because of which the hairs are highlighted. The colourants are easily applied. This colour is not lost with one wash, but is gradually lost in 5 - 8 washes with shampoo. Fragrance may be added in the composition of the colourant.

Ingredients: The semi-permanent hair colourants are composed of the following constituents.

(a) Dye
(b) Water
(c) Organic solvent like alcohol, derivatives of glycol.
(d) Fatty acid, fatty acid amide.
(e) Thickener.
(f) Surfactant
(g) Perfume
(h) Aliphatic primary amines which work as co-solvent and buffer.
Example: 2-amino, 2-methylpropanol.

3. Oxidative Dyeing Systems:

These dyes are also called as 'para dyes'. At the time of application, these dyes are colourless, but turn to a particular colour after undergoing chemical reactions on the hair. The chemical reactions include the following reactions in alkaline pH, which are oxidation and coupling and condensation.

Ingredients: The ingredients of these dyes which render the above reactions are bases, couplers and oxidizing agent.

4. Gradual Colourant:

It includes heavy metals in its composition. The hair is gradually coloured with several application of the colourant. The heavy metals used are lead or bismuth in their salt forms. The salts of the heavy metals are made into solutions and are used in the preparations. The preparation is applied many times because the colour develops gradually.

Demerit: Since, the preparation includes heavy metals, it offer negative effects on the health. Therefore the use of these colourants is declined.

5. Natural dyes:

Since, antiquity, plant materials are looked upon as beneficial sources for various ailments and other purposes. The leaves are used as colourants:

(a) Henna: The leaves of henna are powdered and sold. The paste is formed by mixing the henna powder in hot water. The paste is directly applied on hair and a warm towel is wrapped around the head to enhance the colouring effect. lt gives reddish colour to the hair. Henna is non-toxic and non-sensitizing.

The active constituent of henna is lawsone, which is chemically 2-hydroxy-l4 - naphthaquinone. It is responsible for imparting the colour. Indigo leaves or synthetic indigo is added to henna to alter the colour. Apart from this, pyrogallic acid and metallic salts like copper sulphate are added. An increased level of pyrogallic acid added to henna, gives darker shades.

(b) Camomile: The flowers of camomile are used to obtain the colour. The flowers which contain the active principle are powdered. Its paste is made by mixing the powder with hot water and applied on the hair. A warm towel is wrapped over the head to enhance the colouring effect. The colour achieved is due to the navy blue volatile oil obtained in the process.

7.7.2 Formulations of Hair Dyes

1. Formulation bases
2. Alkalizing agents.
3. Dye components: It includes oxidation base and coupling agent.
4. Oxidizing agents
5. Antioxidant.
6. Solvents
7. Surfactants

1. **Formulation bases:** They are used as vehicles for dyes (amino dyes) and modifiers. The vehicle is one which uniformly distributes the colourant mixture on the hair. Example: In amino dyes, a mixture of water (48-7945%), ethyl alcohol (20-50%) glycerin (0.5 - 2%) is used because the amino dye has low aqueous solubility.
2. **Alkalizing agents:** The alkalizing agents are added.
   - To increase the pH of the formulation to an optimal level.
   - To generate active oxidizers from hydrogen peroxide.
   - To swell the hair fibres for absorption of dye.

   Examples of alkalizing agents include ammonia, Monoethanolamine.
3. **Dye:** Dyes are used to impart the desired colour shade to the hair.
4. **Oxidizing agents:** Oxidant is added in the composition of the colourants to generate active species (like p-phenylene diamine, benzoquinone monoamine) for coupling. Oxidants are used to bleach melanin present in the hair. Light colour shades are obtained when the grey and pigmented hair are coloured evenly by using semipermanent colourants.
5. **Antioxidant:** During the manufacturing of dyes, especially amino dyes, an atmosphere of nitrogen is maintained to prevent the darkening of the dye. Since dyes (amino dye) are darkened on exposure to air. Instead of maintaining nitrogen atmosphere, chemical antioxidant like sodium sulfite is included in the preparation.
6. **Solvents:** The constituents of the colourants which are not soluble in water, are dissolved by using solvents, so that a homogenous system is obtained.
7. **Surfactant:** It reduces the surface tension between the different ingredients, to make a homogeneous preparation.

Method of Preparation of Colourant:

Formula	Quantity for 100 g
Quaternary ammonium compound (colour)	10-12 g
Anionic surfactant (surfactant)	8-10 g
Acid (buffer)	6-8 g
Alkanolamide (surfactant)	4-6 g
Dye stuff (colour)	1-2 g
Water(solvent)	To make 100 g

- A mixture of alkanolamide and anionic surfactant is prepared.
- The dye is added to the above mixture* and is dissolved.
- The acid and quaternary ammonium compounds are dissolved in water.
- This aqueous solution is added to the solution of dye with stirring.
- This dye is investigated for the effects of quaternary ammonium compound, pH, aldehydes and alcohols additions.

- Now the viscosity of the dye is adjusted by adding hydrophilic colloids like methylcellulose, natural gum etc.
- The viscosity of the colourant is increased by the addition of non-ionic thickener in its composition. The addition of amphoteric surfactant in the colourant accompanied by basic dyes.

7.7.3 Evaluation of Hair Colourant

The following tests are carried out to evaluate hair colourants:

1. The Sensitization Test: The test is carried out on animal skin. The colourants applied on the skin and is kept under observation for 24 hrs. If no reaction occurs, then the colourant is said to be non-sensitizing or non-irritant. Histopathological study is carried out as per requirements.

2. The Toxic Effect Test: Toxic effects are studied in animals to know about the long term effects of the preparations.

7.8 SUNSCREEN

- Sunscreen, also known as sun block, sun cream or suntan lotion, is a lotion, spray, gel, foam (such as an expanded foam lotion or whipped lotion), stick or other topical product that absorbs or reflects some of the sun's ultraviolet (UV) radiation and thus helps to protect against sunburn.
- The purpose of sunscreen is to either scatter sunlight effectively or to absorb the erythema part of sun's radiation.
- Diligent use of sunscreen can also slow or temporarily prevent the development of wrinkles, moles and sagging skin.
- The use of sunscreen preparation has attained importance in the cosmetic field suntan preparation are divided into three classes
  (i) Preventive
  (ii) Simulatory
  (iii) Therapeutic
- Sunburns may be prevented by the shading of the surface of the body as well as by the use of the chemicals that screen out certain rays of the sun.

7.8.1 Classification of Sunscreens

1. Chemical sunscreens (i.e., those that absorb the UV light)
2. Physical sunscreens (i.e., those that reflect the sunlight)

1. Chemical (Organic) Sunscreens:

- Organic UV filters are active ingredients that absorb UV radiation within a particular range of wavelengths, depending on their chemical structure.
- Once the UV filter absorbs energy, it moves from a low-energy ground state to a high-energy excited state.

2. Inorganic (Physical) Sunscreens:

- Zinc oxide
- Titanium dioxide
- Others: iron oxide, petrolatum, kaolin, calamine, Ichthammol (Aluminum Bituminosulfate), talc
- Inorganic agents function by reflecting, scattering or UV radiation (Opaque)
- Their opaque nature and "whitening effect" are an inherent disadvantage, which may be minimized by the use of micronized or ultrafine particles.

7.8.2 Benefits of Sunscreen

- Sunscreen use can help to prevent melanoma and squamous cell carcinoma.
- There is little evidence that it is effective in preventing basal cell carcinoma.
- Sunscreen can slow or temporarily prevent the development of wrinkles and sagging skin.
- Reduces skin discolouration.
- Skin lighting benefits.
- High UVA and UVB protection.
- Prevention of brown spots and pigmentation,
- Protection against pollutants.

7.8.3 Ideal Characteristics of Sunscreen

- It should absorb erythmogenic radiations in the range of 290-320 nm without its break down.
- It should allow full transmission of radiation in the range of 300-400 nm for tanning effect.
- It should be non-volatile.
- It should have suitable solubility characteristics in suitable vehicle.
- It should be stable to heat, light and perspiration.
- It should be mild or odorless.
- It should be non-toxic, non-irritant and non-sensitizing.
- It should be capable of retaining its sun screening property for several hours.
- It should not stain the body.
- It should be neutral.

7.8.4 Sunscreen Preparation

1. Sunscreen Lotion (Solution Type):

Method:

- Heat the water, dissolve the borax in it and add the salicylate.
- Stir until dissolved.
- Mix the perfume with the alcohol, add the glycerin and stir this into the methyl salicylate solution.
- Filter, if it is desired to colour the solution, add sufficient quantity of alcohol soluble colourant.

Formula	%
Methyl salicylate	9.0
Glycerin	3.0
Borax	2.0
Alcohol	15.0
Water	70.5
Perfume	0.5

2. Sunscreen Cream:

Part A

Formula	%
Coca butter	6.0
Petrolatum and lanolin alcohol	3.0
Stearic acid	5.0
Ethyl dihydroxy propyl PABA	8.5
Methyl gluceth-20	5.0
Sesquistearate	2.0
Propyl Paraben	0.1

Part B

Formula	%
Aloe vera gel	50.0
Water	36.5
Methyl gluceth-10	4.0
Quaternium-6	1.5
Triethanolamine	1.0

Part C

Formula	%
Methyl Paraben	0.1
Diazolidinyl urea	0.3
Fragrance and colour	q.s.

Method:

- Heat part (A) and part (B) separately to 70^{o}C
- Add (B) to (A) with mixing.
- Let it cool to approximately 45-50 ^{o}C.
- Add preservative, diazolidinyl urea and fragrance.
- SPF is aproximatly 8-10.

QUESTIONS

Long essay questions: (10 marks each)

1. Define lipstick. Write a note on formulation and preparation of lipsticks.
2. Define and classify shampoo. Give an account of antidandruff shampoo.
3. Write the differences between old and vanishing cream. Enlist and discuss the compositions and formulations of vanishing cream.

Short essay questions: (5 marks each)

1. Define cold cream? Why it is called so? Give some formula and ideal procedures of cold creams.
2. Write a note on sunscreens lotions.
3. Give a detail on ideal properties and formulations of tooth paste.
4. Write the differences between permanent and temporary hair dyes. Give some formulations of natural and metallic dyes.

Short answer questions: (2 marks each)

1. Define shampoo. Give example.
2. What is the use of humectants? Give some example.
3. What is the use of alkali in vanishing cream? Give some examples.
4. What do you mean by thickening agents used in cream? Give some examples.

Chapter 8 ...

AEROSOLS

Upon completion of the chapter, students will be able to understand:

- *Aerosols depend on the power of compressed or liquefied gas to expel the contents from container.*
- *Packaging of therapeutic active ingredients in a pressurized system.*
- *A dose can be removed without contamination of materials.*
- *It provides efficacy of drugs.*
- *Irritation can be reduced.*
- *It protects the photosensitive medicaments and oxygen sensitive materials.*
- *A specific amount of dose or drug can be removed.*
- *Patients tend to prefer the painless route for drug administration. Therefore, pharmaceutical aerosols came to existence to meet patient compliance.*
- *Many variations in excipients with respect to compatibility to drugs, stability and economy are being used to improve the aerosol system of drug delivery.*
- *Pharmaceutical aerosol system as per target delivery and faster onset action.*
- *Presently, aerosol drug delivery system has become beneficial as far as faster pharmacological action and economy are concerned.*

8.1 AEROSOLS

Definition: *Aerosols* are pressurized packages in which product containing therapeutically active ingredients are dissolved, suspended or emulsified form in a propellant or a mixture of solvent and propellant and intended for topical administration or for administration into body cavities.

Synonyms:

1. Pressurized package
2. Pressurized packaging
3. Pressurized product
4. Pressure package

Advantages:

1. The pressure package is easy and convenient to use.
2. A dose can be removed without any contamination.
3. Sterility of the preparation can be maintained.
4. Stability of the drugs sensitive to oxygen &/or moisture can be enhanced.
5. The medication can be delivered directly to the affected area in a desired form, such as spray, stream, quick breaking form, or stable foam.

6. Irritation produced by the mechanical application of topical medication is reduced or eliminated.
7. Medication can be applied as a thin layer over the skin with no waste due to use of a cotton swab or other applicators.
8. If necessary, regulation of dose can be done by using Metered valves.
9. Expensive drugs like steroids and antibiotics can be supplied. It is more advantageous over topical preparations such as metered valve, as ointments, creams or lotions where accurate dose cannot be delivered.
10. Since the package is sealed. There is no danger of contamination of the unused portion of the medication in the container.
11. The cooling effect may be desirable in certain skin conditions, which is possible with liquefied gas aerosols.

Advantages of Nasal Aerosols (Inhalations):

1. Response to drugs administered by inhalation is prompt, faster in onset of activity compared with response to drugs given orally.
2. Drugs that are normally decomposed in the gastro intestinal tract can be safety administered by inhalation.
3. The use of the self-pressurized aerosol package makes inhalation therapy simple, convenient, and acceptable compared to the use of atomizers and nebulizers, which are bulky and require cleaning.

Disadvantage: Cost

Drugs that can be supplied are:

1. Local Anesthetics
2. Anesthetics
3. Germicides
4. First aid preparations
5. Body rubs
6. Dermatological preparations
7. Foot preparations
8. Spray on protective films.

8.1.1 Classification of Aerosols

1. Based on Particle Size:

(a) Space sprays: These products permit dispensing of active ingredients as a finely subdivided spray of dispersed particles not larger than 50μm in diameter.

(b) Surface coating sprays: This coat the surface with large particles as a wet or coarse spray. The particles are not larger than 200μm in diameter.

(c) Aerated sprays (foams): These dispense the products in the form of a foam or froth. For example medicated foams, vaginal foams, shaving creams, etc.

2. Based on Use:

(a) Topical aerosols (External use).

(b) Inhalation aerosol / Oral aerosols (Internal use).

8.1.2 Components of Aerosol Package

1. Propellant
2. Container
3. Valve and actuator (valve assembly)
4. Product Concentrate

8.2 PROPELLANTS (HEART OF AEROSOL PACKAGE)

8.2.1 Functions of Propellants

The propellant is an agent responsible for,

1. Developing the proper pressure within the container.
2. Expelling the product when the valve is opened.
3. Aiding in the atomization or foam production of the product.
4. Acting as a solvent and diluents.
5. Determining the characteristics of the product.

8.2.2 Classification of Propellants

1. **Liquefied Gases:**
   - **(a) Halogenated Hydrocarbons:** (Chlorofluro Carbons), Hydrofluoro carbons
     Examples: Fluorinated chlorinated Hydrocarbons
     Trichloro monofluoro methane (11)
     Dichloro difluro methane (12)
     Dichloro tetra fluoro ethane (114)
   - **(b) Hydrocarbons:**
     Examples: Propane
     Butane
     Isobutane
2. **Compressed Gases:**
   - **(a) Soluble gases:**
     Examples: Carbon dioxide
     Nitrous oxide
   - **(b) Insoluble gases:**
     Examples: Nitrogen

8.2.3 Hydrocarbons

Advantages:

1. Hydrocarbons are propellants of choice.
2. They are less expensive than halogenated hydrocarbons.
3. They are environmentally friendly.
4. They have greater range of stability compared to halogenated hydrocarbons.
5. Hydrocarbons are extremely effective in dispersing the active ingredients into a fine mist or foam depending on the foam desired.
6. They maintain constant pressure in the containers.

7. They have a large expansion ratio. For example, 1ml of dimethyl ether will occupy a volume approximately 350 ml, if allowed to vaporize.
8. A range of desired pressures can be obtained by mixing various hydrocarbons in varying proportions.
9. As the density of hydrocarbons is less than 1, and their immiscibility with water, makes them useful in the formulation of three phase aerosols.
10. As hydrocarbons are not halogenated, generally they possess better solubility characteristics than the fluorinated hydrocarbons.

Disadvantages:

1. They are flammable.
2. To some extent they are toxic.
3. Since the hydrocarbons are naturally occurring products, their purity varies.

Preparation:

Hydrocarbon propellants are produced by distillation of petroleum. They are purified to remove impurities, especially unsaturated hydrocarbons that are prone to undergo chemical reaction. However their purity varies. Therefore the blending is done on the basis of desired final pressure and not on the percentage of each component present.

8.2.4 Halogenated Hydrocarbons

Advantages:

1. Blends (mixtures or combinations) of various halogenated hydrocarbons are used. By changing the proportion, desired vapour pressure can be obtained.
2. Halogenated hydrocarbons are safely used for oral and inhalation aerosols.
3. These propellants are extremely effective in dispersing the active ingredients into desired form (ranging from a fine mist to foam).
4. They are relatively inert and non-toxic.
5. The pressure within the container remains constant.
6. They are non flammable.
7. They have a large expansion ratio. 1ml of liquefied gas will occupy a volume approximately 240 ml, if allowed to vaporize.

Disadvantages:

1. These are costly.
2. They are not environmental friendly.
3. They undergo hydrolysis to form HCl. Therefore not preferred for aqueous products.

Preparation:

These propellants are primarily derived from methane, ethane and cyclobutane. These are prepared by replacing one or more of the hydrogens of these compounds with chlorine and/or fluorine.

For example,

$$2\,CCl_4 + 3\,HF \xrightarrow{\text{Catalyst}} CCl_3F + CCl_2F_2 + 3\,HCl$$

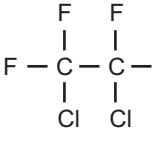
$$CCl_2 = CCl_2 + Cl_2 + 4\,HF \xrightarrow{\text{Catalyst}} CClF_2 + CClF_2 + 4\,HCl$$

Nomenclature:

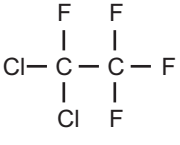
In order to represent easily to the fluorinated hydrocarbons, a relatively simple system of nomenclature was developed some time ago by the refrigeration industry.

1. All propellants are designated by three digits when the first digit is zero, the propellant is designated by two digits.
2. The first digit is one less than the number of carbon atoms in the compound. Where there are only 2 digits, zero is understood to be this figure and indicates a methane derivative (1+0). When this digit is 1, the propellant is an ethane derivative.
3. The second digit is one more than the number of hydrogen atoms in the compound.
4. The last digit represents the number of fluorine atoms.
5. The number of chlorine atoms in the compound is found by subtracting the sum of the fluorine and the hydrogens atoms from the total number of atoms which can be added to saturate the carbon chain.
6. In the case of isomers each has the same number and the most symmetric one is indicated by the number alone. As the isomers become more and more asymmetric, the letter a, b, c, etc follows the number.
7. For cyclic compound, C is used before the number.

The use of this system can be exemplified as follows: Propellant 114 is an ethane derivative, has no hydrogen and contains 4 fluorine atoms. Since 6 atoms are required to saturate the carbon chain of necessity there must be 2 chlorine atoms. These can be arranged in two different ways. However, since there is no letter following the numerical designation, the symmetrical structure refers to propellant 114.



Propellent 114



Propellent 114 a

C	H	F
No – 1	No + 1	
Cl = C – (H + F)		

Vapour Pressure:

Vapour pressure can be defined as the pressure exerted by a liquid in equilibrium with its vapour. When the vapour pressure exceeds atmospheric pressure, boiling and vaporization takes place. However if the vapourized molecules are prevented from leaving the container (by placing the propellant into a sealed container) they will fill the head space and eventually cause an increase in pressure. The pressure developed at equilibrium is the vapour pressure.

In aerosols to achieve desired pressure, mixture of propellants is used. The vapour pressure of a mixture of propellants can be calculated according to Dalton's law. It states that the total pressure in any system is equal to the sum of the individual or partial pressures in the various components.

Raoult's law: The law states that the depression of the vapour pressure of a solvent upon the addition of a solute is proportional to the mole fraction of solute molecules in the solution. Given ideal behavior, the vapour pressure of a mixture consisting of two individual propellants is equal to the sum of the mole fraction of each component present multiplied by the Vapour pressure of each pure propellant at the desired temperature. This relationship can be shown mathematically,

$$P_a = \frac{n_a}{n_a + n_b} P_A^o = N_A P_A^o$$

where P_a = partial vapour pressure of propellant A

P_A^o = vapour pressure of pure propellant A

n_a = moles of propellant A

n_b = moles of propellant B

N_A = mole fraction of component A

Similarly partial vapour pressure of propellant B is,

$$P_b = \frac{n_b}{n_a + n_b} P_B^o = N_B P_B^o$$

The total vapour pressure of a system is

$$P = P_a + P_b$$

where P is the total vapour pressure of the system.

Problem: Calculate the vapour pressure at 70oF of a propellant blend consisting of propellant 12/11 (30 : 70). (Given molecular weight of a propellant-12 is 120.93 and propellant-11 is 137.38, molecular weight of P-11 is 13.4 and P-12 is 84.9)

Solution: Number of moles of propellant-11 in a mixture

$$= \frac{\text{Weight 11}}{\text{Moleular weight 11}}$$

$$= \frac{70}{137.38} = 0.5095$$

Number of moles of propellant-12 in a mixture

$$= \frac{\text{Weight 12}}{\text{Moleular weight 12}}$$

$$= \frac{30}{120.93} = 0.2481$$

From Raoult's law,

$$P_{11} = \frac{n_{11}}{n_{11} + n_{12}} P_{11}^o$$

$$P_{11} = \frac{0.5095}{0.5095 + 0.2481} \times 13.4 = 9.01 \text{ psia}$$

$$P_{12} = \frac{n_{12}}{n_{11} + n_{12}} P^{o}_{12}$$

$$P_{11} = \frac{0.2481}{0.5095 + 0.2481} \times 84.9 = 27.8 \text{ psia}$$

Vapour pressure of propellant-12/11 (30 : 70) is

$$P = P_{11} + P_{12}$$

$$P = 9.01 + 27.80 = 36.81 \text{ psia}$$

P in terms of gauge pressure is

$$P_{sia} - 14.7 = P_{sig}$$

$$36.81 - 14.7 = 22.11\ P_{sig}$$

8.2.5 Compressed Gases

Advantages:

1. By using these propellants, depending on the nature of the formulation and the valve design, the product can be dispensed as a fine mist, foam or semisolid.
2. Aerosol with these propellants can be used for food and non-food products to dispense in its original form as a semisolid.
3. Used in dental creams, hair preparations, ointments and aqueous antiseptic and germicidal aerosols.
4. These gases are almost chemically inert and do not react with the product concentrate.
5. The solubility of carbon dioxide (CO_2) in certain beverage food products is advantageous in that a slight degree of carbonation can be obtained.
6. Since these gases are generally inert and replace the air in the head space, the stability of drugs is sometimes increased.
7. Since compressed gases do not have a chilling effect, they are applicable to topical preparations.

Disadvantages:

1. A serious drawback to the use of these gases is the loss of propellants through product misuse or leakage. Once the propellant is lost, the package becomes inoperative.
2. Compressed gases possess little expansion power, only to the extent of 3 to 10 times their original volume.
3. As expansion power is less, these will produce a fairly wet spray and foams are not as stable as liquefied gases producing foams.
4. Since compressed gases are utilized in the gaseous state and not in the liquid state, a higher initial pressure is required. Also larger headspace required.
5. A drop in pressure is noted during use of a compressed gas aerosol.
6. The initial pressure of a compressed gas aerosol is usually about 90 psig.

8.3 CONTAINERS FOR AERROSOLS

The containers used for manufacture of aerosol must withstand pressures as high as 140 to 180 psig at 130°F. The following aerosol containers have been used to package aerosol products.

(A) Metal Containers:

1. Tin plated steel:
   (a) Side-seam (Three-piece)
   (b) Two-piece or drawn
   (c) Tin free steel
2. Aluminium:
   (a) Two-piece
   (b) One-piece (extruded or drawn)
3. Stainless steel

(B) Glass Containers:

1. Uncoated glass
2. Plastic-coated glass

8.3.1 Metal Containers

1. Tin-plated Containers:

In order to produce an aerosol container which is light and relatively inexpensive, tin plated steel is used for aerosol containers. The tin plated steel container consists of a sheet of steel plate that is electroplated on both sides with tin.

(a) Side-seam (three-piece) Containers:

Manufacture of container: Tin plated steel is obtained in thin sheets. The sheet is cut into desired sizes that suit for body, top and bottom. The body is shaped into a cylinder and seamed via a flanging and soldering operation. The bottom is joined to the body by a double-seaming operation. The top is pressed into shape and curled into a 1 inch opening. This is then attached to the body by a double-seaming operation. This process of manufacture makes the container exceptionally strong. These containers are available in sizes ranging from 90 ml to 720 ml.

The tin plate that is used consists of steel plate coated with varying thickness of tin. The thickness of the tin coating is described in terms of its weight, for example, #25, #50, #75, #100. (#25 tin-plated indicates that ½ lb of tin is used to coat both sides of 112 sheets measuring 20 X 14 inches). In many instances the body of the container is made to have a certain thickness of tin and the ends would have another thickness. This is done in order to obtain increased stability in the container.

Protection/Resistance of a container: For certain products the tin affords sufficient protection so that no further treatment is necessary. Hair lacquers generally can be packaged in this type of container.

Sometimes, the addition of water and other corrosive ingredients or other substances, which attack tin, require a container having an additional protective coating. This coating is

usually organic in nature and may consist of an oleoresin, phenolic, vinyl or epoxy coating. The liner (single or double coat) is added to the container either prior to fabrication (to tin sheets) or after fabrication (final container). Adding coating to thin sheets is easy, cheap and fast process. Whereas, adding coating to the finished container is slower and expensive but coating will be continuous and durable.

(b) Two-piece or drawn Containers:

The container body is obtained by drawing a thin tin sheet under 100 lb pressure by a multiple die drawing process. The bottom is concave and double seamed into place. The opening is made to hold the standard 1 inch valve. The organic coating is generally applied by a spray process after fabrication. Containers made in this way are available in sizes ranging from 180ml to 360ml.

2. Aluminium Containers:

Manufacture: These are produced by an impact extrusion process. Hence the container is seam less. This will give added strength to the container. Containers made in this way are available in sizes ranging from 15 ml to 150 ml.

Resistance: Many existing pharmaceuticals are packaged in aluminium containers, because these containers have lesser danger of incompatibility due to seamless nature and greater resistance to corrosion. However aluminium is corroded by pure water and pure ethanol. The combination of ethanol and propellant-11 in an aluminium container has been shown to produce hydrogen, acetyl chloride, aluminium chloride, propellant-21 and other corrosive products. Resistance can be given to container by coating the inside of a container with organic materials such as epoxy, vinyl and phenolic resins.

3. Stainless Steel Containers:

(i) These containers are limited to the smaller sizes, owing to production problems as well as cost.
(ii) The containers are available in sizes ranging from 5ml to 30ml.
(iii) They are extremely strong.
(iv) They are resistant. In most cases, no integral organic coating is required.
(v) These containers are used for inhalation aerosols.

8.3.2 Glass Containers

Advantages:

1. Glass containers are preferred containers for medicines/pharmaceuticals due to the absence of incompatibilities.
2. Glass containers appear good.
3. Glass is basically stronger than most metallic containers.
4. Glass allows a greater degree of freedom in design of container.

Limitations:

1. If the container is dropped accidentally, container breaks and the total contents lost.
2. Glass containers are restricted to the products having a lower pressure and lower percentage of propellant.

Types of Glass Containers:

Following two types of glass containers are available:

1. **Uncoated glass containers:** These containers have the advantage of decreased cost and high clarity. The contents can be viewed at all times.
2. **Plastic coated glass containers:** These are protected by a coating, which prevents the glass from shattering in the event of breakage.
   (a) The plastic coating adheres the container totally (except for the neck ring) and becomes an integral part of the container.
   (b) The plastic coating fits over the glass container

8.4 VALVES

Uses of valves:

1. The valve exerts a major effect on the character of the dispensed product.
2. The valve can be easily opened and closed.
3. The valve is capable of delivering the contents in the desired form when needed and prevents loss at other times.
4. The valve can deliver a given amount of medication.

8.4.1 Continuous Spray Valve Aerosols

It consists of many parts made up of different materials. These parts are assembled using high-speed production techniques. The details of the valve parts are discussed below and are shown in Fig. 8.1.

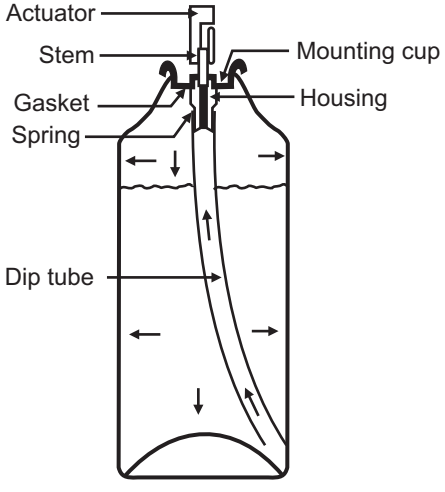


Fig 8.1: Parts of valve assembly

1. Ferrule or Mounting Cup:

(i) Ferrule is made up of tin plated steel (rarely aluminium).

(ii) Ferrule is used to mount the valve properly to the container.

(iii) Under side of the ferrule is exposed to the contents of aerosol and oxygen. As a result corrosion may take place. To prevent corrosion, a single or double epoxy or vinyl coating can be added.

(iv) The ferrule is attached to the container in two ways.
   (a) By rolling the end under the lip of the bottle.
   (b) By clenching the metal under the lip.

2. Valve Body or Housing:

(i) The housing is made from nylon or delrin.

(ii) The housing contains an opening at the point of attachment of the dip tube, which ranges from about 0.013 to 0.08 inch.

(iii) The housing may or may not contain another opening referred to as "Vapour Tap" (optional).
   (a) The vapour tap allows the escape of vapourised propellant along with liquid product.
   (b) The vapour tap produces a fine particle size thereby prevents clogging of the valve by insoluble materials.
   (c) The vapour tap allows the product to be satisfactorily dispensed by the container even in inverted position.
   (d) The vapour tap reduces the chilling effect of the propellant on the skin.
   (e) The vapor tap allows for a decrease in flame extension in the case of hydrocarbon propellants.
   (f) The vapour tap openings are available in sizes ranging from about 0.013 to 0.080 inch.

3. Stem:

(i) The stem is made from nylon, delrin, Brass, SS.

(ii) The stem contains one or more orifices.

(iii) The orifices of stem range in diameters from 0.013 to 0.040 inch.

4. Gasket:

(i) Gasket is made from Buna-N and Neoprene rubber.

(ii) These gasket materials are compatible with most pharmaceutical formulations.

5. Spring:

(i) The spring is made from SS

(ii) The spring serves to hold the gasket.

(iii) When the actuator is depressed and released, the spring returns the valve to its closed position.

6. Dip Tube:

(i) Dip tube is made from polyethylene or poly propylene.

(ii) The inner diameter of the commonly used dip tube varies;
   (a) For common use : 0.120 to 0.125 inch
   (b) Capillary dip tubes : 0.050 inch
   (c) For high viscous products : 0.195 inch

The dip tube serves several purposes:

(a) It conveys the liquid from the bottom of the container to the dispensing valve at the top.

(b) It prevents the propellant from escaping without dispensing the contents of the package.

The dip tube comes into intimate contact with both product and propellant. Therefore dip tube should be resistant to both physical and chemical attack.

The dip tube should extend almost to the bottom of the container. If the tube is too short, the entire product will not be dispensed. On the other hand a tube touching the bottom of the container will tend to block the passage of liquid.

7. Actuator:

Actuator is a specially designed button fitted to the valve stem. This is used to ensure that the product is delivered properly in the desired form. The actuator allows for easy opening and closing of the valve. Different types of actuators are available to produce different discharge. They are:

(i) Spray actuators
(ii) Foam actuators
(iii) Solid stream actuators
(iv) Special actuators

(i) Spray actuators: These actuators consist of 1 to 3 openings measuring the diameter ranging from 0.016 to 0.040 inch. When the actuator is activated, the mixture of the product concentrate and propellant pass through these openings to disperse into small particles. Propellant, opening size and internal channels together determines the spray particle size range.

If a low boiling propellant (propellant 12, propane etc) is used, then actuators with large orifices can be used. When these actuators are used with low quantities of propellant, then the product dispensed is stream rather than spray. This is because the propellant present in the product is not sufficient to disperse the product fully. In such cases, a mechanical breaker actuator is used. Mechanical break up actuator breaks a stream into fine particles by causing the stream to 'swirl' through various channels built inside.

Use: A spray type actuator is used in spray on bandages, antiseptics, local anesthetics and foot preparations.

(ii) Foam actuators: These actuators consist of relatively large orifices ranging in the diameter form 0.070 to 0.125 inch. The orifices allow the passage of the product into a relatively large chamber, where it can expand and be dispensed.

(iii) Solid – stream actuators: These actuators consist of relatively large orifices. Semisolid dermatological preparations like ointments require these actuators. Ointments pass through the valve stem and then into the actuator. These are similar to foam actuators.

(iv) Special actuators: Many pharmaceuticals require a specially designed actuator to serve a specific purpose. These are available for throat, nose, eye and vagina.

8.4.2 Metered Valve Aerosols

Commonly used aerosols deliver the product continuously as long as actuator button is pressed. However, recently some metering types of valves have been designed which permit only a special specified quantity of the product to come out for single actuation. Such valves actually consist of two valved chambers, both of which are connected to the actuator button (as shown in Fig. 8.2).

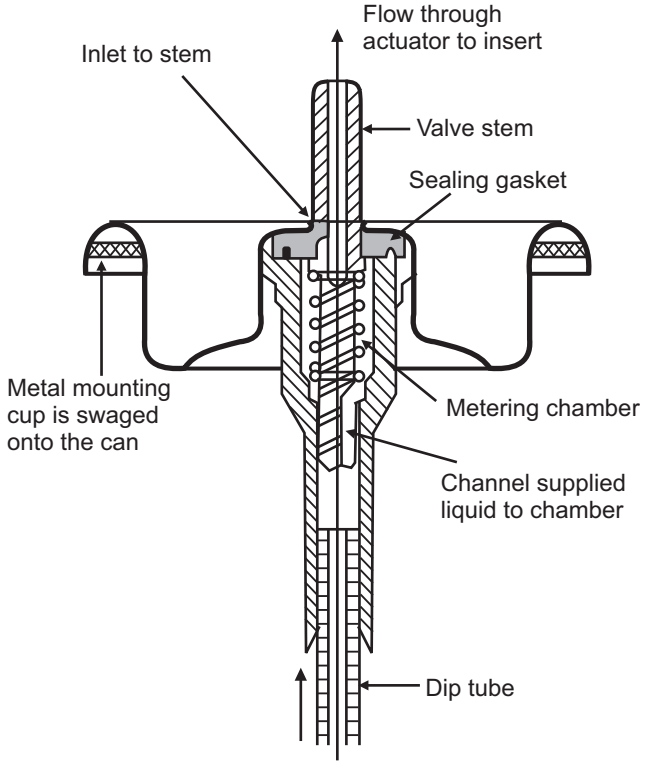


Fig. 8.2: Metered valve aerosols

When the actuator button is in closed position, the lower chamber valve is in open position and the upper chamber valve in the closed position. The product fills itself upto the chamber valve in the stationary position. As soon as the actuator button is pressed, the lower chamber valve gets closed preventing any further flow of product from the container. At the same time the upper chamber valve opens allowing the product present between the upper and lower chamber valves to flow out. On releasing of actuator button the positions of the upper and lower chamber valves get reversed.

Apart from delivering pre determined doses and thus minimizing overdoses of active compounds, metering valves offer still another safety feature from the standpoint of aerosol packages for medical use i.e. they prevent the discharge of large volumes of comparatively high pressure gas into body cavities. This is particularly true for nasal and oral applications.

8.5 MANUFACTURE OF AEROSOLS

1. Selection of drug
2. Selection of propellant
3. Selection of container
4. Selection of type of aerosol
5. Selection of filling procedure
6. Quality control

8.6 TYPES OF AEROSOL SYSTEMS

8.6.1 Solution Systems (Two-phase Systems)

This type of aerosol systems consists of two phases, namely liquid and vapour. The solution system may be defined as "a solution of active ingredients in pure propellant or a mixture of propellant and solvent". The solvent is used to dissolve the active ingredient and / or to retard the evaporation of the propellant. This is the simplest of all aerosol systems. Therefore a large number of aerosol products are formulated in this manner. The preparation becomes easy because the ingredients are soluble in the propellant.

When the valve of solution aerosol is depressed, a mixture of active ingredients, solvents, and propellants is emitted into the atmosphere. As the liquid propellant encounters the warm surrounding air, it tends to vaporize. In an attempt to vaporize, propellant breaks up the active ingredients and solvents into fine particles. Depending on their size, the particles remain suspended in air for relatively long periods of time. The size of these droplets will depend on the nature of the propellant, the amount of propellant, the nature of the product concentrate, and the valve design.

Size of particles:

- Metered dose inhalers : < 8 μm
- Nasal aqueous aerosols : 50 - 75 μm
- Topical sprays : 100 μm
- Space sprays : < 1 μm - 50 μm
- Surface coating sprays : 50 μm - 200 μm

Applications:

Space insecticides, room deodorants, vaporizer sprays, hair dyes, perfumes, paints, and protective coatings.

Examples:

- Isoproterenol HCl : 0.25 % w/w
- Ascorbic acid : 0.10 % w/w
- Ethanol : 35.75 % w/w
- Propellant 12 : 63.90 % w/w

8.6.2 Water Based Systems (Emulsion Systems)

This type of aerosol consists of three phases namely water, liquid propellant and vapour. Relatively large amounts of water can be used to replace all or part of the non-aqueous solvents used in aerosols. Since the liquid propellant and water are not miscible, the liquid propellant will separate as an immiscible layer.

Fluorocarbon type propellant will fall to the bottom of the container because of its higher density than water. On the other hand, hydrocarbon propellant will float on top of the aqueous layer because of its lighter density than water.

In this system, active ingredients and solvents are present in an emulsion form in which the propellant is in the external phase. When this product is dispensed, the propellant vaporizes and disperses the active ingredients into minute particles. A spray is produced by the mechanical action of an exceedingly small valve orifice through which the liquid is forced by the vapour pressure of the propellant. The vapour layer is continuously replaced by vapours from the liquid layer of propellant. No part of the liquefied gas propellant is introduced into the aqueous solution while it is being ejected. Therefore the breakup of the stream is mainly due to the action of the "mechanical breakup actuator"

Surfactants have been used to a large extent to produce a satisfactory homogeneous dispersion.

Modification: Aquasol system .

Advantages:

1. Water-based aerosols developed for use in this system would have the advantage that the chilling effect associated with liquefied gas systems is eliminated.
2. Since only vaporized propellant is dispensed, less propellant in the container is required.
3. With greater use of water as a solvent for active ingredients a greater range of products can be developed.

8.6.3 Suspension Systems (Dispersion Systems)

These are the aerosol systems in which the active ingredients are suspended in the propellant vehicle or a mixture of propellants. Suspension systems are preferred when the active ingredients are insoluble in propellants and in cases where a co-solvent is not desirable. When the valve is depressed, the suspension is emitted, followed by rapid vaporization of the propellant, leaving behind the finely dispersed active ingredients.

The physical stability of aerosol dispersion can be increased by:

1. Control of moisture content of drug and propellant below 300 ppm.
2. Use of derivatives of active ingredients having minimum solubility in propellant system.
3. Reduction of initial particle size to less than 5 microns.
4. Adjustment of density of propellant and / or suspension so that they are equalized.
5. Use of dispersing agent, surfactant, lubricant.

Problems:

1. Caking
2. Agglomeration
3. Particle size growth
4. Clogging of the valve
5. Inaccuracy of dosage due to agglomeration
6. Damage to the liner and to the metal container

Applications:

1. Anti asthmatics
2. Antibiotics for topical use

Examples:

- Ephedrine bitartratte : 0.50 % w/w
- Sorbitan trioleate : 0.50 % w/w
- Propellant 114 : 49.50 % w/w
- Propellant 12 : 49.50 % w/w

8.6.4 Foam Systems

Foam aerosols consists of the following in emulsion form:

- Active ingredient
- Aqueous / non aqueous vehicle
- Surfactant
- Propellants

The propellant present can be the internal phase or external phase. When the propellant is in the internal phase, the propellant vapour must pass through the emulsion formulation in order to escape into the atmosphere. In travelling through the emulsion, the trapped vaporized propellant forms a matrix for foam to develop. Depending on the nature of the formulation and the propellant, the foam can be stable or quick-breaking. When the propellant is in the external phase, the propellant vaporizes and escapes directly into the atmosphere, leaving behind droplets of the formulation, which are emitted as a wet spray.

The use of dip tube is optional. If dip tube is used, then the container is designed for upright use. If dip tube is not used, the container must be inverted prior to use.

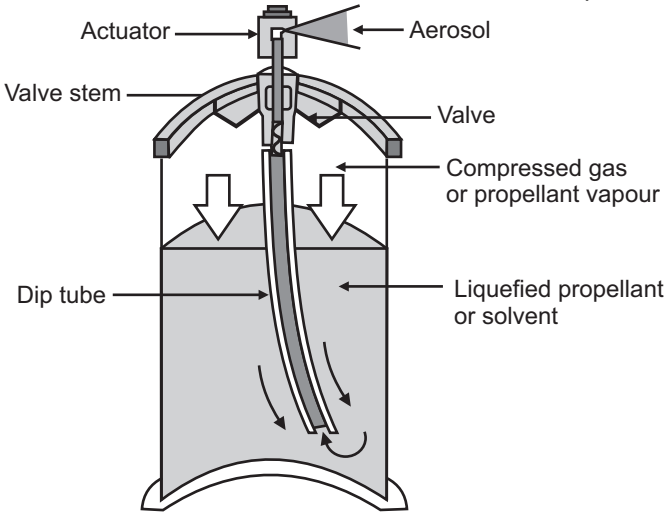


Fig. 8.3: Foam aerosol

Types of Foams:

1. Aqueous stable foams
2. Non aqueous stable foams
3. Quick- Breaking foams
4. Thermal foams

1. Aqueous Stable Foams:

This is an emulsion system where the propellant is in the internal phase, water makes up the external or dispersed phase. The total propellant content may be as high as 5%. As the amount of propellant increases, stiffer and dryer foam is produced. Lower propellant concentrations yield wetter foams.

Examples:

- Active ingredients : 2% w/w
- Emulsion base : 94 - 95% w/w
- Hydrocarbon propellant : 3 - 4% w/w

Applications: Steroids, Antibiotics.

2. Non-aqueous Stable Foams:

This is an emulsion system where the propellant is in the internal phase; non aqueous vehicle like glycols makes up the external phase.

Examples:

- Glycol : 91 - 92.5% w/w
- Emulsifying agent : 4% w/w
- Hydrocarbon propellant : 3.5 - 5 % w/w

3. Quick-breaking Foams:

These foams consist of ethyl alcohol, water, and a surfactant that is soluble in either alcohol or water but not in both. Other miscible solvents can be used in place of alcohol and water. The surfactant can be nonionic, anionic or cationic. The product is dispensed as foam but quickly collapses upon coming into contact with the skin. This is particularly advantageous in pharmaceutical aerosols for topical application, because the foam will reach the affected area and then collapse, so that there is no further injury by mechanical dispersion of the product.

Advantages:

1. Advantage over spray system is that the area with which the product can come into contact is limited.
2. Preparations containing irritating ingredients can be dispensed.
3. The incidence of airborne particles can be substantially reduced, thereby lowering the toxicity of spray products that cause irritation on release and may be inhaled.

Applications: Steroids, burn preparations

Examples:

- Ethyl alcohol : 46 - 66 % w/w
- Surfactant : 0.5 - 5.0 % w/w
- Water : 28 - 42 % w/w
- Hydrocarbon propellant : 3 - 15 % w/w

4. Thermal Foams:

These are the type of aerosol systems that deliver the warm foam. The generation of warm foam is due to exothermic reaction between ingredients. An oxidation reduction reaction is the basis for this exothermic reaction. Of the various oxidizing agents studied, hydrogen peroxide was found to be the most successful. Hydrogen peroxide decomposes according to the following reaction:

$$2\ H_2O_2 \longrightarrow 2\ H_2O + O_2 - 22.6\ \text{kcal/mole}$$

Water is formed as the decomposition product and there is no danger of irritation to the face when the foam is applied.

The choice of reducing agent can be varied. Most commonly used reducing agents include potassium sulfite, sodium sulfite, sodium thiosulfate, thiourea, and substituted thio barbituric acid derivatives.

$$H_2O_2 + SO_3^{--} \longrightarrow H_2O + SO_4^{--} - 87.7\ \text{kcal/mole}$$

Inside the container the two chemicals are separated from each other by a non-permeable membrane. However, when the actuator is depressed these two chemicals reach the valve at same time in given proportion. When they are mixed, an evolution of heat occurs and warms the surrounding media.

Limitations:

1. Breakage of the inner bag may result from stress- cracking, there by releasing the contents.
2. It is difficult to control the amount of each material co- dispensed.
3. Lack of effectiveness
4. Costly

Applications: Shaving foams, incompatible ingredients as they need not be mixed until just prior to use, drugs of limited stability in water like vitamins, effervescent preparations.

Disadvantages: Limited/ no use

8.7 FILLING OF AEROSOLS

Both manufacturing procedures and packaging are carried simultaneously. To prepare and package pharmaceutical aerosols successfully, special knowledge, skills and equipment are required. The concentrate which contains the active ingredients, solvents and co-solvents and other inert ingredients and may even contain a small portion of the propellant, is compounded separately and then mixed with the remainder of propellant. The following methods are used to fill containers with specialized equipment that are capable of handling and packaging materials at relatively low temperatures (about –40^{o}F) or under high pressure.

8.7.1 Pressure Filling Apparatus

The pressure burettes for filling aerosols are shown in Fig. 8.4. The product concentrate is prepared at room temperature. The measured volume of the product concentrate is then added to the can. The valve assembly is crimped to the can. A cylinder of propellant is connected to the valve assembly of the can. The desired amount of propellant is added

through the inlet valve located at the bottom of the cylinder under pressure. Trapped air is allowed to escape through the upper valve. When the pressure is equalized between the burette and the container, the propellant stops flowing.

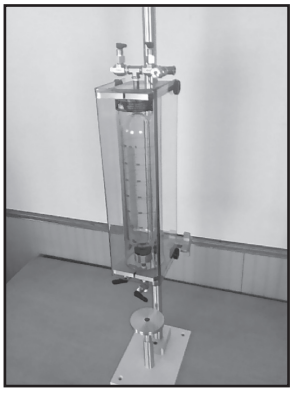


Fig. 8.4: Pressure burettes for filling aerosols

To fill additional propellant a cylinder of nitrogen or compressed air is attached to the upper valve so that the added nitrogen pressure causes the propellant to flow.

Advantages:

1. Less propellant escapes into the atmosphere. Therefore it is environmentally friendly.
2. The filling procedure is carried out at room temperature.
3. Solutions, emulsions, suspensions can be filled successfully which are not possible with cold filling methods.

Disadvantages:

1. This method is not suitable to fill inhalation aerosols fitted with a metered valve.
2. This process is slower than cold filling process.
3. High production speeds can be achieved.

Solution:

Pressure filling equipment that fills through metered valves under high pressure of about 300 to 600 psig are available.

Precaution:

Air entrapped in the container must be removed. Otherwise this air may cause decomposition of the active ingredient, or may give excessive pressure. This can be done by adding one or two drops of propellant into each can before adding the concentrate. The propellant will vaporize and expel most of the air from the can. Alternatively the can must be actuated several times after filling to expel air (in the inverted position for the dip tube products and upright position for products without a dip tube).

Production rate: 35 - 160 cans per minute.

8.7.2 Cold Filling Apparatus

The construction of cold filling apparatus is shown in Fig. 8.5. The product concentrate is prepared either by dissolving or by suspending active ingredients in the part of the

propellant and/or a co-solvent. This product is then chilled to about –30°C. The chilled product is added to previously cooled container. The propellant present in the cylinder is made to pass through chilling unit. Chilling unit consists of an insulated box fitted with copper tubing that has been coiled to increase the area exposed to cooling. Coils are placed in a container that is previously filled with dry ice/acetone (chilling agent). The chilled propellant is finally added into the container. The valve assembly is crimped to the container.

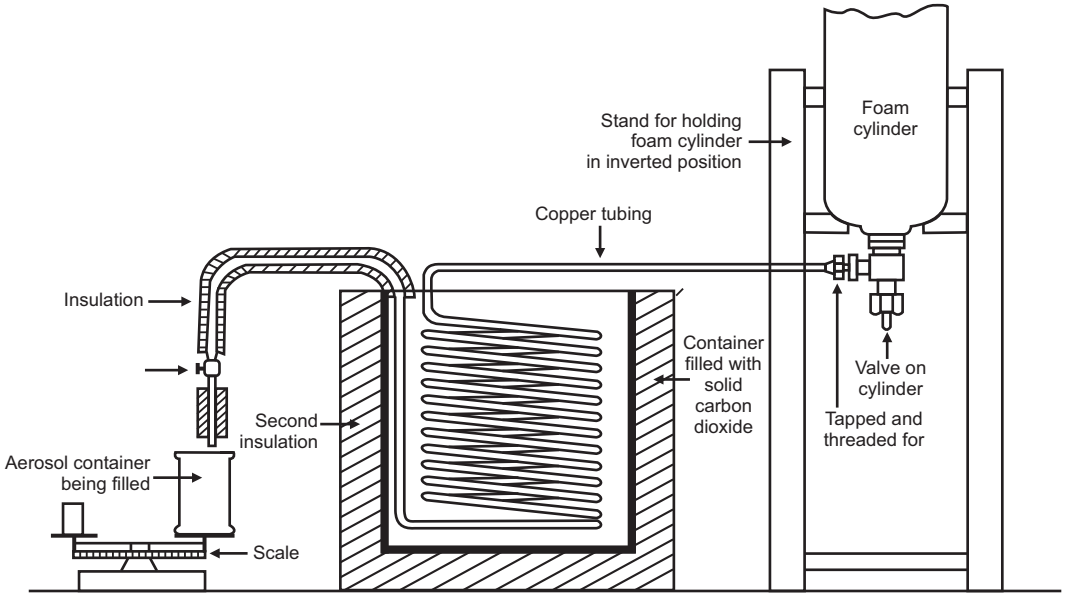


Fig. 8.5: Apparatus for cold filling process

Advantages:

1. This is suitable for both metered valves and non-metered valves.
2. This is suitable for fluorocarbon propellants.
3. This is simpler than pressure filling method.
4. This is faster process than pressure filling.

Disadvantages:

1. Some propellant may vaporize from container before crimping valve. Therefore it is not suitable for hydrocarbon propellants. Excessive amount of propellant escaping and vaporizing may form an explosive mixture at the floor level.

Limitations:

1. It is suitable only for non-aqueous products, which are not affected at low temperatures.
2. Solutions, emulsions, suspensions cannot be chilled.

8.7.3 Compressed Gas Filling Apparatus

The product concentrate is prepared and placed in the container. The valve is crimped in place. The air inside the container is evacuated by means of a vacuum pump. The filling head is inserted into the valve opening and then the valve is depressed. The gas is allowed to flow

into the container. When the pressure within the container is equal to the delivery pressure, the gas stops flowing.

Since the compressed gases are under high pressure, a pressure-reducing valve is required. Attached to the delivery gauge is a flexible hose capable of withstanding about 150 pounds per square inch gauge (psig) pressure and fitted with a filling head.

For those products requiring an increased amount of gas, or for those in which solubility of the gas in the product is necessary, carbon dioxide and nitrous oxide can be used. To obtain maximum solubility of the gas in the product, the container is shaken manually during and after the filling operation. Mechanical shakers are also available for this purpose.

8.8 STABILITY TESTING OF AEROSOLS

The stability testing of aerosols is studied under three areas :

1. Concentrate and propellant
2. Container
3. Valve

1. Concentrate and Propellant:

(a) Soon after manufacture, the following physic-chemical constants of the product are determined.
- Vapour pressure
- Spray rate of value
- pH
- Density/specific gravity
- Refractive index
- Viscosity
- Total weight
- Assay of active ingredients
- IR/ gas chromatography curves
- Colour
- Odour

(b) The samples used for the tests are usually stored on their sides (horizontally). With this type of storage, the product can come into contact with internal surface of the container and valve mounting cup.

(c) The effect of product concentrate/ propellant upon container needs to be studied.

(d) When three-piece metal cans are used, care should be taken to ensure that some samples have liquid as well as gaseous contact with the side seams.

2. Container:

(a) The effect of container on product needs to be studied.

(b) The contents of the container are removed by chilling the contents to a temperature of $0^{o}F$ or less. The container is then examined for signs of corrosion. Corrosion changes are easy to detect with necked eye and/or microscope.

(c) The internal coatings must also be verified. Internal coating should not be softened, dissolved, pealed or blistered by the concentrate.

(d) Special attention should be paid to the side-seam and head space. Because these areas are under danger of attack.
(e) If glass containers are used, then examination is not necessary.
(f) If plastic containers are used, then leaching, sorption like tests are conducted.

3. Valve:

(a) The valve should be examined to ensure that it works properly to dispense the product. Even small changes in the components may result in inoperative package. The functioning of the valve can be determined by dispensing the product.
(b) The valve consists of many parts. These parts are made up of different materials. All of these materials may produce an adverse effect on the product. On the other hand product may cause damage to the components. Therefore the components must be checked for softening, cracking, elongation or distortion.
(c) The valve cup should be examined for evidence of corrosion.
(d) Dip tube may undergo elongation and cracking. Dip tube must be observed for these. If present, corrected.

Since varieties of different materials are used in the construction of container, valve components and dip tube, it is difficult to determine whether a reaction takes place between the materials and the drug. Therefore, to determine the reaction, all materials must be studied separately and collectively. Samples are prepared and packaged in glass aerosol containers as controls.

8.8 QUALITY CONTROL OF AEROSOLS

As pharmaceutical aerosols are "pressurized packages", many tests are necessary to ensure proper performance of the package and safety during use and storage. Pharmaceutical aerosols can be evaluated by a series of physical, chemical and biologic tests.

(A) Flammability and Combustibility Tests:

1. Flash point
2. Flame extension

(B) Physico-chemical Characteristics:

1. Vapour pressure
2. Density
3. Moisture content
4. Identification of propellant (s)

(C) Performance:

1. Aerosol valve discharge rate
2. Spray pattern
3. Dosage with metered valves
4. Net contents
5. Foam stability
6. Particle size determination
7. Leakage

(D) Biologic characteristics:

1. Therapeutic
2. Toxicity

8.8.1 Flammability and Combustibility Tests

1. **Flash Point:** Standard tag open cup apparatus is used to determine the flash point of aerosol product. The product is chilled to a temperature of –25°F. This liquid is placed in the tag open cup apparatus. The temperature of the liquid is increased slowly. The temperature at which the vapours ignite is taken as the flash point.
2. **Flame Projection:** The product is sprayed for about 4 seconds in a flame. Depending on the nature of the formulation, the flame is extended. The length of the extended flame is measured.

8.8.2 Physico-chemical Characteristics

1. **Vapour Pressure:** The vapour pressure is determined by pressure gauge. Excess variation of vapour pressure in the containers indicates the presence of air in the headspace.
2. **Density:** The density of an aerosol system may be accurately determined using *hydrometer* or *pycnometer*. The hydrometer is placed into glass pressure tube. Sufficient sample is introduced through the valve to cause the hydrometer to rise halfway up the length of the tube. The density can be read directly.
3. **Moisture content:** *Karl Fischer apparatus* is used to determine moisture content.
4. **Identification of propellants:** *Gas chromatography* and *infrared spectrophotometry* have been used to identify the propellants. The same techniques can also be used to determine the proportion of each component in a blend.

8.8.3 Performance

1. **Aerosol valve Discharge Rate:** The aerosol is weighed (w_1 g) and discharged for a known period of time (t). The weight of aerosol (w_2 g) after discharge is noted. Then rate is expressed as below;

   $$\text{Aerosol valve discharge rate} = \frac{w_1 - w_2}{t} \text{ g/sec}$$

2. **Spray pattern :** The spray pattern of aerosol valve discharge is determined as follows. An apparatus consists of motor driven rotating disc with an adjustable slit. The filter paper coated with dye talc mixture is attached to rotating disc on one side (depending on the nature of the aerosol, an oil soluble or water soluble dye is used). The aerosol is sprayed on to fitter paper from the other side. The particles that strike the paper cause the dye to go into solution and to be absorbed into the paper.
3. **Dosage with metered valves:** When one attempts to test this, then either of the following must be observed.
   (i) Reproducibility of dosage each time the valve is depressed.
   (ii) Amount of medication actually received by the patient.

Tests:

(i) Aerosol is actuated one or two times so that product is dispensed into solvent. The amount of drug present in the solvent is determined by assay technique.

(ii) Aerosol is actuated one or two times onto a material that absorbs the active ingredients. The amount of the drug that is absorbed is then determined by assay technique.

(iii) The accurate weight of the container (W_I g) is noted. Aerosol is actuated for several doses (n times). Again the weight after dispensing is noted (W_F g).

Dosage with metered valves = $\frac{W_I - W_F}{n}$ g/actuation

(iv) Aerosol is actuated to dispense the drug into an artificial respiratory system. The drug entered into the system is then determined.

4. **Net Contents:** To determine the net contents either of the following methods is used.

(i) Initial weight of empty aerosol container is noted. After filling the weight is noted. Difference in the weights is net contents.

(ii) Weight of the filled container is noted. Aerosol is actuated to dispense the contents completely. Again the weight is noted. Difference in the weight is net contents. (However provision must be made for the amount that is retained in the container).

(iii) Initial weight of filled container is noted. By opening the valve, the total contents are removed. Again the weight of the container is noted. Difference in the weight is net contents.

5. **Foam Stability:** The life of a foam can range from a few seconds to one hour or more. To determine the foam stability any one of the following methods is used.

(i) Actuate an aerosol to form the foam. Note down the time required for a complete collapse of foam by visual observation.

(ii) Actuate an aerosol to form the foam. Note down the time required for a given mass to penetrate the foam.

(iii) Actuate an aerosol to form the foam. Note down the time required for a rod that is inserted into the foam to fall.

(iv) Using rotational viscometer.

6. **Particle size determination:** To determine particle size cascade impactor is used. The principle behind working of cascade impactor is shown in Fig. 8.6. Cascade impactor consists of series of nozzles and glass slides. When aerosol is actuated, larger particles impact first on the lower velocity stage. Then the smaller particles pass on and impact at next stage i.e., higher velocity stage. In such a way the particles ranging from 0.1 to 30 microns can be studied.

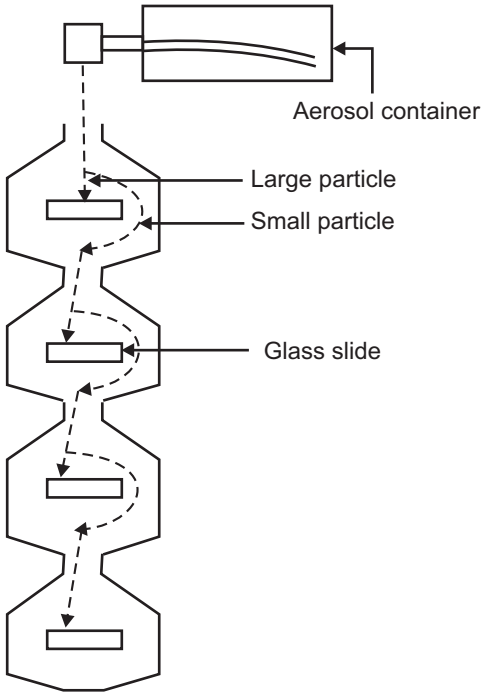


Fig. 8.6: Cascade impactor

7. **Leakage:** Pass the crimped aerosol containers through the water bath. If any leaks are present, evolution of air bubbles can be observed and the container is rejected.

8.8.4 Biological Characteristics

1. **Therapeutic Activity:** Testing of aerosols for therapeutic activity is similar to testing of non aerosol products. Apart from regular tests, dosage is testing for inhalation aerosols. For topical preparations, adsorption of therapeutic ingredients is determined.
2. **Toxicity:** Toxicity testing includes the following;
   (i) Irritation of affected area where dose is administered.
   (ii) Chilling of skin due to evaporation of propellants.
   (iii) Rise in temperature on spraying of aerosol.
   (iv) Inhalation toxicity studies though the preparation is for topical use. This can be done by exposing animals to vapours sprayed from an aerosol container.

Table 8.1

Part of valve assembly	Material of construction
Ferrule or mounting cup	Tin plate steel, Aluminum with underside coated with single or double epoxy or vinyl coating
Valve Body or Housing	Nylon, Delrin
Stem	Nylon, Delrin, Brass, Stainless steel
Gasket	Buna-N, Neoprene
Spring	Stainless steel
Dip tube	Polyethylene, Polypropylene

Table 8.2

Test	Apparatus
Flash Point	Tag open cup Apparatus
Vapour pressure	Pressure gauze
Density	Hydrometer, Pycnometer
Moisture	Karl Fischer Apparatus
Identification of propellants	Gas Chromatography / IR Spectrophotometry
Foam stability	Rotational viscometer
Particle size distribution	Cascade impactor

QUESTIONS

Long-answer questions: (10 marks each)

1. Describe in detail formulation and evaluation parameters of aerosols.
2. Explain manufacture of pharmaceutical aerosols.
3. Write a short note on : Quality control test for aerosols.

Short-answer questions: (5 marks each)

1. Define aerosol. Advantages and disadvantages of aerosol.
2. Components of aerosol. Define Propellants and types of propellants.
3. Define containers. Different types of containers.
4. Different types of valve assembly involved in aerosol preparations.
5. Define actuators and different types of actuators.

☆☆☆

Chapter 9 ...

PACKAGING AND PACKAGING MATERIALS

Upon completion of the chapter, students will be able to understand:

- *Packaging is one of the most important parts of Pharmaceutical industry.*
- *The packaging ensures the protection of the drug during the sale, storage and use.*
- *The objectives of packaging are containment, physical and chemical protection, portion control and security of the drug.*

9.1 INTRODUCTION

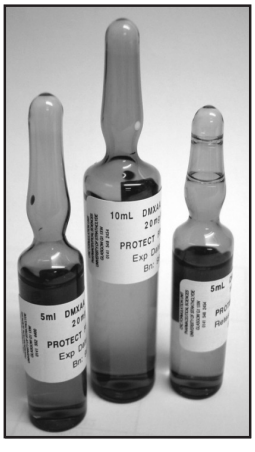


Fig. 9.1

Packaging play important role in maintaining the quality of dosage forms as it is prepared. Packaging can be divided into following two types

1. Packaging of extemporaneous preparations.
2. Repackaging of bulk medicines.

The packaging is done in a container.

The container must:

- Maintain the quality, safety and stability of the medicine.
- Protect the product against
  - physical damage,
  - chemical and microbial contamination,
  - light, moisture and oxygen as appropriate.

- Be user friendly, easy to open and reclose.
- Other factors such as cost and the need for both child resistant closures and tamper evident seals.

Each container is labeled with the:

- Identity and quantity of the medicine.
- Batch no.
- Appropriate storage instructions.
- Product expiry date.
- Requirements for handling and storage.

9.2 PRIMARY AND SECONDARY PACKAGING

1. Primary Packaging:

Which are in direct contact with the product (bottle, closure, blister…..).

Primary containers must:

- Protect the medicine from damage and from extraneous chemical and microbial contamination.
- Support use of the product by the patient.

Primary containers must not:

- allow product leakage,
- chemically react with the product,
- release components,
- Uptake product components.

2. Secondary Packaging:

Are additional packaging materials that improve the appearance of the product and include outer wrappers or labels that do not make direct contact with the product? Also it can supply information about the product and its use. They should provide evidence of tampering with the medicine. In the pharmaceutical industry, it is important that package selected must preserve the integrity of the product.

Types of Primary and Secondary Packaging Materials and Their Use:

Material	Type	Use
Glass	Primary	Metric Medical bottle, ampoule, vial
Plastic	Primary	ampoule, vial, infusions fluid containers, dropper bottle
Plastic	Secondary	Wrapper to contain primary pack
Board	Secondary	Box to primary pack
Paper	Secondary	Labels, patient information, leaflet

9.3 OFFICIAL TERMS OF CONTAINERS

- **Single-dose containers** hold the medicine that is intended for single use. e.g. ampoule.
- **Multidose containers** hold a quantity of the material that will be used as two or more doses. e.g. multiple dose vial or the plastic tablet bottle.

- **Well-closed containers** protect the product from contamination with unwanted foreign materials and from loss of contents during use.
- **Airtight containers** are impermeable to solids, liquids and gases during normal storage and use. If the container is to be opened on more than one occasion it must remain airtight after re-closure.
- **Sealed containers** such as glass ampoules are closed by fusion of the container material.
- **Tamper-evident containers** are closed containers fitted with a device that irreversibly indicates if the container has been opened.
- **Light-resistant containers** protect the contents from the effect of radiation at a wavelength between 290 nm and 450 nm.
- **Child-resistant containers**, commonly referred to as CRCs, are designed to prevent children accessing the potentially hazardous product.
- **Blister packs** are composed of a base layer, with cavities that contain the pharmaceutical product, and a lid. This lid is sealed to the base layer by heat, pressure or both. They are more rigid than strip packs and are not used for powders or semi-solids. Blister packs can be printed with, day and week identifiers to produce calendar packs. These identifiers will support patient compliance.
- **Tropicalized packs** are blister packs with an additional aluminum membrane to provide greater protection against high humidity.
- **Strip packs** have at least one sealed pocket of material with each pocket containing a single dose of the product. The pack is made of two layers of film or laminate material. The nature and the level of protection that is required by the contained product will affect the composition of these layers.
- **Original packs** are pharmaceutical packs that are commercially produced and intended for finite treatment periods.
- **Pressurized packs** expel the product through a valve. The pressure for the expulsion of the product is provided by the positive pressure of the propellant that is often a compressed or liquefied gas.

The selection of packaging for a pharmaceutical product is dependent on the following factors:

- The nature of the product itself, its chemical activity, sensitivity to moisture and oxygen, compatibility with packaging materials.
- The type of patient: If it is to be used by an elderly or arthritic patient or by a child.
- The dosage form.
- Method of administering the medication.
- Required shelf life.
- Product used such as for dispensing or for an over-the counter product.

9.4 GLASS AS A PACKAGING MATERIAL

9.4.1 Composition of Glass

Chemical composition of glass is mainly of sand (SiO_2), soda ash (Na_2CO_3), limestone ($CaCO_3$), and cullet. Cullet is broken glass that is mixed with the sand, soda ash and limestone to acts as a fusion agent for the entire mixture. The composition of glass varies and is usually adjusted for specific purposes. The most common cations found in pharmaceutical glassware are:

1. Silicon,
2. Aluminum,
3. Boron, (borosilicate glass)
4. Sodium,(soda lime glass)
5. Potassium,
6. Calcium,
7. Magnesium,
8. Ferrous (amber coloured glass)
9. Zinc, and
10. Barium.

The only anion of consequence is oxygen. Many useful properties of glass are affected by the kind of elements it contains. Reduction in the proportion of sodium ions makes glass chemically resistant; however, without sodium or other alkalies, glass is difficult and expensive to melt. Boron oxide is incorporated mainly to aid in the melting process through reduction of the temperature required. Lead in small traces gives clarity and brilliance, but produces a relatively soft grade of glass. Alumina (aluminum oxide), however; is often used to increase the hardness and durability and to increase resistance to chemical action.

1. Colored Glass - Light Protection:

Glass containers for drugs are generally available in clear flint or amber color. For decorative purposes, special colors such as blue, emerald green and opal may be obtained from the glass manufacturer. Only amber glass and red glass are effective in protecting the contents of a bottle from the effects of sunlight by screening out harmful ultraviolet rays. The USP specifications for light-resistant containers require the glass to provide protection against 290 to 450 nm of light. Amber glass meets these specifications, but the iron oxide added to produce this color could leach into the product.

2. Glass for Drugs:

The USP and NF describe the various types of glass (type I, type II, type III and type NP) and provide the powdered glass and water attack tests for evaluating the chemical resistance of given glass. These tests are the measures of the amount of alkalinity leached from the glass by purified water under controlled elevated temperature conditions. The powdered glass test is performed on crushed grains of a specific size and is meant for type I, type III, and type NP glass. The water attack test is conducted on whole containers and is used only with type II glass.

The chemical stability of glass for pharmaceutical use is given by the resistance of the glass to the release of soluble minerals into water contacting the glass. This is known as hydrolytic resistance.

Glass as a Packaging Material:

Glass is the preferred packaging material. Glass does have several advantages:

- It is inert to most medicinal products.
- It is resistant to air and moisture.
- It allows easy inspection of the container contents as it is transparent.
- It can be colored (amber coloured) to protect contents from harmful wavelengths of UV light.
- Easy to clean and sterilize by heat.
- It is moldable in variously shaped containers.

Disadvantages of Glass:

- Fragile (it is easily broken): Glass fragments and cracks.
- Costlier in comparison to plastic.
- As it is heavy transport cost is high.
- Certain types of glass release alkali into the container contents.

9.4.2 Types of Glass

1. Type-I glass
2. Type-II glass
3. Type-III glass

1. Type-I Glass:

Composition: Neutral glass, borosilicate glass [silica (silicon dioxide, SiO_2)] and boron oxide).

Advantages:

- It possesses a high hydrolytic resistance.
- It is the most inert type of pharmaceutical glass.
- It has the lowest coefficient of thermal expansion (and hence suitable for sterilization by heat for ampoules and vials).

Disadvantages:

- It has very high glass transition temperature so needs complicated processing.
- And therefore expensive.

Uses:

- Type I glass is suitable for packing all pharmaceutical preparations.
- It is widely used as glass ampoules and vials to package fluids for injection.
- In contrast to the other types of glass (type II and III), this type has no/little amounts of basic oxides, so it is used to package solutions that could dissolve basic oxides in the glass.

2. Type-II Glass:

Composition: soda-lime-silica glass.

Soda (Na_2CO_3) is used to decrease the glass transition temperature of silica. However, soda would increase water solubility of silica, so lime (CaO) is used to increase the hydrolytic resistance. This type would also contain other oxides.

Advantages:

- This glass has a lower melting point than Type I glass. It is thus easier to produce and consequently cheaper.
- High hydrolytic resistance due to surface treatment of the glass.

Uses:

- Type II glass used to package aqueous preparations.
- However, as it contains basic oxides, it is not used to package parenteral formulations with a pH < 7 (i.e. acidic); this would increase the pH of the formulation and could affect the drug stability and potency.
- It is the glass used to produce containers for eye preparations and other dropper bottles.

3. Type-III Glass:

- Composition: soda-lime-silica glass: It has a similar composition to Type II glass but contains more leachable oxides.
- Properties and uses: Type III glass offers only moderate resistance to leaching and is commonly used to produce dispensary metric medical bottles. It is also suitable for packaging non-aqueous parenteral products and powders for injection.
- **Type NP :** General-purpose soda-lime glass.
- Containers made of soda-lime glass are supplied for non-parenteral products.

9.4.3 Drug-Glass Considerations

Although glass exhibits many advantages over other packaging materials, it has two principal faults namely the release of alkali and the release of insoluble flakes to liquids stored in the container. By decreasing the soda content in the glass or replacing the sodium oxide with other oxides, it has been possible to overcome the property of glass to release alkali cations into solution.

Surface treatment:

Several approaches have been used to enhance the resistance of glass to alkali release by surface treatment.

1. Treating the surface of soda-lime glass to produce a fire-polished skin of silica, which is more resistant than the inner layers of glass.
2. Treating the surface of the glass with sulfur dioxide in the presence of water vapor and heat. This causes the surface alkali to react with the sulfur dioxide, and the glass becomes more resistant. The stability of the drugs with high potency and consequently of low dosage can be readily affected by the release of soluble alkali from glass containers. As a safety factor, whenever the dosage form is liquid, the solution is buffered to eliminate any effect due to possible change in pH if some alkali were released from the glass.

The type of glass employed plays a major role in whether flake formation takes place. For example: flake formation may occur in non-borosilicate glass immediately after autoclaving, whereas in borosilicate glass, it occurs at temperatures much higher than those normally used for autoclaving. Glass containers may possess various additives such as oxides of boron, sodium, potassium, calcium, iron and magnesium which alter physical and chemical properties of the glass. For example, when formulating sulfate salts (drug substances or antioxidants) the glass container should have minimal amounts of calcium and barium to prevent the formation of insoluble inorganic salts. Many pharmaceutical preparations exhibit physical or chemical changes due to the radiant energy of light. Light radiations can cause color development or color fading and initiate an oxidation-reduction reaction resulting in drug degradation, rancidity of oil formulations, flavor and odor loss.

Flint glass, which is the most widely used multipurpose container material, has the disadvantage of being transparent to light rays above 300 mμ. As a result amber glass, which has the property of shutting out certain portions of the light spectrum, has been used extensively by the pharmaceutical industry. The transmission curves for flint and amber glass show that although flint glass transmits significantly from 300 mμ, amber glass does not begin to transmit to any appreciable extent until 470 mμ.

9.4.4 Types of Glass Containers

1. **Bottles:**
   - These are either amber metric medical bottles or ribbed (fluted) oval bottles. Both types are supplied with a screw closure.
   - Amber metric medical bottle are used for packaging a wide range of oral medicines.
   - Ribbed oval bottles are used to package various products that should not be taken orally; this includes liniments, lotions, inhalations and antiseptic solutions.
2. **Containers for Parenteral Products:**
   - Small-volume parenteral products, such as subcutaneous injections, are typically packaged in various containers made of Type I glass.
3. **Jars:**
   - Powders and semi-solid preparations are generally packed in wide-mouthed cylindrical jars made of clear or amber glass.
4. **Dropper Bottles**:
   - Eye drop and dropper bottles for ear and nasal use are hexagonal-shaped amber glass containers fluted on three sides. They are fitted with a cap, rubber teat and dropper as the closure.
   - Packaging materials

9.5 PLASTICS AS PACKAGING MATERIAL

Plastics in packaging have proved useful for a number of reasons, including the ease with which they can be formed, their high quality, and the freedom of design to which they can be changed. Plastic containers are extremely resistant to breakage and thus offer safety to consumers along with reduction of breakage losses at all levels of distribution and use. Plastic containers for pharmaceutical products are primarily made from the following polymers:

Examples:

1. Polyethylene,
2. Polypropylene,
3. Polyvinyl chloride,
4. Polystyrene, and
5. To a lesser extent, poly ethyl methacrylate, polyethylene terephthalate, polytrifluoro-ethylene, the amino formaldehydes and polyamides.

Plastic containers consist of one or more polymers together with certain additives. The amount and nature of the additives are determined by the nature of the polymer, the process used to convert the plastic into the containers, and the service expected from the container. For plastic containers in general, additives may consist of antioxidants, antistatic agents, colors, opact modifiers, lubricants, plasticizers, and stabilizers.

There are two types of plastics:

(i) Thermosets (screw caps) and

(ii) Thermoplastics.

Advantages of Plastics:

The advantages of plastics for packaging are as follows:

1. Release few particles into the product.
2. Flexible and not easily broken.
3. Are of low density and thus light in weight.
4. Can be heat sealed.
5. Are easily mounded into various shapes.
6. Suitable for use as container, closure and as secondary packaging.
7. Cheap.

Disadvantages of Plastics:

The disadvantages of plastics are:

1. They are not as chemically inert as Type-I glass.
2. Some plastics undergo stress cracking and distortion from contact with some chemicals.
3. Some plastics are very heat sensitive.
4. They are not as impermeable to gas and vapor as glass.
5. They may possess an electrostatic charge which will attract particles.
6. Additives in the plastic are easily leached into the product.
7. Substances such as the active drug and preservatives may be taken up from the product.

9.5.1 The Principal Plastic Materials used in Pharmaceutical Packaging

Plastic polymer	Properties	Uses	Notes
Low-density polyethylene (LDPE)	Soft, flexible and easily stretched.	Squeeze bottles as eye drop bottles.	• Disadvantages. of PE (LDPE and HDPE): • Softened by flavoring agent and aromatic oils, • Unsuitable for packaging oxygen sensitive products, • Adsorb antimicrobial preservative agents, • Crack on contact with organic solvents.
High-density polyethylene (HDPE)	Strong, stiff, less permeable to gases than LDPE.	Bottles for solid dosage forms.	
Polypropylene	Strong and stiff, good resistance to cracking when flexed.	Used for closures with hinges. Used also for tablet containers and IV bottles.	—
Polyvinyl chloride (PVC)	Rigid	Laminate (for blisters) and the main constituent of IV bags.	—
Polystyrene (PS)	Clear, hard, brittle with low impact resistance.	Used for tubes and amber- tinted bottles. It is also used for jars for ointments and creams with low water content.	• Its use in drug packaging is limited due to its high permeability to water vapor

9.5.2 Types of Plastic Containers

1. Closures
2. Collapsible tubes
3. Unit dose packaging (blister, strip)
4. Paper

9.5.3 Storage and Stability of Medicines

Medicines cannot be kept indefinitely. Some can be kept for only a short time. There are six general causes for the limited time for which medicines can be kept and these are:

1. Loss of drug (such as hydrolysis or oxidation).
2. Loss of vehicle (such as evaporation of water or other volatile ingredients).
3. Loss of uniformity (such as caking of a suspension or creaming of an emulsion).
4. Change in bioavailability (particularly with tablets where ageing van reduce availability).
5. Change of appearance (such as colour changes).
6. Appearance of toxic or irritant products (as a result of a chemical change General notes for storage and expiry date Storing in a cool place means 8-15°C, in a refrigerator means at 2-8°C.

- **Expiry date** is the date after which the medicine should not be used. The expiry date is calculated from the shelf life at the time of preparation.
- **Shelf life** is normally the time that a medicine can be kept before the potency has fallen to 90% of the original.
- **Shelf life for manufactured products** is based on accelerated stability studies (Arrhenius plot).
- **The shelf for extemporaneous preparation** may be found in an appropriate monograph, if available. If no monograph is available, the product is labeled with as short an expiry date as possible.
- **Freshly prepared** is defined as prepared not more than 24 hours before issue.
- **Recently prepared** is defined as discarded after 4 weeks

At present, a great number of plastic resins are available for the packaging of drug products. A general description of the more popular ones is presented here.

9.5.4 Plastics used for Packaging

1. Polyethylene:

The density of polyethylene, which ranges from 0.91 to 0.96, directly determines the following basic physical characteristics of the blow-molded container:

- Stiffness,
- Moisture-vapor transmission,
- Stress cracking,
- Clarity or translucency.

Since these polymers are generally susceptible to oxidative degradation during processing and subsequent exposure the addition of some antioxidant is necessary in the level of hundreds of parts per million are used. Antioxidants generally used are butylated hydroxy toluene or dilauryl thiodipropionate and antistatic additives are often used in bottle grade polyethylenes. They minimize airborne dust accumulation at the surface bottle during handling, filling, and storage. These antistatic additives are usually polyethylene glycols or long chain fatty amides and are often used at 0.1 to 0.2% concentrations in HDPE.

Advantages :

- It is a good barrier against moisture but a relatively poor one against oxygen and other gases.
- Most solvents do not attack polyethylene, and it remains unaffected by strong acids and alkalies.
- Polyethylene in all its variations offers the best all-around protection to the greatest number of products at the lowest cost.

Disadvantages:

- Lack of clarity.
- Relatively high rate of permeation of essential odors, flavors, and oxygen militate against the use of polyethylene as a container material for certain pharmaceutical preparations.

2. Polypropylene (PP):

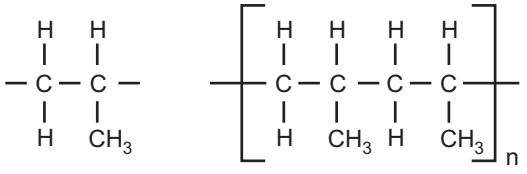
Polypropylene (PP) has recently become popular because it has many of the good features.

Advantages:

- Polypropylene does not stress-crack under any conditions.
- Except for hot aromatic or halogenated solvents which soften it, this polymer has good resistance to almost all types of chemicals including strong acids, alkalies and most organic materials.
- Its high melting point makes it suitable for boilable packages and for sterilizable products.
- Polypropylene is an excellent gas and vapor barrier.
- Its resistance to permeation is slightly better than that of HDPE.
- It is superior to low-density or branched polyethylene (LDPE).

Disadvantages:

- Lack of clarity.
- It is brittle at low temperature.
- In its purest form, it is quite fragile at 0°F and must be blended with polyethylene or other materials to give it the impact resistance required for packaging.



Propylene (Monomer) Polypropylene (Polymer)

3. Poly-Vinyl Chloride (PVC):

Advantages:

- They can be produced with crystal clarity, provide a fairly good oxygen barrier and have greater stiffness.
- It is an inexpensive, tough, clear material that is relatively easily processed.
- PVC is an excellent barrier for oil, both volatile and fixed alcohols, and petroleum solvents.
- It retains odour and is a good barrier for oxygen, moisture and gases.
- PVC is not affected by acids or alkalies except for some oxidizing acids.
- It may also be used as a skin coating on glass bottles. This is accomplished by dipping the bottle in a polyvinyl chloride plastisol and curing the coating, which produces a shatter-resistant coating over the glass bottle.
- It is impermeable to moisture and gas.
- It is inexpensive and versatile which has led to the widespread use in blister packs.

Disadvantages:

- In its natural state, polyvinyl chloride has poor impact resistance.
- PVC is seldom used in its purest form.
- If overheated it starts to degrade at 280°F and the degradation products are extremely corrosive.
- The colour of PVC becomes yellow when exposed to heat or ultraviolet light, unless a stabilizer is included by the resin supplier.
- It is virtually impossible to process vinyls at elevated temperatures without a stabilizing agent.
- In the formulation of PVC compounds with calcium-zinc stabilization materials, all ingredients are used in concentrations below their maximum extractable concentrations.
- It is possible to incriminate in the development of cancer of the liver (angiosarcoma) in some persons exposed to vinyl chloride monomer and polyvinyl chloride during manufacture.

4. Polymonochloro-Trifluoroethylene (PCTFE):

PCTFE comes under the trade name Aclar.

Advantages:

- It is one of the most inert plastics
- It has low permeability to moisture.
- It is the most expensive plastic and has so far only been used in packaging as a thin layer (laminated to PVC) for blister packing. Three copolymers are in use: 22A, 33C and 88A. 33 C is the cheapest and has a similar permeability at approximately half the thickness.
- New homopolymers Rx 160, ultRx 2000 and 3000, SupRx 900 offer certain advantages over the copolymers, including lower costs.

Disadvantages:

- The basic monomer chlorofluoroethylene C,C1/73, is associated with toxicity.
- PCTFE is a good barrier against moisture, but a poor one against O_2, N_2 and CO_2 relatively to PVdC.

5. Polystyrene:

Advantages:

- It is a rigid, crystal clear plastic.
- It is relatively low in cost.
- The plastic has a high water vapor transmission (in comparison to high-density polyethylene) as well as high oxygen permeability.
- It is resistant to acids, except strong oxidizing acids, and to alkalies.

Disadvantages:

- Polystyrene is not useful for solid dosage products.
- Depending on the methods of manufacture and other factors, polystyrene containers are easily scratched and often crack when dropped.

- It easily builds up a static charge; it has a low melting point (190°F) and therefore cannot be used for hot items or other high-temperature applications.
- It is attacked by many chemicals, which cause it to craze and crack so it is used for packaging dry products only.

Remedy:

- To improve impact strength and brittleness (both of which are sometimes referred to as practical toughness), general purpose polystyrene may be combined with various concentrations of rubber and acrylic compounds which diminishes certain properties with impact polystyrene e.g. clarity and hardness.
- The shock resistance or toughness of impact polystyrene may be varied by increasing the content of rubber in the material.

6. Nylon (Polyamide):

- Nylon is made from a dibasic acid combined with a diamine. So there is a -great variety of nylons. The type of acid and amine that is used is indicated by an identifying number: nylon 6/10 has 6 carbon atoms in the diamine and 10 in the acid.
- Nylon and similar polyamide materials can be fabricated into thin-wall containers.
- Nylon can be autoclaved.

Advantages:

- It is extremely strong and quite difficult to destroy by mechanical means.
- The widespread acceptance of nylon is due to its resistance to a wide range of organic and inorganic chemicals.
- It is highly impermeable to oxygen.
- It is not a good barrier to water vapor, but when this characteristic is required; nylon film can be laminated to polyethylene or to various other materials.

Disadvantages:

- Its relative high-water transmission rate and the possibility of drug-plastic interaction have reduced the potential of nylon for long term storage of drugs.

7. Polycarbonate:

Polycarbonate can be made into a clear transparent container. This relatively expensive material has many advantages.

Advantages:

- It has ability to be sterilized repeatedly.
- The container is rigid like glass thus has been considered a possible replacement for glass vials and syringes.
- Polycarbonate is resistant to dilute acids, oxidizing or reducing agents, salts, oils (fixed and volatile), greases, and aliphatic hydrocarbons.
- The impact strength of polycarbonate is almost five times greater than other common packaging plastics; components can be designed with thinner walls to help reduce cost.
- Polycarbonate articles can be subjected to repeated sterilization in steam or water without undergoing significant degradation.

Disadvantages:

- It is only moderately chemically resistant and only a fair moisture barrier.
- It is FDA-approved, although its drug-plastic problems have not been investigated adequately.
- It is attacked by alkalies, amines, ketones, esters, aromatic hydrocarbons, and some alcohols.
- Polycarbonate resins are expensive and consequently are used in speciality containers.

8. Acrylic Multipolymers (Nitrile Polymers):

Advantages:

- These polymers represent the acrylonitrile or methacrylonitrile monomer.
- They have unique properties such as gas barriers, good chemical resistance, excellent strength properties, and safe disposability.
- They are advantageous in food packaging due to the oil and grease resistance as well as minimal taste transfer effects which is regulated to standards set by the Food and Drug Administration.
- This medium cost material produces a fairly clear container (not as brilliant as styrene).
- The present safety standard is less than 11 ppm residual acrylonitrile monomer, with allowable migration at less than 0.3 ppm for all food products.

9. Polyethylene Terephthalate (PET):

Polyethylene terephthalate is generally called as PET which is a condensation polymer typically formed by the reaction of terephthalic acid or dimethyl terephthalate with ethylene glycol in the presence of a catalyst.

Advantages:

- It is used as a packaging film since late 1950s, its growth has recently escalated with its use in the fabrication of plastic bottles for the carbonated beverage industry.
- The development of the biaxially oriented PET bottle has a major impact on the bottling of carbonated beverages, accounting for an estimated annual resin usage of approximately 350 million pounds.
- Its excellent impact strength and barrier properties make it attractive for use in cosmetics, mouth washes as well as in other products in which strength, toughness, and barrier are important considerations.
- The resin has been sanctioned for over 25 years by the FDA for food contact applications and has been the recipient of a favorable environmental impact statement.

10. Acetal Polyoxymethylene (POM):

POM is available under trade name Delrin and Kemetal. It is obtained from the polymerization of formaldehyde.

Advantages:

- It is basically an engineering plastic with high tensile strength, stiffness, and good fatigue endurance.
- Its Usage usually lies with devices, aerosol valves and similar engineering components. The density of POM is approximately 1.41.
- POM less hygroscopic than nylons, and if correctly stored it does not require pre-drying.
- Being a polymerization product of formaldehyde, residues may have to be checked.

11. Regenerated Cellulose:

Although it is a derivative of wood pulp comes under plastics.

Properties:

- Uncoated regenerated cellulose film is very hygroscopic.
- Highly permeable to water.
- Has poor dimensional stability.
- Coated film is strong, flexible and transparent with good grease resistance.
- Coated films are mainly used as transparent overwraps, strip packs and as an outer ply in laminations which comes under trade names such as cellophane and rayophane.

12. Other Plastics:

- Coextruded resins are being used to fabricate bottles and thermoformed blisters with barrier characteristics.
- Coextrusion technology allows the use of high-barrier resins such as ethylene vinyl alcohol which could not be used alone because of either high cost or physical/ dimensional instability.
- The resins used in the coextrusion can be selected to provide optimum performance characteristics for the particular product needs.
- A coextrusion such as polypropylene/ethylene-vinyl-alcohol/ polypropylene provides the moisture barrier of polypropylene coupled with the enhanced gas barrier of ethylene vinyl alcohol.
- It also provides packaging alternatives for products that previously were packaged only in glass.
- High-barrier plastics that might compete with glass and metal containers may be available through a new processing technology developed by Du Pont Co which involves dispersing nylon in a polyolefin resin so that the final polymer matrix contains unique laminar arrangement of nylon platelets, which provide a series of overlapping barrier walls.
- It is reported that this technique produces a plastic which when compared with the polyolefins demonstrates a 140-fold increase as a barrier against certain hydrocarbons and an 8 fold increase as a barrier for oxygen.

9.5.5 Drug-Plastic Considerations

The chief disadvantage of plastic containers when compared with glass is the problem of permeation in two directions:

- From the solution into the container,
- From the ambient environment through the plastic into the preparation.

Materials can be leached from the plastic container/adsorbed/absorbed into the liquid preparation and in certain instances; the contents of the container can chemically or physically react with the plastic components of the container causing container deformation. Drug-plastic considerations have been divided into following:

1. Permeation
2. Leaching
3. Sorption
4. Chemical reaction and
5. Alteration in the physical properties of plastics or products.

1. Permeation:

The transmission of gases, vapors, or Liquids through plastic packaging materials can have adverse effects on the shelf-life of a drug.

(i) For example: Penicillin tablets were found to degrade in polystyrene containers leading to permeation of water vapor.

(ii) A change in colour and taste of tetracycline suspension was observed owing to permeation of air through the walls of a polyethylene container.

Factors Influencing Permeability:

- Temperature and humidity are important factors influencing the permeability of oxygen and water through plastic.
- An increase in temperature reflects an increase in the permeability of the gas. Great differences in permeability are possible depending on the gas and the plastic used. Whereas molecules do not permeate through crystalline zone as a result increase in crystalline of the material should decrease permeability.
- Ex: hydrophilic material such as nylon is poor barriers to water vapor whereas hydrophobic materials such as polyethylene provide much better barriers.
- Whereas formulations containing volatile ingredients might change when stored in plastic containers and often, the aroma of cosmetic products becomes objectionable, owing to transmission of one of the ingredients, and the taste of medicinal products changes for the same reason.

2. Leaching:

Most of the plastic contains some small amount of ingredients to stabilize or impart a specific property to the plastic, the prospect of leaching or migration from the container to the drug product is present. Problems can arise with plastics when dyes are added to the formula in relatively small amounts. Special dyes can migrate to a parenteral solution and cause a toxic effect. Emissions of a component from the plastic container to the drug product can lead to drug contamination and necessitate removal of the product from the market.

3. Sorption:

This process involves the removal of agents from the pharmaceutical composition by means of the packaging material. Sorption can have serious consequences for pharmaceutical compositions containing important ingredients in solution. Since high-potency drugs are administered in low doses, sorption losses may significantly affect the therapeutic effectiveness of the formulation. In practice, the loss of preservatives is often a problem. These agents act at low concentrations, and their sorption caused by sorption can be high enough to prevent the product from being protected from microbial growth.

Factors Influencing Characteristics of Sorption from Product:

- Chemical structure
- pH
- Solvent system
- Concentration of active ingredients
- Temperature
- Length of contact and
- Area of contact.

4. Chemical Reactivity:

Other ingredients used in plastic structure can respond to chemicals in one or more drug products. Sometimes the ingredients in formulation can be touched by plastic. Even small items of non-chemical substances can change the appearance of plastic or drug products.

5. Alteration in the Physical Properties of Plastics or Products:

Physical and chemical changes in packaging materials due to pharmaceuticals are called a **correction**. Phenomena such as penetration, sorption, and leaching play the role of changing the properties of plastics and may also lead to its degradation. Deformation of polyethylene containers is often caused by the penetration of gases and vapors from the environment, or the loss of contents from the walls of the container.

For example: Isteris has been found to be responsible for the considerable change in the mechanical properties of the plastic. Fluorinated hydrocarbons attack polyethylene and polyvinyl chloride. Changes in polyethylene caused by some agents have been noted.

- In other cases, the contents may extract plasticizers, antioxidants, or stabilizers, which change the flexibility of the package. Polyvinyl chloride is an excellent barrier to petroleum solvents, but the plasticizer in polyvinyl chloride is extracted by the solvent. This action usually leaves the plastic hard and hard. In some cases, this effect may not be immediately recognized as the solvent softens the plastic or substitutes for the plasticizer.
- Plastic containers used for emulsion preparations must be thoroughly evaluated for physical and chemical changes. Certain materials in an emulsion have a tendency to migrate toward the polyethylene wall, causing either a change in the emulsion or a collapse in the container. Since polyethylene has a tendency toward elastic recovery, air is continuously drawn into the plastic container, increasing the chance of

oxidation and drying out of the preparation. The air can cause the emulsion to break down, owing to dehydration or oxidation of the oil phase. This phenomenon is known as "breathing". It can also be responsible for the loss of flavor and perfume ingredients from products packaged in plastic containers.

QUESTIONS

Long-answer questions:

1. Define Packaging of Pharmaceutical Products. Function of packaging.
2. Explain different types of packaging of pharmaceuticals.
3. Write the factors influencing the choice of packaging.
4. What are the types of containers used as primary packaging for liquid orals?
5. Write the properties of packaging materials.
6. Define : (i) Glass containers, (ii) Composition of glass, (iii) Types of packaging material used for pharmaceutical packaging.
7. Explain the manufacture of glass.
8. Define ampoules, bottles, vials and syringes.
9. Define plastic container. Write its advantages and disadvantages.
10. Define closure function. Write characteristics, composition and types of closure.
11. Define rubber and metal. Write advantages and disadvantages. What are the different types of rubber and metal used in pharmaceutical packaging?
12. Define blister packaging and application pharmacy.

Short-answer questions: (2 marks each)

1. Define primary packaging system.
2. What is ideal requirement of pharmaceutical packaging material?
3. Write short notes on:
   (a) Selection of packaging material.
   (b) Containers of pharmaceutical packaging
   (c) Preparation of glass materials.
   (d) Types of glass materials.
   (e) Advantages and disadvantages of glass materials.
   (f) General properties of plastics.
   (g) Types of plastics.
   (h) Properties of rubbers.
   (i) Tamper resistance packaging.

☆☆☆