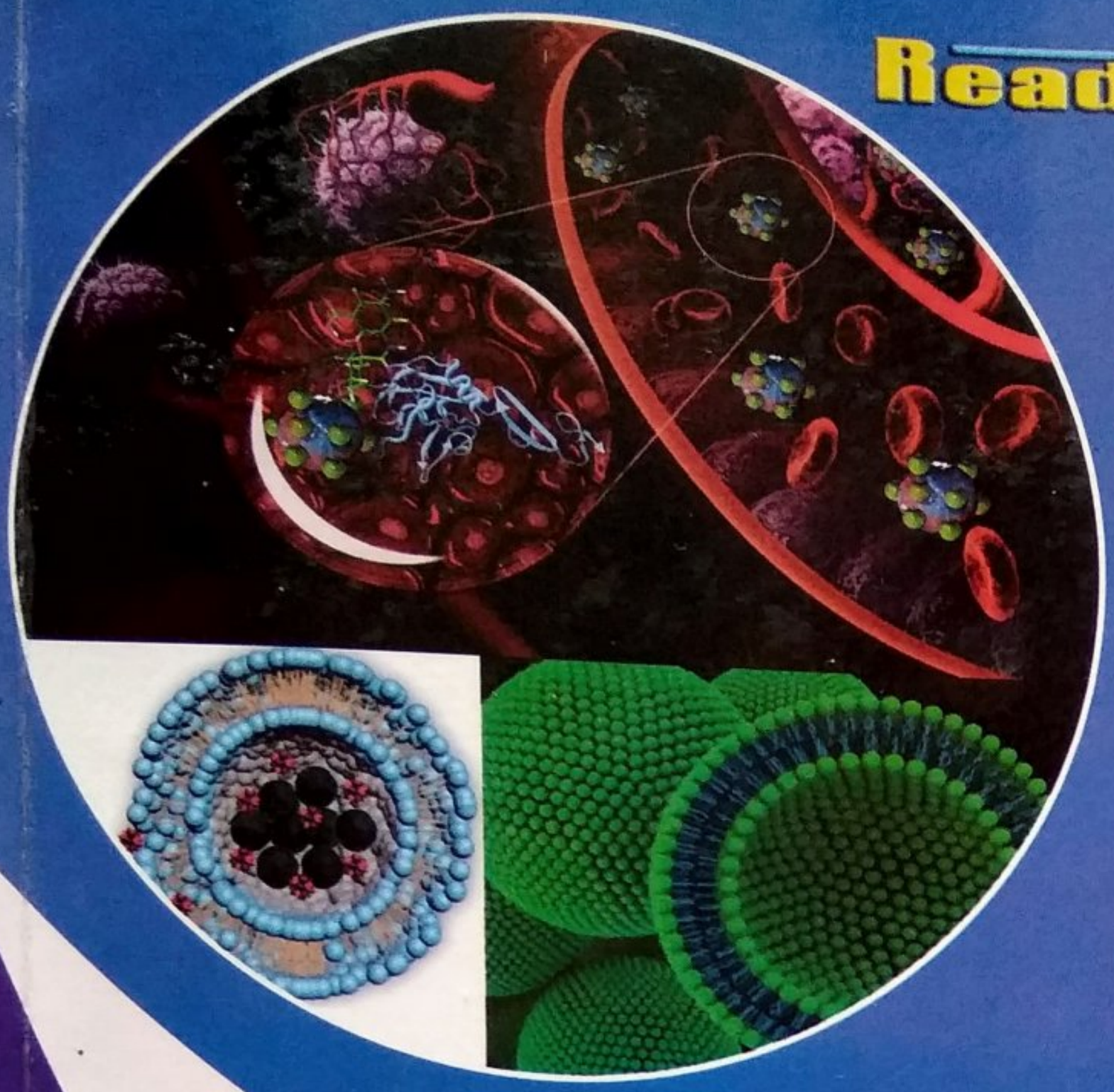
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AS PER (PCI) SYLLABUS
B.Pharma
7th
Semester

Novel Drug Delivery System

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CHAPTER 1

Controlled Drug Delivery Systems

1.1. CONTROLLED DRUG DELIVERY SYSTEMS

1.1.1. Introduction

Controlled drug delivery system maintains suitable and desired drug release over an extended time period. A controlled dosage form is formulated using hydrophilic polymer matrix. An ideal controlled drug delivery system releases adequate amount of drug at regular time intervals and at the target site of action to maintain therapeutic levels of drug in blood plasma.

The oral controlled drug delivery system offers potential advantages of controlled release rate and dose maintenance in plasma. The controlled release formulations are incorporated with swelling polymers or waxes or both for controlling the drug release rate. Reservoir system also provides the desired controlling release rate.

Controlled release drug delivery system aims to reduce the dosing frequency, reduce the dose, and deliver the drug uniformly. Thus, controlled release dosage form releases the drugs continuously at a predetermined rate for a fixed time period, either systemically or locally to the target organ. Controlled release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effects, increased efficacy, and constant delivery.

1.1.2. Terminologies/Definitions

The related terminologies for controlled drug delivery or modified release delivery systems are as follows:

1) **Controlled-Release Formulation:** The controlled release system maintains a constant supply of the drug at zero-order rate by continuously releasing the drug for a certain time period in amount equivalent to that eliminated by the body. An ideal controlled drug delivery system delivers the drugs either locally or systematically at a predetermined rate for a specific time period.

2) **Repeat Action Preparation:** A drug dose, equivalent to a single dose of the conventional drug formulation, is initially released immediately after administration. After a certain time period, a second single dose is released. In some preparations, a third single dose is also released after a certain time.

3) **Extended-Release Formulation:** This dosage form allows two-fold reduction in dosage frequency in comparison to the immediate-release (conventional) dosage form. **Examples** of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.

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4) **Delayed-Release Preparation:** This dosage form releases a discrete portion(s) of drug at a time or at specific time intervals after administration, although one portion may be released immediately after administration. An **example** of delayed-release dosage form is enteric-coated dosage form.

5) **Targeted-Release Drug Product:** This dosage form releases drug at or near the intended physiological site of action. These dosage forms may have either immediate or extended-release characteristics.

6) **Site-Specific Targeting System:** This system targets a drug directly to a certain biological location. The target is adjacent to or in the diseased organ or tissue.

7) **Receptor Targeting System:** This system targets a drug directly to a certain biological location. The target is the particular receptor for a drug in an organ or tissue. Site-specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are considered as controlled drug delivery systems.

8) **Controlled Action System:** This system provides a prolonged duration of drug release with predictability and reproducibility of drug release kinetics. The drug absorption rate is equal to the drug removal rate from the body.

9) **Sustained Action System:** This system initially provides a sufficient amount of drug to the body to produce the desired pharmacological action. The remaining drug amount is released periodically and maintains the maximum initial pharmacological activity for a desirable time period in excess of time expected from usual single dose.

10) **Prolonged Action System:** This system releases the drug over an extended time period during which pharmacological response is obtained, but it does not maintain the constant blood level.

1.1.3. Rationale

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters essential in a selected administration route. Thus, for designing optimum controlled release systems, a thorough understanding of the pharmacokinetics and pharmacodynamics of drug is required.

However, if the doses are not administered at scheduled time, the resulting peaks and valleys reflect less than optimum drug therapy. **For example**, if a drug is administered at frequent doses, it will reach its Minimum Toxic Concentration (MTC) and will also result in toxic side effects. If doses are missed, periods of sub-therapeutic drug blood levels or those below the Minimum Effective Concentration (MEC) will result, with no patient benefit.

The **medical rationale** for the development of controlled drug delivery system is important for the following aspects:

1) **Reduced Dosing Frequency:** Use of conventional drug therapy limits the frequency of dosing, i.e., a chance of skipping a dose; this problem can be resolved with the development of controlled release dosage form that releases the drug over an extended time period and maintains the desired drug concentration in blood.

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By increasing the time interval between the doses, the number of doses can be reduced from 3-4 times to 1-2 times. Proteins and peptides can be delivered into the body using a controlled release system. Tumour therapies can also be improved with enhanced targeting. Therapeutic efficacy and safety of drugs are improved by targeting the drugs in the body in a more precise manner, and by reducing the dosing frequency.

2) **Reduced Drug Exposure to the Biological Environment:** The CRDDS alters either the pharmacokinetic or pharmacodynamic profile of the active metabolites. Designing of such a system involves a property of rate controlling and achieving better plasma concentration. The CRDDS system controls the drug concentration in cells and tissues of the target sites.

A drug is released in a controlled manner by either temporal control or distribution control. The **temporal control** allows the system to deliver the drug over an extended time period at specific intervals within the treatment regimen. This approach is useful for the drugs having a fast metabolism rate. Conversely, the **distribution control** allows the system to deliver the drug at the target sites within the body. Drugs like steroids, antibiotics, and hormones can be delivered using either of these approaches.

3) **Minimised Plasma Concentration Fluctuations:** With the use of conventional tablets or capsules, only a single and transient type of burst occurs, when the drug effect is above minimum effective concentration. The response is observed pharmacologically, but a problem arises when the response is narrow; in this case, CRDDS is used to reduce the fluctuations in plasma levels by retarding the absorption rate, accompanied by slower drug release.

The drug formulation is modified to reduce the fluctuations during the dosing interval. This approach is beneficial for the drugs having short half-lives and low therapeutic indices, for which maintenance of therapeutic drug concentrations is mandatory. Formulating such drugs (**e.g.,** procainamide and quinidine) in CRDDS improves patient compliance and reduces the chances of toxicity.

4) **Better Patient Compliance:** Development of any dosage form aims to provide better patient compatibility. Designing a dosage regimen for a drug influences its duration of action, bioavailability, absorption rate, and elimination rate. These factors in turn influence the therapeutic response of the dosage form. The CRDDS are ideal for delivering the drug at the target site of the body over an extended time period, and thus for maintaining relationship between the plasma concentration levels and the therapeutic response, and for improving patient compliance.

Some drugs are unstable on oral administration, and thus are administered through a different route to improve the drug bioavailability and therapeutic response in the body, **e.g.,** nitroglycerine. The CRDDS is more sophisticated than just delaying the release and delivering the drug with controlled release rates within the specific time period. This system maintains the drug levels within the required range with only few administrations.

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5) **Lower Adverse/Side Effects:** The dose and dosing intervals of each drug designed as conventional dosage form are varied. Each drug produces a different therapeutic response in plasma concentrations; the unbalanced response results in improper therapeutic effect or undesirable side effects. In rate-controlled dosage forms, the dosing intervals are increased and fluctuations in plasma levels are reduced to minimise the risk of undesirable side effects. Incidences of side effects is a part of plasma concentration, and can be minimised by handling plasma drug concentration at a particular time.

For example, by administering levodopa in the form of CRDDS, the risk of dyskinesis that the drug may cause is reduced. The CRDDS reduce the risk of side effects in the GIT and produce effective results. **For example,** potassium chloride and ferrous sulphate cause GIT irritation, which can be reduced by slowing the drug release.

6) **Augmented Efficacy:** For designing an ideal drug delivery system, two prerequisites should be fulfilled. Firstly, the drug should be delivered at a rate that a body requires over a time period. Secondly, the action should be at the specific site at specific receptors. These goals can be achieved by using CRDDS.

This system is biologically irresponsive to the external environment. The prolonged release dosage form slows down the absorption rate due to the slow release rate of the drug by small bursts over time, which improves the efficacy of CRDDS. By increasing the time interval between the doses, the total number of doses is reduced, thereby reducing the dosing frequency, and thus improving patient compliance.

The **biological rationale** for the development of controlled drug delivery system is important for the following aspects:

1) **Absorption:** The extent and rate of drug absorption should be considered while developing a CRDDS. Drugs having a very slow absorption rate show poor bioavailability, and thus are not suitable candidates to be formulated into CRDDS. Drugs having rapid absorption rate, however, can be formulated into successful controlled release products. Absorption window also affects the bioavailability of drugs administered orally. It can even hinder the development of CRDDS as some drugs undergo absorption in a specific region of GIT, which after absorption in the absorption window can go waste.

Drug release is a rate-limiting step in CRDDS; therefore, fast drug absorption is required from a dosage form in terms of extent and rate of drug absorption, especially for drugs administered orally. The amount of drug absorbed from conventional dosage forms is lower than that absorbed from CRDDS because of drug degradation due to metabolism or physical loss. **For example,** pilocarpine gets absorbed in the cornea in 1% ratio of applied dose, as it suffers loss due to drainage and absorption in non-specific tissues. By formulating pilocarpine into controlled release dosage form improves its bioavailability and maintains a constant level in specific tissues for the desired time.

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2) **Drug-Protein Binding:** It is a reversible process. If the drug concentration in blood is decreased, the drug-protein complex dissociates and leaves free drug to maintain balance. This reversible process of drug-protein binding maintains the drug level in the blood for an extended time period. Binding of drug with protein can function as a drug store for generating long-term action. **For example**, blood proteins recirculate in the body and are not eliminated; they act as a depot for drugs having controlled release profile; Quaternary ammonium compounds bind with mucin in the GIT, and the resultant complex then acts as a depot and enhances the absorption.

3) **Distribution:** Drug distribution in body is an important criterion to determine the overall elimination kinetics of the drug. Drugs whose volume of distribution (Vd) is higher than the real volume of distribution have a lesser half-life. While designing CRDDS, volume of distribution plays an important role as it affects the amount of drug in systemic circulation or reaching the target. The effect is not easy to determine because the volume of distribution is unpredictable.

Designing of CRDDS demands knowledge of drug disposition, but the fate is decided on the basis of pharmacokinetic parameters, like the volume of distribution. It affects the drug concentration in blood, and also the elimination kinetics of a drug. A drug's distribution property is described by volume of distribution by either extent of distribution in the body or by relative distribution of the drug in compartments.

These two parameters are independent of each other; **for example,** the relative distribution of procainamide is 10 times that of pentobarbital; however, both the drugs have same volume of distribution. Similarly, the relative distribution for procainamide is much larger than that of digoxin, and its volume of distribution at steady state is lower than that of digoxin.

4) **Elimination:** Every biological response parameter is beneficial in designing CRDDS. Most of the drugs undergo elimination within 20 hours of their administration. The zero-order rate of release is directly proportional to the elimination rate and is given by the biological half-lives. The drugs having short half-lives require frequent dosing, thus are suitable to be formulated into CRDDS; while the drugs having long half-lives do not require frequent dosing, thus are considered poor candidates to be formulated into CRDDS. Drugs having half-lives < 1 hour (**e.g.,** ampicillin and penicillin) and > 8 hours (**e.g.,** digitoxin and digoxin) are also considered poor candidates to be formulated into CRDDS.

5) **Dose-Dependent Bioavailability:** Effect of dose is another factor that influences the designing of CRDDS. **For example**, bioavailability of propoxyphene is dose-dependent, thereby restricting its use in CRDDS, because of the rate at which CRDDS should be able to achieve reproducible bioavailability. Bioavailability is another important factor that should be taken into account while formulating CRDDS. The CRDDS formulation should be able to present about 80% of bioavailability in comparison to the conventional dosage form.

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6) **Duration of Drug Residence within the Therapeutic Window:** Duration of drug residence and the drug's half-life should be taken into consideration while designing CRDDS. Most of the marketed drugs exhibit half-lives of 1-20 hours. Drugs having short half-lives require frequent dosing to maintain the desired drug plasma concentrations, thus such drugs are formulated into CRDDS.

A drug's pharmacokinetic profile in a steady state concentration indicates that the release rate of the drug is directly proportional to its elimination rate. Drugs showing linear kinetics have a constant half-life and do not follow a change. Metabolism, distribution, and elimination are the factors influencing the half-life of drugs. The limit of half-life for CRDDS is not yet defined and the exact half-life value for a good CRDDS is not known.

The drug candidate with this half-life value has a ratio value of sustaining dose to immediate dose of 2, if it shows release up to 12 hours. The controlled release product in this case can be developed for 1gm amount with the drug having a dose of 325mg. **For example**, due to its dose, procainamide is administered after every 3 hours to reduce fluctuations in plasma drug concentration. The CRDDS of procainamide maintains plasma level for 8 hours.

7) **Better Safety Margin:** Therapeutic Index (TI) is the most common approach used for defining the safety margin of drugs by the following equation:

$$TI = \text{Median toxic dose} / \text{Median effective dose} \quad \text{.....(1)}$$

This ratio provides a rough estimate of the relative safety of drugs; the drug candidate is considered safe if its TI value is > 10. **Larger the ratio, safer the drug**. This approach plays an important role in monitoring a drug therapy, especially for drugs having either narrow therapeutic index or narrow therapeutic concentration, **e.g.,** antiarrhythmic drugs, like digoxin and digitoxin.

8) **Individualisation in a Diseased Condition:** The diseased state of a body is an important part in consideration of drug candidate for CRDDS. **For example**, aspirin is still used in the treatment of rheumatoid arthritis, but due to its biological half-life (6 hours), it is not considered a good candidate for formulation into CRDDS. Whereas, a controlled release dosage form tends to maintain a therapeutic concentration and provides release for up to 10 hours, which is more than non-controlled formulation. Safety margin of the drug can be made out using TI of the drug, along with its plasma concentration value, to make it therapeutically effective. This approach is valuable for drugs having a narrow absorption window and a narrow therapeutic range concentration.

The drug release pattern should be precise to achieve safe therapeutic range; other factors, like drug accumulation due to frequent dosing and variability in patients, can alter plasma level. By controlling the TI, the drug concentration can be controlled.

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1.1.4. Advantages

Controlled drug delivery system has the following advantages over a conventional dosage form:

1) It improves patient convenience and compliance by reducing the dosing frequency.
2) It reduces fluctuation in steady-state levels, and provides better control of disease condition and reduced intensity of local or systemic side effects.
3) It increases the safety margin of highly potent drugs due to better control of plasma levels.
4) It allows maximum utilisation of drug, thereby reducing the total amount of dose administered.
5) It reduces the healthcare costs through improved therapy, shorter treatment period, reduced dosing frequency, and reduction in personnel time to dispense, administer and monitor patients.
6) It maintains the drug levels within the desired range.
7) It offers slow release of water-soluble drugs and fast release of low solubility drugs.
8) It eliminates the incidences of over- or under-dosing.
9) It improves the efficiency of treatment.
10) It obtains less potentiation or deduction in drug activity with chronic use.
11) It reduces drug accumulation with chronic dosing.
12) It improves bioavailability of drugs.
13) It maintains the required drug concentration in plasma, and thus eliminates failure of drug therapy and improves the efficiency of treatments.
14) It is a suitable delivery system for drugs having a short biological half-life (3-4 hours) and for drugs that undergo rapid elimination from the body.

1.1.5. Disadvantages

Controlled drug delivery system has the following disadvantages:

1) It decreases systemic availability (in comparison to immediate release conventional dosage forms) due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site-specific absorption, pH-dependent solubility, etc.
2) It shows a poor in vitro-in vivo correlation.
3) It may give rise to dose dumping due to food, physiologic or formulation variables, or chewing of oral formulations by the patients, and thus, increases the risk of toxicity.
4) Retrieval of drug is difficult in case of toxicity, poisoning, or hypersensitivity reactions.
5) It reduces the potential for dosage adjustment of drugs administered in varying strengths.
6) Its formulation cost is high.
7) Its drug release period is influenced and limited by GI residence time.
8) It shows poor patient compliance as drugs having short half-lives require frequent administration, and some patients may miss the dose.

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9) The unavoidable fluctuations of drug concentration may result in under- or over-medication in narrow therapeutic index drug.
10) It gives a typical peak-valley plasma concentration-time profile due to which attainment of steady state condition is impossible.
11) Its major disadvantage is dumping, i.e., rapid release of a relatively large quantity of drug from a controlled release formulation. This phenomenon is hazardous with potent drugs.
12) It is difficult to optimise the accurate dose and dosing interval.
13) Patient variability, like GI emptying rate, residential time, fasting or non-fasting condition, etc., affects the drug release rate.

1.1.6. Differences Between Conventional, Sustained Release, and Controlled Release Dosage Forms

Table 1.1 enlists the major differences between conventional, sustained release, and controlled release dosage forms:

Table 1.1: Differences Between Conventional, Sustained Release, and Controlled Release Dosage Forms

Conventional Dosage Forms	Sustained Release Dosage Forms	Controlled Release Dosage Forms
The drug solubilises in the gastric contents. These dosage forms do not sustain either their dissolution or their absorption.	These dosage forms maintain the drug release rate over a sustained period.	These dosage forms lead to predictable and constant plasma concentrations, independently of the biological environment of the application site.
These dosage forms release the drug in a single action following a first-order kinetics.	The dose in these dosage forms is of less significance than the release rate from the therapeutic system.	These dosage forms release the drug in a pre-determined pattern over a fixed time period following zero-order kinetics.
These dosage forms are related to all types of dosage forms.	These dosage forms are related to oral dosage forms.	The dosage forms are related to oral, vaginal and transdermal dosage forms.
The time interval *versus* drug plasma concentration profile for these dosage forms is short and show peak and valley effect.	The drug concentration for these dosage forms is maintained for a certain time period and then reduced.	The uniform drug concentration for these dosage forms is maintained for a pre-determined time period without fluctuations.

1.1.7. Selection of Drug Candidates

Selection of drug candidates for controlled release dosage forms is vitally important. Drugs that undergo or may undergo hepatic first-pass metabolism should not be formulated in a controlled release dosage form, because this will reduce their absorption rate, unless justified by the fact that this process gives rise to an active metabolite. Conversely, a little medical justification exists for the drugs having a long biological half-life (i.e., > 12 hours) and are to be formulated in a controlled release formulation, since these drugs are long-acting, unless the development of a controlled release formulation offers some convenience to the patient and improves patient compliance.

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Ideal Properties of a Drug Suitable for Sustained Release Drug Delivery System (SRDDS)

1) It should get effectively absorbed on oral administration and should remain stable in gastrointestinal fluid.
2) It should have a short half-life (2-4 hours), **e.g.,** captopril, salbutamol sulphate, etc.
3) Its dose should not be less than 0.5gm and its maximum dose for designing SRDDS should be 1.0gm, **e.g.,** metronidazole.
4) It should have a wide therapeutic range so that any variation in drug release does not result in concentration beyond the minimum toxic levels.

Compounds that are Unsuitable for Controlled Release Drug Delivery System (CRDDS)

Certain drug candidates are not considered suitable to be formulated in controlled release dosage forms owing to some of their properties. **For example,** drugs with an elimination half-life < 2 hours, or drugs having large doses to administer within the body, or drugs having a half-life > 8 hours are not required to be formulated as controlled release dosage form.

Thus, drugs with the following properties are considered inappropriate for designing CRDDS:

1) Drugs with a short and long half-life,
2) Drugs undergoing hepatic first pass metabolism,
3) Drugs with a low solubility, and
4) Drugs requiring to be administered in a large number of doses.

1.1.8. Properties of Drugs Relevant to Controlled Release Formulations

The release rate of drugs from controlled drug delivery system are affected by the following two major factors:

1) Physicochemical factors, and
2) Biological factors.

1.1.8.1. Physicochemical Properties

The following physicochemical properties of the drugs should be considered while selecting drug candidates for controlled and sustained release dosage forms:

1) **Molecular Size and Diffusivity:** Drugs formulated in sustained release dosage forms should diffuse through various biological membranes and also through a rate controlling membrane or matrix. **Diffusivity** is a drug's ability to pass through membranes, and it is a function of its molecular size or weight. Molecular size of the diffusing species has a significant influence on the diffusivity value (D) of polymers. Thus, the value of D is related to the size and shape of the cavities and of the drugs.

The diffusion coefficient values of drugs having intermediate molecular weight (150-400), through flexible polymers, range from 10^{-6} to 10^{-9} cm^2/sec; and the values in 10^{-8} order are the most common. The diffusion coefficient values of drugs having molecular weight >500 are so small (i.e., < 10-

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$12cm^2/sec$) that their quantification is difficult. Thus, drugs having high molecular weight should display very slow release kinetics in sustained release devices where diffusion through polymeric membrane or matrix is the release mechanism.

2) **Aqueous Solubility:** Drugs are mostly weak acids or weak bases. Drugs are formulated into sustained release dosage forms with very difficulty if their water solubility is low. While, it is difficult to delay the dissolution rate of drugs having a high water solubility and rapid dissolution rate. Drugs having a high water solubility readily dissolve in water or gastrointestinal fluid, are released in a burst, are quickly absorbed, and thus their concentration in blood is more than the drugs having low water solubility. Incorporating a highly water-soluble drug in the dosage form and retarding the drug release is a difficult task, especially when the drug dose is high. The pH-dependent solubility in physiological pH range is another problem for sustained release dosage forms due to the variation in pH of GIT and in dissolution rate.

3) **pH and pKa:** Highly ionised drugs are poor candidates for oral sustained release formulations. Unionised drugs undergo appropriate absorption, while the ionised drugs undergo negligible permeation as their absorption rate is 3-4 times less than that of the unionised drugs. An acidic drug with pH-sensitive ionisation has a pKa range around 3.0-7.5; while a basic drug with pH-sensitive ionisation has a pKa range around 7.0-11.0; and such drugs are ideal for optimum positive absorption. The drug should be unionised at the site to an extent 0.1-5.0%.

4) **Partition Coefficient:** It is the fraction of drug in an oil phase to that in an adjacent aqueous phase. Partition coefficient (K) influences drug permeation across the biological membranes, and also drug diffusion across the rate controlling membrane or matrix between the drug administration time and drug elimination time. The drug should diffuse through various biological membranes that act as lipid-like barriers. Apparent oil or water partition coefficient is the major evaluation criterion of the drug's membrane permeability (i.e., its ability to penetrate these lipid membranes), and is expressed as:

$$K = \frac{C_a}{C_w}$$

Where,

C_a = Equilibrium concentration of all forms of drug in an organic phase at equilibrium.

C_w = Equilibrium concentration of all forms of drug in an aqueous phase.

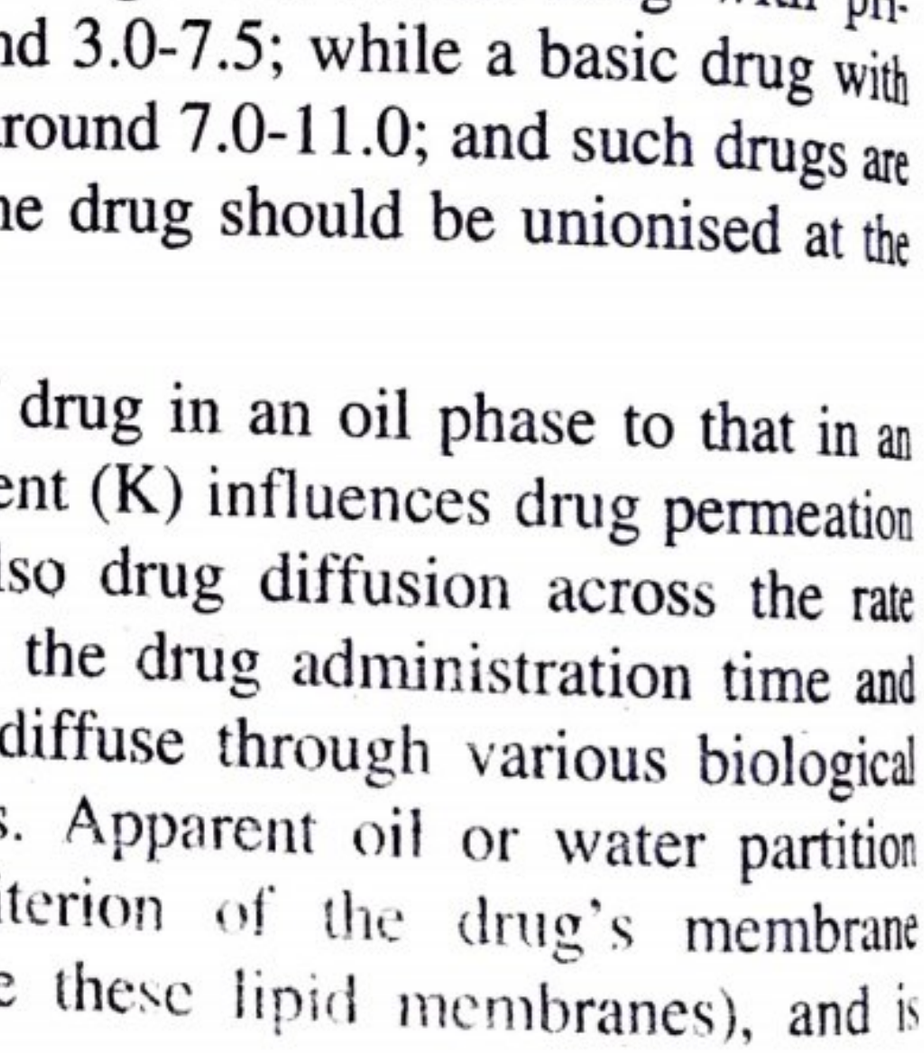


Figure 1.1: Relationship between Drug Action and Partition Coefficient

Generally, the drugs having a high K value are highly oil-soluble and readily partition into the membranes. **Hansch correlation** defines the relationship between tissue permeation and partition coefficient for the drug. This correlation describes a parabolic relationship between the logarithms of its partition coefficient (**figure 1.1**).

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5) **Permeability:** Log P, expressed lipophilicity, and molecular size of the drug are the three drug properties that influence the drug's permeability for passive transport across intestinal epithelium. Another important factor that determines the drug permeability is the polarity of drug, which is measured by the number of H-bond acceptors and H-bond donors on the drug molecule.

6) **Mechanism and Site of Absorption:** Drugs to be absorbed by carrier-mediated transport are not suitable to be formulated as controlled release systems. **For example**, vitamin B_{12} (a water-soluble vitamin) is required for several metabolic reactions and for preventing medical problems, especially hematopoietic conditions and spinal cord related neuropathies. Vitamin B_{12}, ingested in its free or non-protein bound form, will bind to a carrier protein, namely R-binders or *trans*-cobalamin I, that is secreted by the salivary glands in oropharynx and by the gastric mucosal cells in stomach.

7) **Drug Stability:** Loss of drug through acid hydrolysis and/or metabolism in GIT is an important factor for oral dosage forms. A solid drug degrades at a much slower rate than a drug in suspension or solution form; thus, the relative bioavailability of a drug that is unstable in stomach can be improved. The most appropriate controlling unit for the drugs that are unstable in intestine is the one that releases its contents only in the stomach; therefore, drugs with stability problems in any particular part of the GIT are considered as poor candidates to be incorporated into controlled release systems that deliver their content uniformly throughout the length of GIT. In controlled drug delivery systems, the drugs are protected from enzymatic degradation as they are incorporated into a polymeric matrix; thus, these systems are beneficial for highly unstable drugs.

1.1.8.2. Biological Properties

The following biological properties of the drugs should be considered while selecting drug candidates for controlled- and sustained-release dosage forms:

1) **Absorption:** Rate, extent and uniformity of drug absorption are the factors that should be taken into account for a drug to be formulated into a sustained release dosage form. Drug release from a dosage form (and not absorption) is the rate-limiting step in drug delivery from a sustained release system; thus, rapid rate of drug absorption relative to its release is essential for an efficient system. In controlled release dosage forms, Kr <<< Ka, and this is critical in case of oral administration. If a drug's transit time through the absorption half-life is 4 hours, a minimum absorption rate constant (Ka) of 0.17-0.23 hour is necessary for a drug to undergo 80-95% absorption over a transit time of 9-12 hours. A drug having a rapid absorption rate (ie., Ka >> 0.23-1 hour) has the first-order release rate constant (Kr) < 0.17-1 hour, and this results in poor bioavailability in many patients. Therefore, slowly absorbed drugs are difficult to formulate as controlled release dosage forms, in which the drugs should essentially meet the Kr <<< Ka criteria.

2) **Distribution:** Drug distribution in tissues and cells lowers the concentration of circulating drug and can also be rate-limiting in its equilibrium with blood and extravascular tissue, thus it majorly affects the drug elimination kinetics. Distribution involves binding of a drug to the tissues and blood proteins. Protein-bound drug molecules are inactive and cannot permeate the biological

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membranes. Also, a high degree of protein binding results in prolonged therapeutic action. Apparent volume of distribution (an important parameter of the drugs) is the magnitude of distribution and protein binding in the body. It is the proportionality constant of plasma drug concentration to the total amount of drug in the body. Thus, prior to designing sustained release systems, one should gather information regarding the drug disposition.

3) **Protein Binding:** Many drugs bind to plasma proteins and show related effects on the duration of drug action. Drug bound to blood proteins are mostly re-circulated (rather than getting eliminated). Drug bound to plasma proteins serve as a drug depot for a prolonged release of drug. The rate and extent of oral absorption of drug is also affected by the drug interaction and the binding period with mucin-like protein.

4) **Metabolism:** Drug metabolism involves either inactivation of an active drug or conversion of an inactive drug into an active metabolite. It occurs in various tissues, containing more enzymes. Drugs that get metabolised before absorption, either in the lumen or in the intestinal tissues, are released at a slower rate, and thus result in reduced bioavailability. The intestinal wall enzyme systems are mostly saturable. As the drug is released to these regions at a slower rate, less total drug is presented to the enzymatic process during a specific period, and thus the drug completely converts into its metabolites. Formulating these enzymatically-susceptible compounds as prodrugs is another feasible solution.

Drugs that can induce or inhibit enzyme synthesis are considered as poor candidates for sustained release delivery systems as they cannot maintain uniform blood levels. Also drugs whose bioavailability varies due to hepatic first-pass metabolism or intestinal metabolism are not considered suitable candidates for sustained release delivery systems.

5) **Elimination or Biological Half-Life:** An oral sustained release product aims to maintain therapeutic blood levels for an extended time period. For this, the drug should enter the blood circulation at a rate similar to its elimination rate (quantitatively described by the half-life). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, i.e., metabolism, urinary excretion, and the processes that eliminate the drug from blood circulation. Drugs having a short half-life are considered the best for sustained release delivery systems, as this reduces the dosage frequency. However, drugs having a very short biological half-life have limited use as extremely large amounts of drug are required in each dosage unit in order to maintain the sustained effect, thereby making the dosage form limiting large. In other words, drugs having a half-life < 2 hours are considered unsuitable for sustained release delivery systems. Drugs having a long half-life, i.e., > 8 hours, are also considered unsuitable for sustained release delivery systems as their effect is already sustained.

6) **Duration of Action:** The drug's duration of action plays a significant role in the formulation of controlled release delivery system. Distribution, metabolism, and elimination of the drug, however, affect the drugs' duration of action. Half-life of the drug is its residence time in the body. Drugs having

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higher elimination half-lives (> 8 hours) are already sustained in the body, and thus are not formulated as controlled release dosage forms. On the other hand, drugs having shorter half-lives (< 2 hours) are also not formulated as controlled release dosage forms as it may require large amounts of drug.

7) **First-Pass Metabolism:** It is the intestinal and hepatic degradation or alteration of an orally administered drug, after its absorption, removing some of the active substances from the blood before it enters the systemic circulation. Liver is the major site of first-pass metabolism of an orally administered drug; however, GIT, blood, vascular endothelium, lungs, and the arm from which venous samples are taken are other potential sites. Amitriptyline, 5-fluorouracil, hydralazine, isoprenaline lignocaine, lorcainide, pethidine, metoprolol, morphine, neostigmine, nifedipine, pentazocine, and propranolol are the **examples** of drugs that undergo first-pass metabolism.

Drugs undergoing extensive hepatic first-pass metabolism when administered in controlled release forms are not delivered to the body in desired concentrations. Drugs whose bioavailability varies due to first-pass metabolism cannot be easily formulated as controlled release systems as the problem of drug loss would be dose-dependent, and this will reduce the bioavailability if the drug is slowly released over an extended time period. If a drug undergoes extensive first-pass metabolism, the blood concentration to achieve the desired therapeutic effect is adversely affected.

8) **Size of the Dose:** For drugs to be administered orally, there is an upper limit to the bulk size of the dose. A single dose of 0.5-1.0gm is generally considered maximal for a conventional dosage form as well as for sustained release dosage forms. Drugs requiring large dosing size can be given in multiple amounts or formulated as liquid systems. The safety margin involved in the administration of large amounts of a drug with narrow therapeutic range is also considered.

9) **Dosing Frequency:** It is the number of times a drug dose is administered within a specific time period. The dose frequency is reduced in well-designed controlled release delivery systems. Also, such systems maintain the steady drug concentration in blood and in target tissue cells. **For example,** nanoformulation of natamycin suspension (5%) has reduced the dosing frequency; the initial dosing frequency was one or two drop(s) hourly, and this reduced to one drop in every 5 hours; this reduced the dose to one-fifth of the initial one, prolonged the release of natamycin, and also improved patient compliance.

10) **Margin of Safety/Therapeutic Index:** It is the ratio of median toxic dose to median effective dose.

Therapeutic index = LD_{50}/ED_{50}

11) A drug is considered to have a high safety margin if its therapeutic index is more than 10; thus indicating that **larger the ratio, more safe is the drug.** Safety margin of the drugs determined on the basis of therapeutic index is the range of plasma concentration in which the drug is considered to be safe

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and therapeutically effective. Drugs having narrow therapeutic index should have a more precise release pattern to maintain the plasma concentration within the narrow therapeutic and safety range. Drugs having unfavourable therapeutic index can be made desirable by employing sustained release mechanisms.

12) **Disease State:** Disease state and circadian rhythm are not drug properties, but are still considered while formulating sustained release delivery systems. **For example**, aspirin is the drug of choice for rheumatoid arthritis, but it is not suitable for sustained release dosage form; still, aspirin sustained release dosage form maintains therapeutic concentrations, mainly throughout the night, and eases morning stiffness. Asthma attacks commonly occur before bedtime due to low cortisol level. The cortisol level is highest between 12 midnight and 4 a.m. These variations necessitate the designing of an oral sustained release delivery system in accordance to circadian rhythm.

13) **Side Effects:** Some drugs develop side effects due to their fluctuating plasma concentrations. The frequency of side effects can be reduced by maintaining the concentration within therapeutic range at any given time. Sustained release delivery system is widely used to incidences of the local gastrointestinal side effects, rather than a systemic side effect. The drug properties causing local or systemic side effects can be bypassed or improved by formulating the drugs as a suitable oral sustained release delivery system that works on a specific controlled release mechanism.

1.2. APPROACHES TO DESIGN CONTROLLED RELEASE FORMULATIONS

1.2.1. Introduction

The controlled release system, based on its release pattern, is divided into the following classes:

1) Rate pre-programmed drug delivery system,
2) Activated modulated drug delivery system,
3) Feedback regulated drug delivery system, and
4) Site targeting drug delivery system.

1.2.2. Rate-Programmed Drug Delivery System

In this drug delivery system, the drug release is pre-planned with particular flow rate profile of medicine. The rate-programmed delivery system controls the molecular diffusion of drug molecules in or across the barrier medium within or surrounding the delivery system.

1.2.2.1. Dissolution-Controlled Drug Delivery System

In this delivery system, the controlled-release characteristics are imparted to the drug dosage form by either of the two rate-limiting phenomenon:

1) **Slow Dissolution Rate of the Drug:** In this system, the drug present may be either of the two types:

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i) Drug having a slow dissolution rate, **e.g.,** griseofulvin, digoxin, and nifedipine. Such drugs act as natural prolonged release products.

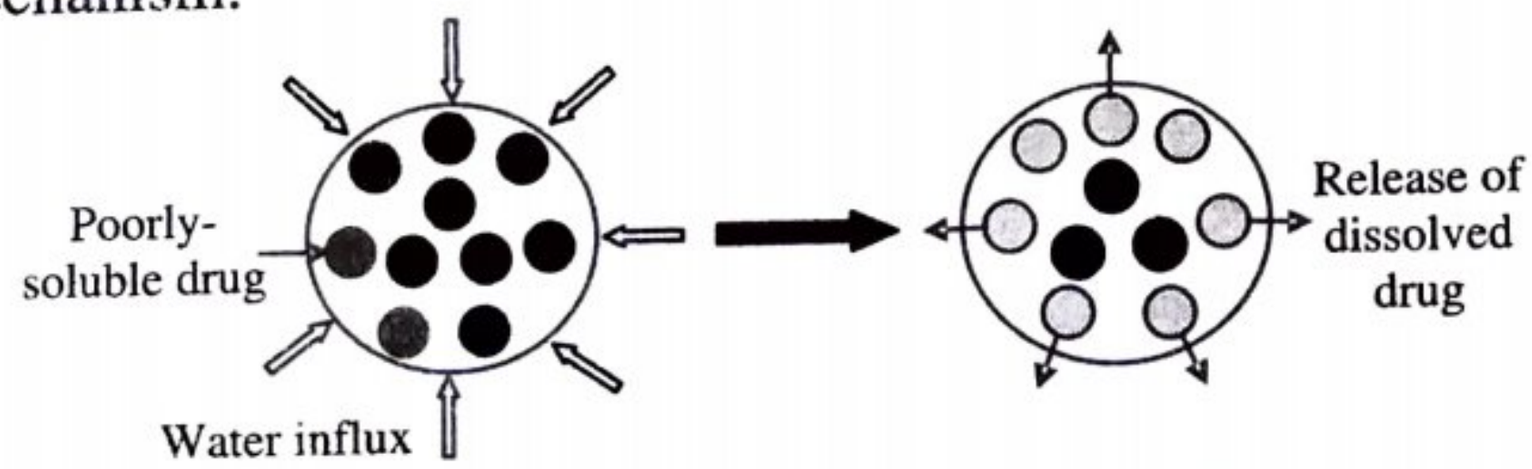
ii) Drug that transforms into a slow dissolving form when in contact with GI fluids, **e.g.,** ferrous sulphate.

2) **Slow Dissolution Rate of the Reservoir Membrane or Matrix:** In this system, the drug present may have high aqueous solubility and dissolution rate, **e.g.,** pentoxifylline and metformin. The major challenge in designing such systems is controlling the drug dissolution rate by employing any one or by combining the following **two techniques**:

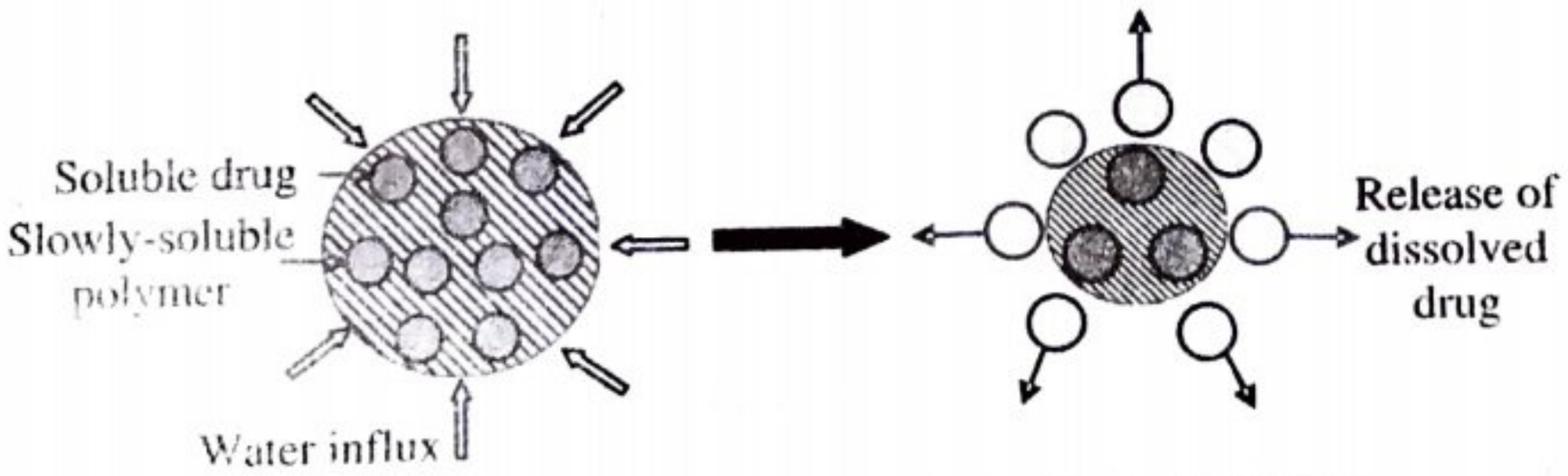
i) **Embedment in Slowly Dissolving, Degrading or Erodible Matrix:** The matrix used in this approach may have low porosity or poor wettability.

ii) **Encapsulation or Coating with Slow-Dissolving, Degrading or Erodible Substances:** This approach involves controlling the rate of dissolution, fluid penetration and/or wettability of the reservoir system.

Figure 1.2 represents the types of dissolution-controlled DDS and their drug release mechanism.



a) Drug-Dissolution Rate-Controlled DDS



b) Polymer/Matrix Dissolution Rate-Controlled DDS

Figure 1.2: Types of Dissolution-Controlled DDS and Mechanism of Drug Release

1.2.2.2. Diffusion-Controlled Drug Delivery System

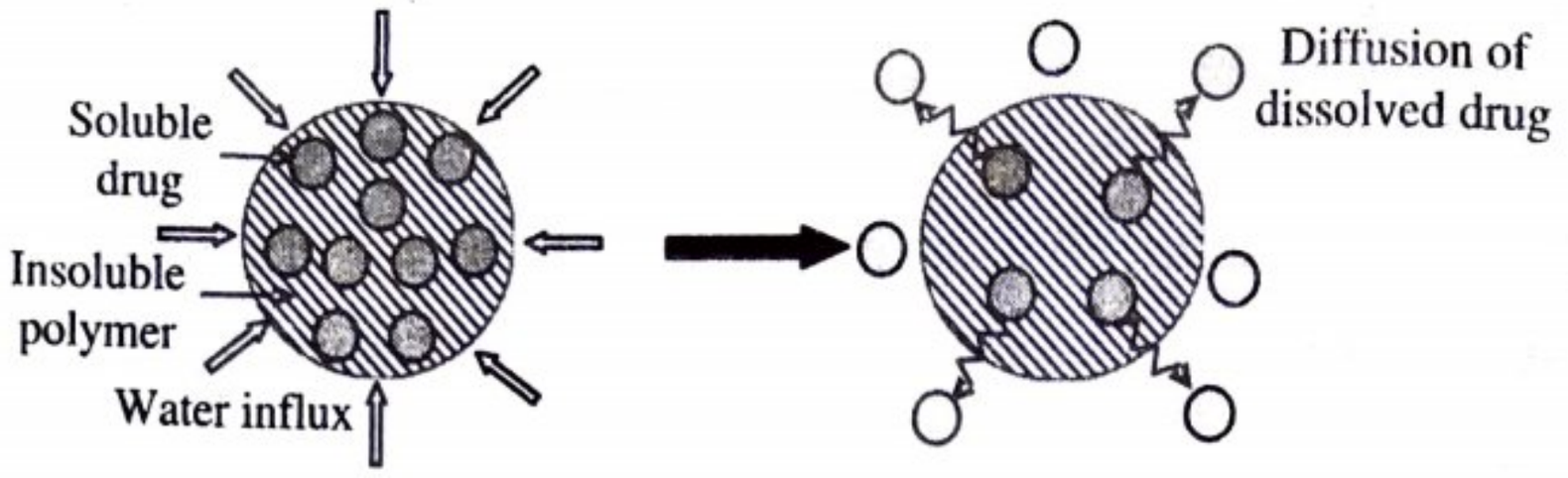
In this drug delivery system, the rate-controlling step is the diffusion of dissolved drug molecule through the rate-controlling element (insoluble, non-erodible, and non-degradable), and not the drug dissolution rate or release-controlling element. However, the rate-controlling element is porous and allows the dissolved drug to undergo diffusion. Diffusion-controlled drug delivery system are classified into the following **two categories** depending on the mechanism by which the rate-controlling element controls drug diffusion:

1) **Porous Matrix-Controlled System:** In this system, the rate-controlling element is either a water-swellable hydrophilic polymer and gums (**e.g.,** xanthan gum, guar gum, high viscosity grades of HPMC and HPC, alginates, etc.) or a non-swellable water-insoluble polymer (**e.g.,** ethylcellulose).

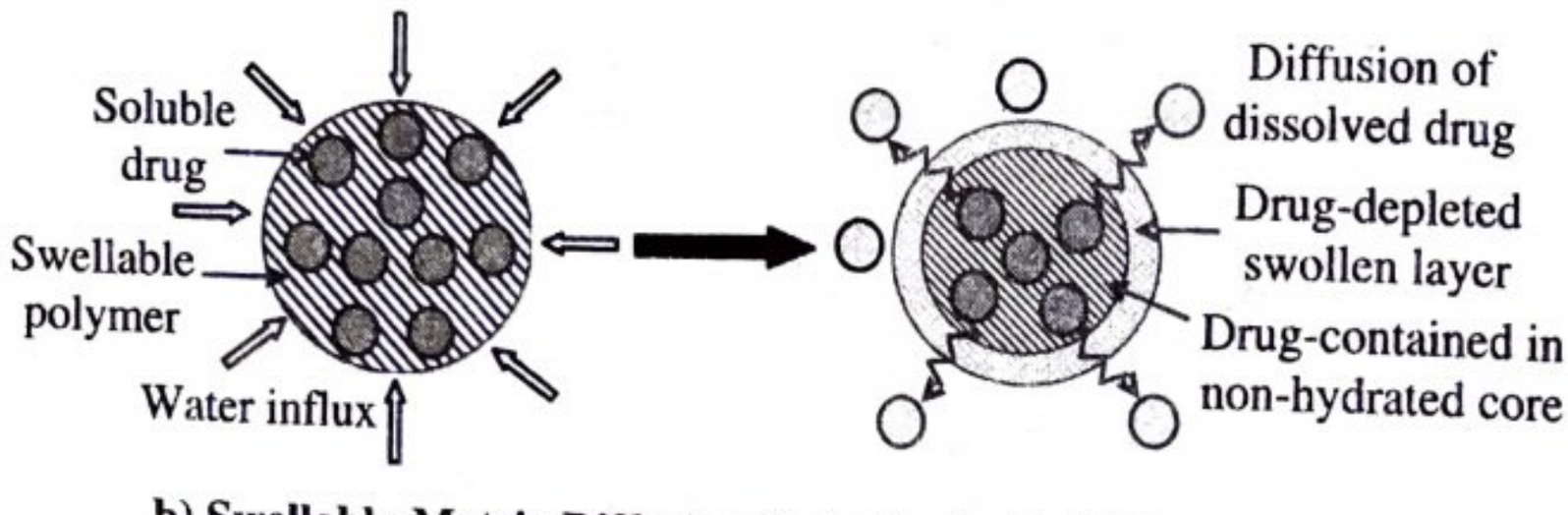
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2) **Porous Membrane-Controlled System:** In this system, the rate-controlling element is a non-swellable water-insoluble polymer (**e.g.,** ethylcellulose or polymethacrylate) that controls drug release through the micropores in their membrane or matrix structure.

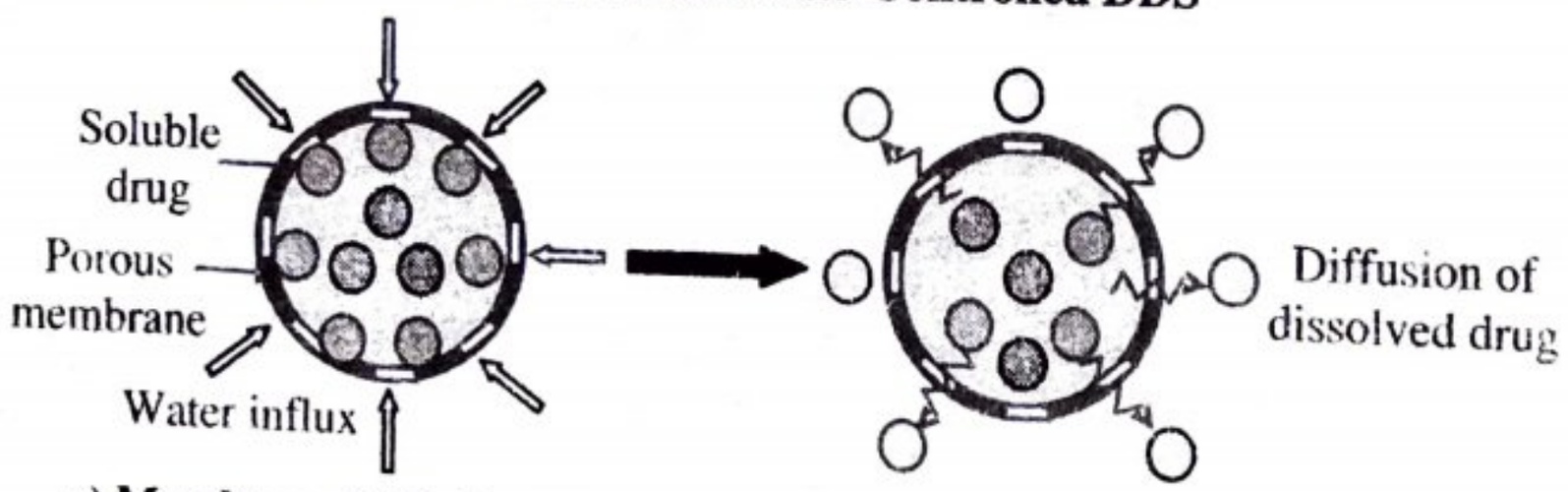
Figure 1.3 represents the types of diffusion-controlled DDS and their drug release mechanism.



a) Non-Swellable Matrix Diffusion Rate-Controlled DDS



b) Swellable-Matrix Diffusion Rate-Controlled DDS



c) Membrane Diffusion Rate-Controlled DDS (Reservoir-Type Systems)

Figure 1.3: Types of Diffusion-Controlled DDS and Mechanism of Drug Release

1.2.2.3. Erosion-Controlled Drug Delivery System

Erosion is the physical disintegration of a polymer/wax matrix (or coating) as a result of degradation. It is characterised by material loss from the polymer in the physical state. Erosion is affected by some external stimuli, thus erosion-controlled drug delivery systems are classified under stimuli-activated drug delivery system depending on the type of stimuli, i.e., physical (**e.g.,** osmotic pressure), chemical (**e.g.,** pH), or biological (**e.g.,** enzyme). **Examples** of erodible materials are hydrophobic materials, like ethylcellulose and various waxes.

Polymers or waxes undergo either surface erosion or bulk erosion, depending on their mechanism:

1) **Surface Erosion:** It occurs from the surface layers of the device only. It gradually decreases the size of the device, while the bulk phase remains undegraded. Since a difference in erosion rate exists between the surface and the centre of matrix, the process is also termed as **heterogeneous erosion**. Surface erosion occurs when water penetration is restricted to device surface.

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2) **Bulk Erosion:** It occurs throughout the polymer bulk, and thus the process is also termed as **homogeneous erosion**. Bulk erosion occurs when the water readily penetrates the device matrix.

Figure 1.4 represents the types of erosion-controlled DDS and their drug release mechanism.

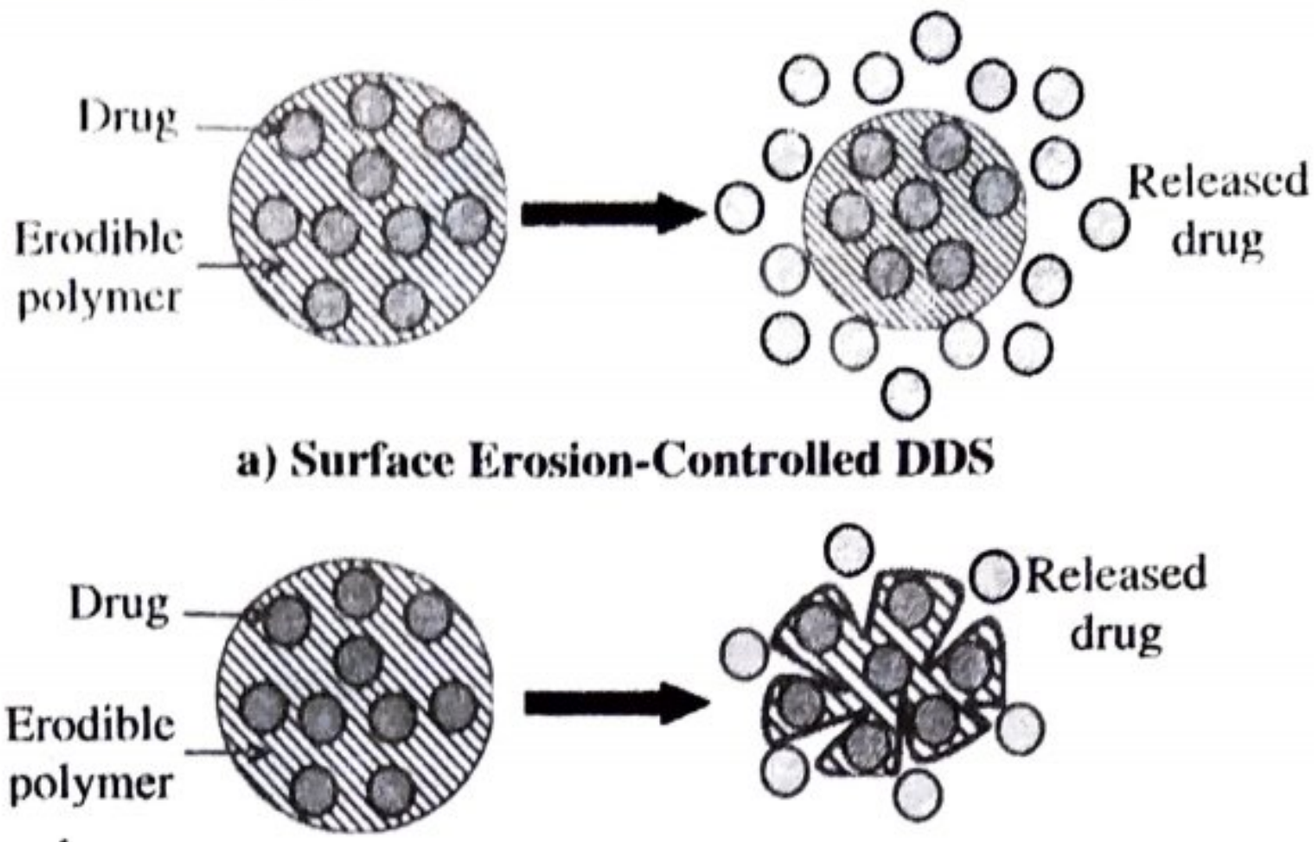


Figure 1.4: Types of Erosion-Controlled DDS and Mechanism of Drug Release

1.2.2.4. Dissolution, Diffusion and/or Erosion-Controlled Drug Delivery System

In this drug delivery system, the drug release rate is controlled by drug/polymer dissolution, drug diffusion, and/or polymer erosion. Thus, this system is a combination of two or more of the three types of systems discussed above. These systems are classified into the following:

1) **Reservoir System (Membrane-Controlled DDS):** In this system, the drug is present as a core in a specifically-shaped compartment that is encapsulated within a rate-controlling wall, film or membrane of well-defined thickness. The drug in the core dissociates from the crystal lattice, dissolves in the surrounding medium, partitions, and ultimately diffuses through the membrane.

   Reservoir systems are of the following **two types**, depending on the physical properties of the membrane:

   i) **Non-Swelling Reservoir System:** In this system, the polymer membrane does not swell or hydrate in an aqueous medium. **Examples** of the commonly used polymers in such systems are ethylcellulose and polymethacrylates.

   ii) **Swelling-Controlled Reservoir System:** In this system, the polymer membrane swells or hydrates on coming in contact with the aqueous medium. The drug release is delayed for the time period required for hydration of barrier, and drug release proceeds at a constant rate after attaining barrier hydration. **Example** of a commonly used polymer in such systems is HPMC.

2) **Matrix System (Monolithic DDS):** In this system, the drug is uniformly dissolved or dispersed in a release-retarding material. Such devices can be formulated as conventional matrix, or bi- or tri-layered matrix systems. Matrix system is of the following **two types**, depending on the physical properties of the matrix:

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i) **Hydrophilic Matrix:** In this matrix system, the release-retarding material is water-swellable or swellable cum erodible hydrocolloid. **Examples** of some release-retarding materials are high molecular weight HPMCs, HPC, HEC, xanthan gum, sodium alginate, guar gum, locust bean gum, polyethylene oxide, and cross-linked polymers of acrylic acid. Hydrophilic matrix is a porous system, and is of the following **two types** depending on the swelling behaviour of hydrophilic polymer:
   a) **Free-Swelling Matrix:** In this type, polymer swelling is unhindered.
   b) **Restricted-Swelling Matrix:** In this type, the device surface is partially coated with an impermeable polymer film that prevents the swellable matrix material to undergo hydration.

ii) **Hydrophobic Matrix:** In this matrix system, the release-retarding material is either of the following two:
   a) Slowly soluble, erodible or digestible, **e.g.,** waxes such as glyceryl monostearate, cetyl alcohol, hydrogenated vegetable oils, beeswax, carnauba wax, etc.
   b) Insoluble or non-digestible, **e.g.,** ethylcellulose, polymethacrylates, etc.

Hydrophobic matrix is of the following **types**, depending on the manner in which the drug is incorporated in the matrix:

a) **Porous (Heterogeneous) Matrix:** In this type, the drug is mixed with release-retarding matrix microparticles and compressed into a tablet, or the drug is dispersed in the polymer solution and the solvent is evaporated.

b) **Non-Porous (Homogeneous) Matrix:** In this type, the release-retarding matrix material is melted and the drug is incorporated in it by thorough mixing. The resultant mass is congealed while stirring. Non-porous matrix system is of the following **two types**:
   - **Dissolved Drug Non-Porous System:** In this system, the drug is dissolved in the molten release-retarding matrix material.
   - **Dispersed Drug Non-Porous System:** In this system, the quantity of drug is more than its solubility in molten matrix polymer.

3) **Hybrid System (Membrane cum Matrix DDS):** In this system, the drug in matrix of release-retarding material is coated with a release-controlling polymer membrane. Such a device combines the constant release kinetics of reservoir systems with the mechanical robustness of matrix system.

1.2.3. Activated Modulated Drug Delivery System

In this drug delivery system, the drug release is controlled or activated by some physical, chemical and biological process or by any supplied external energy source. Drug release from this delivery system is also controlled by energy input or any applied process. This activation process can be classified into the following categories:

1) Activation by physical processes,
2) Activation by chemical processes, and
3) Activation by biological processes.

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1.2.3.1. Activation by Physical Processes

The physical processes that control drug release from activated modulated drug delivery system are:

1) **Osmotic Process-Activated DDS:** This system releases drug based on the osmosis principle at a pre-determined zero-order rate. Osmosis is the natural movement of solvent through a semi-permeable membrane into a solution of higher solute concentration, leading to equal concentration of solute on either side of the membrane. Osmotic system imbibes water from the body into an osmotic material through a semi-permeable membrane. The material dissolves in the water, increases in volume, and generates osmotic pressure that results in slow and uniform drug delivery through an orifice.

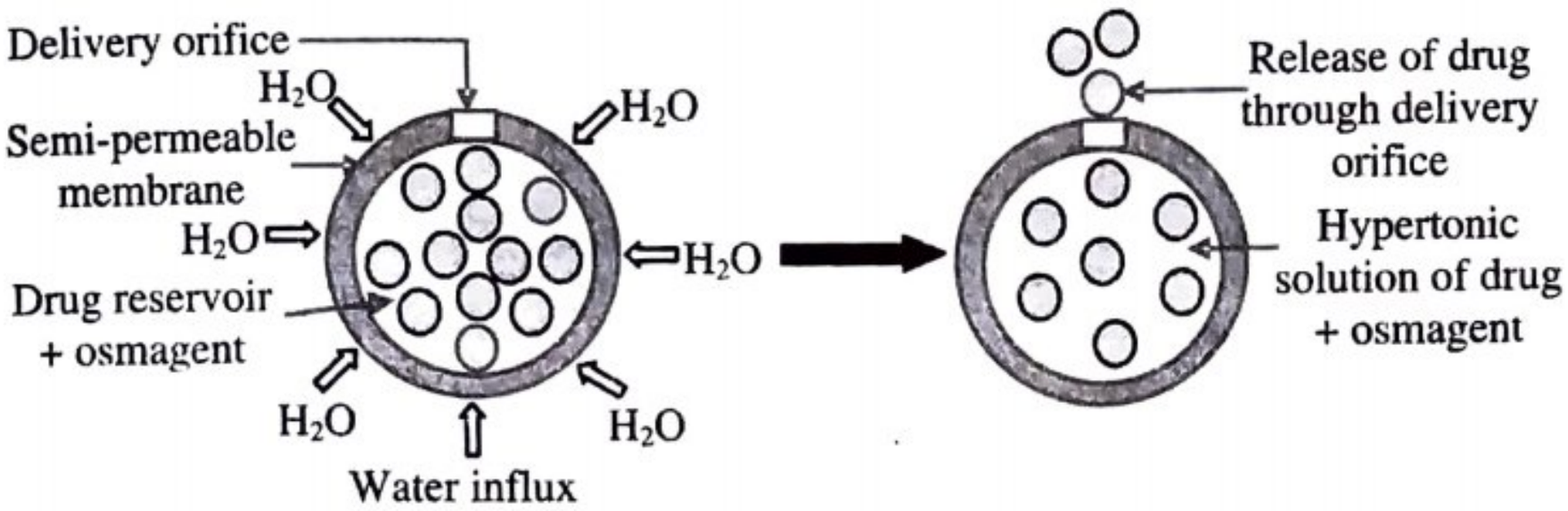


Figure 1.5: Mechanism of Drug Release from Osmotic Pressure-Activated DDS

2) **Hydration/Hydrodynamic Pressure-Activated DDS:** This system is similar to osmotic system as it also releases drug at zero-order rate. However, it differs from osmotic system due to the presence of a hydrodynamic pressure-generating agent. It is a water-swellable hydrocolloid (such as HPMC) contained in a compartment and the drug solution/dispersion in another collapsible reservoir. Both the compartments are held in a rigid, shape-retaining but water-permeable housing. The hydrocolloid imbibes water, swells, and generates hydrodynamic pressure that pushes the drug reservoir compartment, and thus forces the drug at a slow and uniform rate through an orifice **(figure 1.6)**.

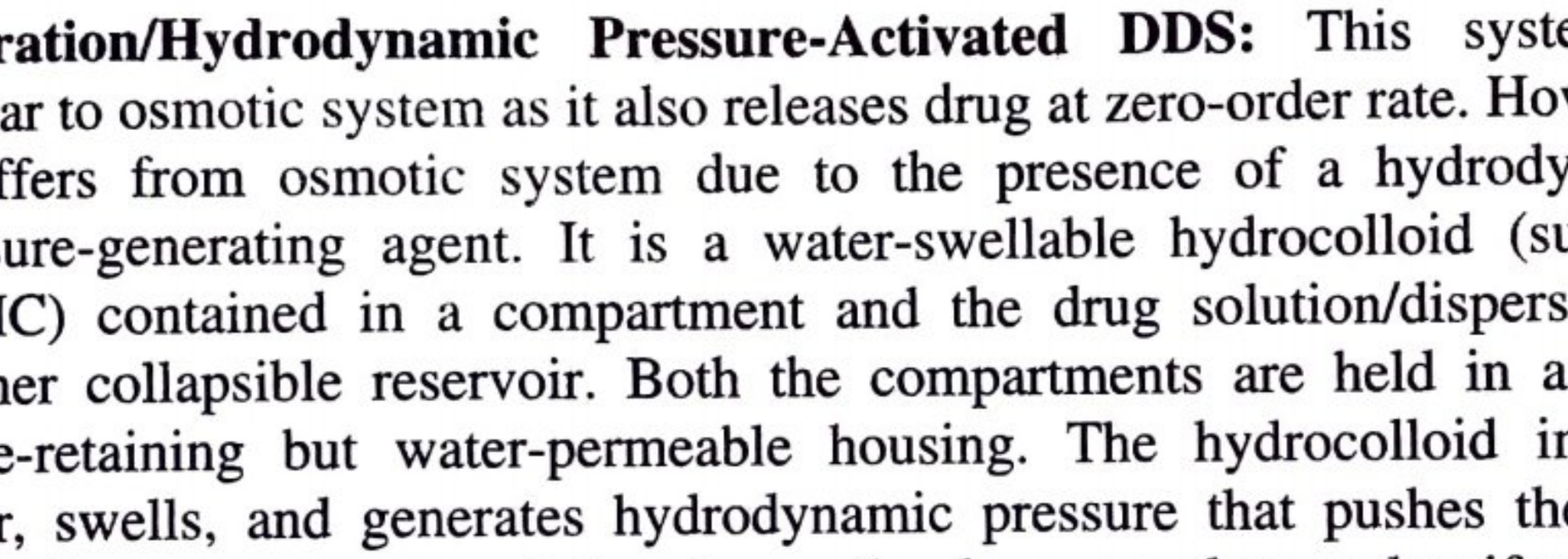


Figure 1.6: Mechanism of Drug Release from Hydrodynamic Pressure-Activated DDS

3) **Magnetically-Activated DDS:** In this system, a tiny dough-nut-shaped magnet is kept in the centre of a hemi-spherical biocompatible polymer matrix, containing the dispersed drug. Then, the external surface of the medicated polymer matrix is coated with a pure polymer (**e.g.,** ethylene-vinyl acetate copolymer or silicone elastomers); however, one cavity at the centre of the flat surface of the hemisphere is left uncoated. This uncoated cavity allows the release of a peptide drug (such as insulin). When the magnet is activated to vibrate by an external electromagnetic field, it releases the drug by diffusion process at a zero-order rate.

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4) **Thermally-Activated/Temperature-Responsive DDS:** Depending on the origin of thermosensitivity to aqueous media, the temperature-sensitive polymers are classified into the following **two groups**:
   i) Polymers that interact with water, and
   ii) Polymers that interact with water and show polymer-polymer interaction.

   When a polymer in a solvent swells, a negligible or small positive enthalpy is generated, but its aqueous solution shows opposite effect. This uncommon behaviour is related to polymer-phase separation phenomenon as the temperature is increased to reach a critical value, termed as the Lower Critical Solution Temperature (LCST). Polymers characterised by LCST shrink as the temperature is increased above LCST; while, the polymers, **e.g.,** N-alkyl acrylamide homopolymers and copolymers, swell as the temperature is decreased below LCST. Drugs can be immobilised in such temperature-sensitive polymers for affecting controlled-release.

5) **Photo-Activated DDS:** The physical and chemical properties of photoresponsive system (i.e., gels) undergo reversible change on photoradiation. A photoresponsive polymer comprises of a photoreceptor, a photochromic chromophore, and a functional part. The molecules of photochrome capture the optical signal, and isomerisation of the chromophores in the photoreceptor converts it to a chemical signal.

6) **Photomechanical Waves (Laser) Activated DDS:** Photomechanical waves (or laser-generated stress waves) are the pressure pulses produced by ablation of a material target by lasers. Photomechanical waves increase the drug permeability through stratum corneum for transdermal delivery; however, the mechanism of this process is not yet clear.

7) **Vapour Pressure-Activated System:** In this system, a liquid exists in equilibrium with its vapour phase and pressure of the independent fluid volume. A device used for pressure control delivery, comprises of two chambers, one containing the drug solution and the other containing a vaporisable fluid (**e.g.,** fluorocarbon). After shooting of ding, volatile liquid vaporises at the body temperature and generates a vapour pressure that compresses the lower chamber, and hence releases the drug in a controlled manner.

8) **Mechanically-Activated System:** This system comprises of a drug reservoir equipped with a mechanically activated pumping system. Drug is released into the body cavity (such as nose or mouth) in a controlled amount, through a spray system that works on mechanically drug delivery pumping system. The spray volume of delivered drug is fixed in each pumped spray; an **example** is metered-dose nebuliser for the Luteinising Hormone-Releasing Hormone (LHRH).

9) **Sonophoresis-Activated System:** This system employs an ultrasonic device for the activation of drug delivery. This device is battery-operated handheld system containing a control unit, ultrasonically generated horn, disposable coupling medium sealed unit, and a return electrode. These devices are fabricated by biodegradable and non-degradable polymer. The ultrasonic device uses a very low frequency (55kHz) ultrasonic wave for a very short time (15seconds) for drug delivery through the skin.

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10) **Electrically-Activated DDS (Iontophoresis and Electroporation):** This controlled release system utilises electrical current for activating and modulating the diffusion of a charged drug molecule across a biological membrane (like skin), similar to passive diffusion under a concentration gradient at a faster rate. Like charges repel each other, hence applying a positive current drives away the positively charged drug molecules from the electrode and into the tissues; and *vice versa*.

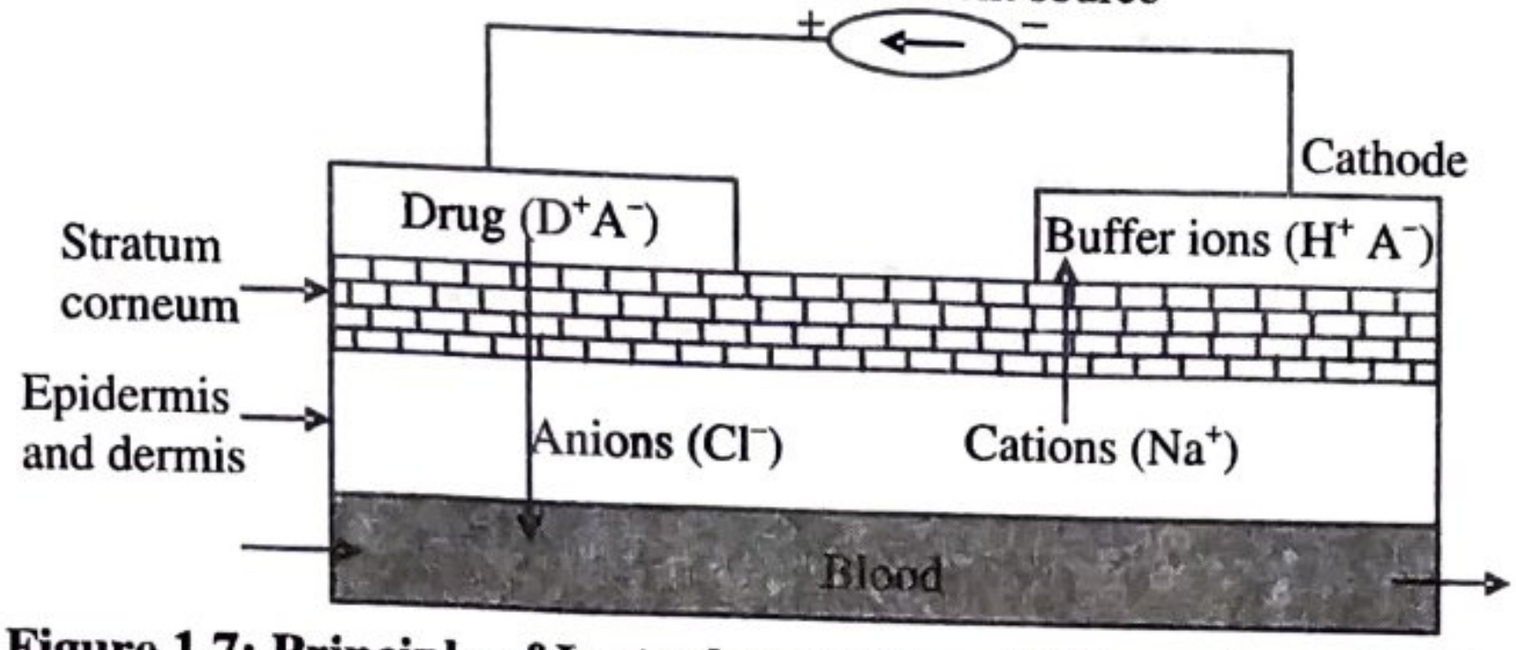


Figure 1.7: Principle of Iontophoretic Drug Delivery through Skin

In **iontophoresis**, the flux is related to the total charge transported through the system due to low voltage constant current density; while in **electroporation**, relatively high voltage but transient pulses transiently increase the stratum corneum permeability to affect drug transport through the skin. An **example** of electrically-activated system is percutaneous penetration of anti-inflammatory drugs (such as dexamethasone) to surface tissues.

1.2.3.2. Activation by Chemical Processes

The chemical processes that control drug release from activated modulated drug delivery system are:

1) **pH-Activated System:** In this system, drugs are made to target the drug delivery in the intestinal tract (and not in the stomach). Drugs are coated with gastric fluid-sensitive drug, along with intestinal fluid-insoluble polymers, **e.g.,** ethyl cellulose and hydroxyl methyl cellulose phthalate. Coated drugs are resistant against the gastric fluid (pH < 3), thus the drugs do not degrade under acidic conditions. In small intestine, the intestinal fluid due to high pH (pH > 7.5) dissolves the coated membrane of drugs. Thus, pH controls the delivery of drugs inside the human body.

2) **Ion-Activated DDS:** This system relies on the fact that GIT has a relatively constant level of ions, and controls the delivery of an ionic or an ionisable drug at a constant rate. The ion-activated drug delivery system is prepared by complexing an ionisable drug with an ion-exchange resin. A cationic drug is complexed with a resin, containing SO_3^- group, while an anionic drug is complexed with a resin, containing $N(CH_3)_3^+$ group. In GIT, hydronium and chloride ions diffuse into the CRDDS and interact with the drug-resin complex to activate the dissociation and release of ionic drug.

Acidic drug release:

$$Resin - SO_3^-Drug^+ + H^+ \Leftrightarrow Resin - SO_3^-H^+ + Drug^+$$

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Basic drug release:

$$\text{Resin}-[\text{N}(\text{CH}_3)_3^+]\text{Drug}^- + \text{Cl}^- \Leftrightarrow \text{Resin}-[\text{N}(\text{CH}_3)_3^+]\text{Cl}^- + \text{Drug}^-$$

An **example** of such a formulation is sustained-release liquid-oral with a combination of hydrocodone and chlorpheniramine.

3) **Hydrolysis-Activated DDS:** In this system, the drug release is activated by hydrolysis process. The drug reservoir in this device is either encapsulated in microcapsules or homogeneously dispersed in microspheres or nanoparticles of bioerodible or biodegradable polymers, **e.g.,** polylactide, poly(lactide-glycolide) copolymer, poly(orthoester), or poly(anhydride). Degradation of polymer chains (induced by hydrolysis) activates the drug release from polymer matrix. The drug delivery rate is controlled by the polymer degradation rate.

4) **Chelation-Activated DDS:** This system relies on the ability of metals to induce the hydrolysis of carboxylate or phosphate esters and amides. Attachment of a chelating agent (**e.g.,** quinaldic acid) to a polymer chain (**e.g.,** polyvinyl alcohol) through an ester or amide linkage reduces the renal excretion rate and toxicity. In the presence of metal ions, **e.g.,** Co(II), Zn(II), Cu(II), etc., a complex is formed between the polymer-bonds chelating agent, in which the metal ion triggers hydrolysis, which in turn activates the release of metal-chelator complex and elimination of the chelated metal.

1.2.3.3. Activation by Biological Processes

The biological processes that control drug release from activated modulated drug delivery system are:

1) **Enzyme-Activated DDS:** In this system, the drug reservoir is either physically entrapped in microspheres or chemically bound to polymer chains fabricated from biopolymers, **e.g.,** albumins or polypeptides. Drug release is induced by enzymatic hydrolysis of biopolymers by a specific enzyme in the target tissue. An **example** of enzyme-activated drug delivery system is the development of albumin microspheres that provide controlled release of 5-fluorouracil through protease-activated biodegradation.

2) **Antibody Interaction-Activated DDS:** This system relies on the principle that hapten-antibody interaction suppresses enzymatic degradation of polymer matrix or permeability of polymeric reservoir of drug, **e.g.,** naltrexone. This device is coated by covalently grafting morphine to the surface, and exposing this surface to morphine antibodies results in coating of polymer surface with those antibodies, which in turn block the release of naltrexone. However, exposing this surface to exogenous morphine results in a reverse process, i.e., the antibodies are uncoated and naltrexone is released.

3) **Antigen-Activated DDS:** This system relies on the principle that hydrogel remains shrunk in the absence of free antigen, due to intra-chain antigen-antibody binding in the polymer network; however, hydrogel swells in the presence of free antigen, due to dissociation of intra-chain binding by exchange of the grafted antigen for free antigen. This swelling/shrinking process is reversible.

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4) **Inflammation-Activated DSS:** In this system, the drug-loaded lipid microspheres are dispersed in biodegradable hydrogels of cross-linked hyaluronic acid. This acid is degraded by hydroxyl radicals produced by phagocytic cells (like leukocytes and macrophages) at inflammatory sites.

1.2.4. Feedback Regulated Drug Delivery System

In this drug delivery system, drug release from the carrier is activated by a physiological response. A triggering agent, such as a biochemical substance, activates the process of drug release in the body via some feedback mechanisms. The drug release rate is synchronised by the concentration of a triggering agent that is detected by a sensor used in the feedback regulated drug delivery system.

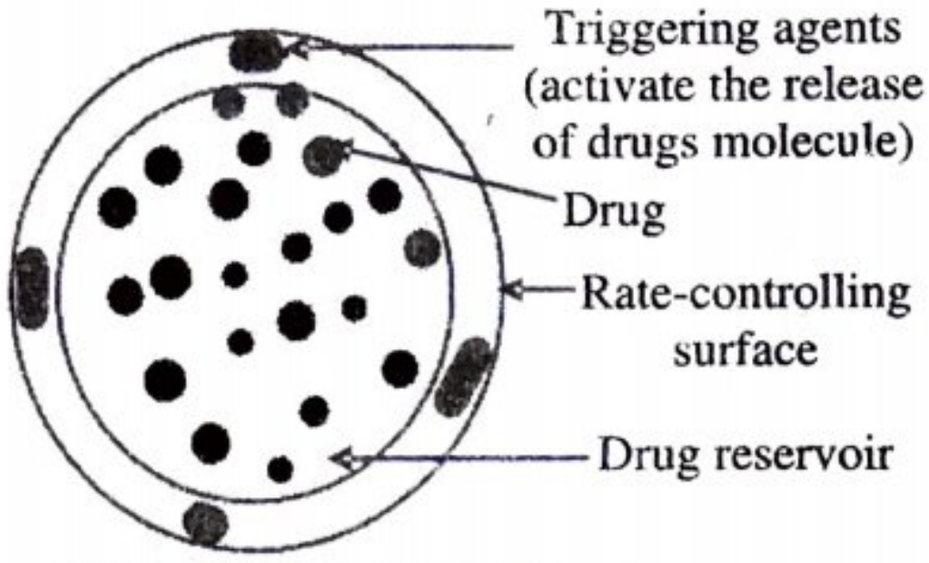


Figure 1.8: Feedback Drug Delivery System

Feedback regulated drug delivery system are divided into **three systems**:

1) **Bio-Erosion Regulated System:** In this system, the drug is fabricated with a polymer (**e.g.,** polyvinyl methyl ether) and coated with immobilised urease. In a solution with almost neutral pH, the polymer erodes slowly; but in the presence of urea, urease forms ammonia at the drug surface and metabolise the urea. The cause of pH change increases the rapid degradation of polymer matrix and release of drug molecules.
2) **Bio-Responsive Regulated System:** In this system, the drug reservoir is enclosed in a bioresponsive polymeric membrane, and the permeability of drug molecule is controlled contraction of biochemical agents in the tissue. An **example** of bio-responsive regulated system is glucose-triggered insulin delivery system, in which insulin reservoir is covered by a hydrogel membrane containing NR_2 (amide group) group. In alkaline solution, NR_2 group is fixed, and the membrane is un-swollen and impermeable to insulin. When glucose enters the membrane, it gets oxidised and forms gluconic acid. This process causes the protonation of NR_2 into N^+R_2H, and thus the hydrogel layer become swollen and permeable to insulin molecule by a self-regulated process.

$$\text{Glucose} \xrightarrow{\text{Oxidase}} \text{Gluconic Acid}$$

$$-NR_2 \xrightarrow[\text{Acidic pH}]{H^+} N^+R_2H$$

3) **Self-Regulating Drug Delivery System:** This system works on a principle regulated by the reversible and competitive binding mechanism for the activation and release of drugs. In this drug delivery system, the drug reservoir is encapsulated in a polymeric semi-permeable membrane, and the drug release is activated by a biochemical agent of the tissue. An **example** of self-regulating drug delivery system is a biological derivative complex (insulin-sugar-lectin) that is encapsulated within a semi-permeable membrane to produce CRDDS. When blood glucose diffuses into this system, it binds with lectin molecules and activates insulin release from the binding site. Thus, insulin concentration depends on glucose concentration. This entire process takes place by self-regulating drug delivery system.

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CHAPTER 2

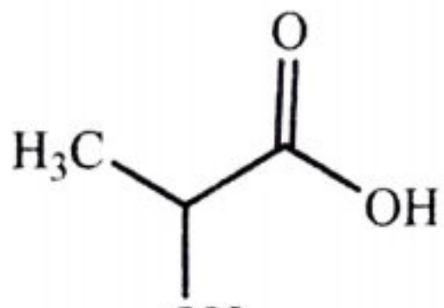
Polymers

2.1. POLYMERS

2.1.1. Introduction

The **compounds having high molecular masses** and **formed by monomers** are termed polymers. The term **polymer** is derived from the Greek words, ***poly*** means **many** and ***meros*** means **unit** or **parts**. Due to their distinctive nature, polymers are used in pharmaceutical industries. In polymer based drug release system, a new technology has been adopted that provides possibilities in drug administration. Polymers are pharmaceutically used in tablets as binders; in liquids, suspensions and emulsions as flow controlling agents; to cover the unpleasant taste of drug as film coating agents; and also as stabilisers and protective agents.

Polymers are broadly used in day-to-day life. Important advancements have been made in the development of several drug delivery devices using polymers. In the 1970s, the earliest drug delivery system was introduced, and it was based on the polymer formed from lactic acid.



Biodegradable polymers are most needed as they undergo degradation within the body and form biologically inert and compatible molecules. If drugs are formulated in biodegradable polymers, different shapes and sizes of dosage forms that release drug for an extended time period can be produced.

2.1.2. Classification

The term **polymer** is generally used to indicate a large number of high molecular weight substances, which are found in many forms and numbers due to the presence of very large number and type of atoms in their molecules. Polymers exhibit different chemical structures, physical properties, mechanical behaviour, thermal characteristics, etc., based on which they are classified in different ways.

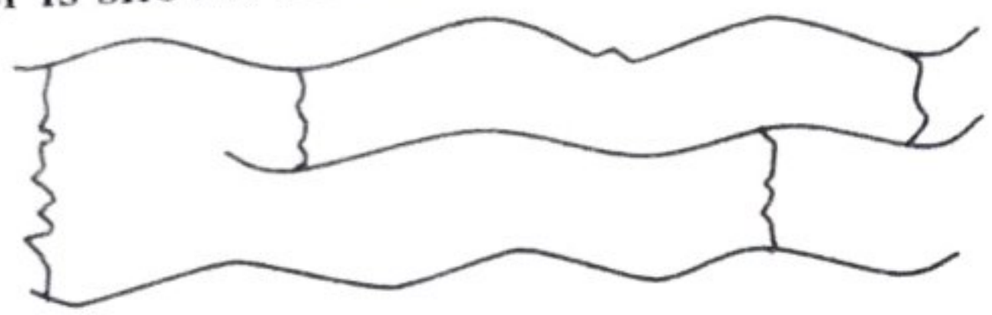
2.1.2.1. Based on the Source

Based on the source from which polymers are derived, they are classified into the following three types:

1) **Natural Polymers:** These polymers occur in nature, and are also known as **biopolymers**. Pectin, chitosan, alginate, gelatin, albumin, collagen, natural rubber, cellulose, natural silk, protein, starch, etc. are the **examples** of natural polymers.

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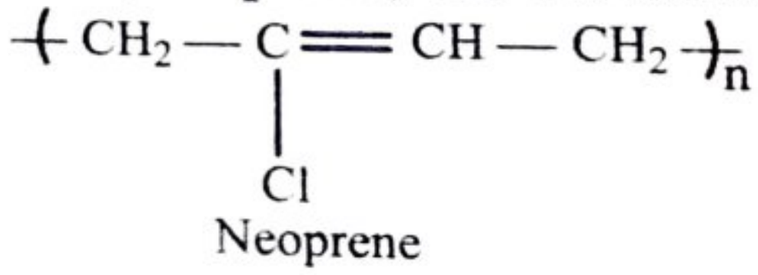
3) **Cross-Linked or Network Polymers:** In these polymers, two linear chains are joined to each other through covalent bonds. These polymers have three dimensional structures. Degree of cross-linking is a number of junction points per unit volume. Polymers cross-linking are hard, rigid, and brittle because of their network structure. Cross-linked polymers do not dissolve in solvents, since the polymer chains are covalently bound to each other; though they can absorb solvents. Bakelite, melamine, formaldehyde resins, vulcanised rubber, etc. are the **examples** of cross-linked polymers. A cross-linked polymer is shown below.



2.1.2.6. Based on the Molecular Forces

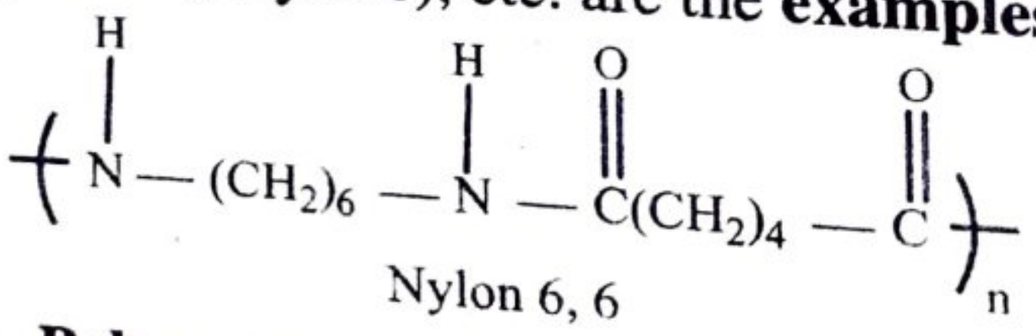
The mechanical properties of polymers, such as tensile strength, toughness, and elasticity, rely on intermolecular forces, such as Van der Waals forces and hydrogen bonding. Based on these forces, polymers are classified into the following types:

1) **Elastomers:** These polymers are rubber-like solids having elastic properties. The polymer chains in elastomers are linked to each other by the weakest intermolecular forces. Due to these weak forces, the polymer becomes stretched. Few crosslinks are added between the chains to help the polymer to retract to its original point after the force is released (as in vulcanised rubber). Buna-S, buna-N, neoprene, etc. are the **examples** of elastomers.



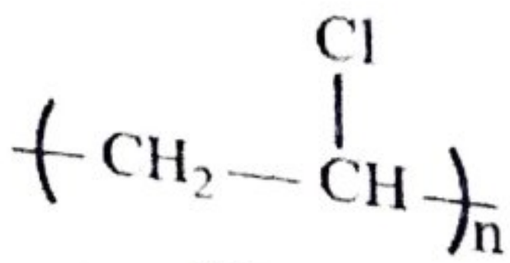
Neoprene

2) **Fibres:** These are thread-forming solids having high tensile strength and modulus. These properties can be allocated to the strong intermolecular forces (such as hydrogen bonding), which lead to close packing of chains and impart crystalline nature. Fibres are used in textile industries. Polyamides (nylon 6,6), polyesters (terylene), etc. are the **examples** of fibres.



Nylon 6, 6

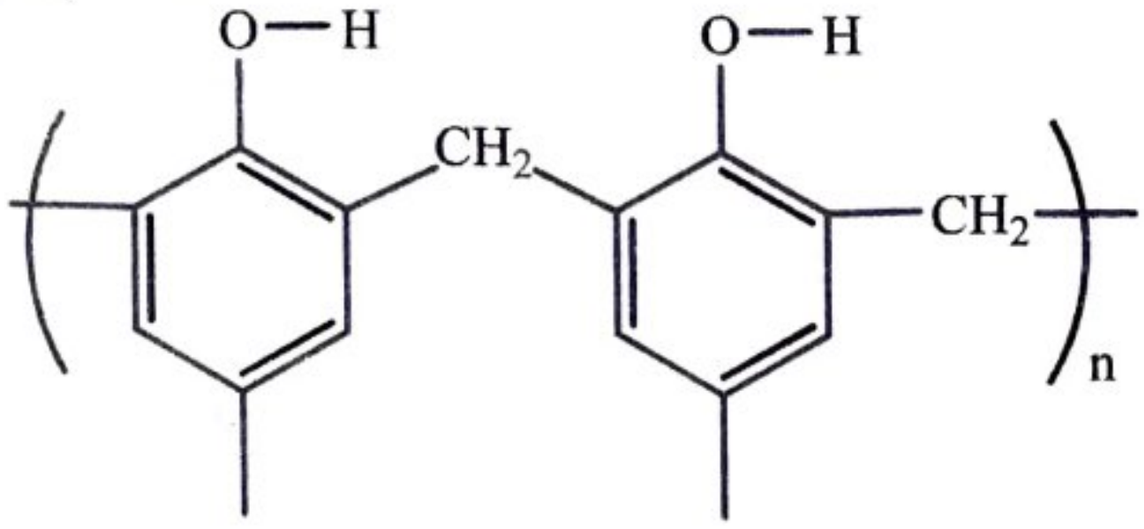
3) **Thermoplastic Polymers:** These polymers have intermolecular forces between elastomers and fibres. They can be softened on heating and toughened on cooling at room temperature. They are either linear or branched chain polymers. They can be recycled multiple times. Polythene, polystyrene, PVC, etc. are the **examples** of thermoplastic polymers.



PVC

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4) **Thermosetting Polymers:** These polymers are hard and become infusible on heating. They do not soften on heating under pressure and they cannot be remoulded. They are either cross-linked or heavily branched molecules. They are not reusable. Bakelite, urea, formaldehyde resins, etc. are the **examples** of thermosetting polymers.



Bakelite

2.1.2.7. Based on the Types of Monomer

Based on the types of monomers, polymers are classified into the following two types:

1) **Homopolymers:** These polymers contain a single type of repeat unit. Polystyrene is an **example** of homopolymer.
2) **Hetropolymers (Copolymers):** These polymers are made up of two different monomers. Butadiene-styrene rubber is an **example** of heteropolymer.

2.1.2.8. Based on the Morphology

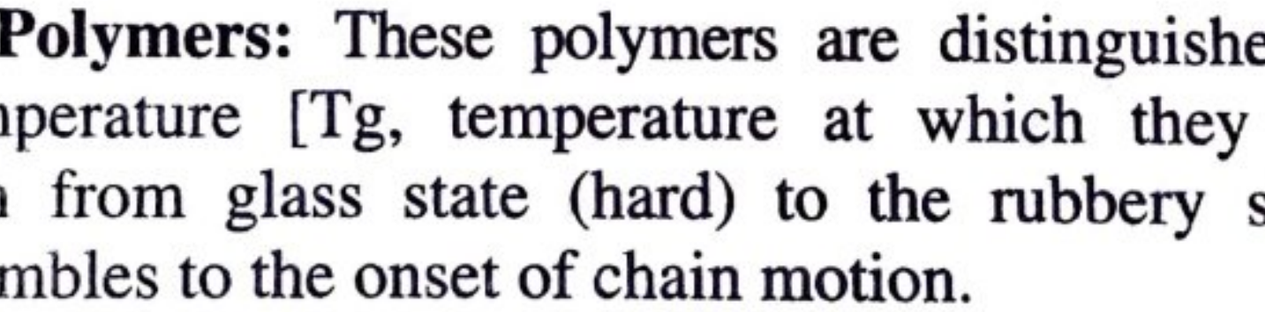
Based on their morphology, polymers are classified into the following two types:

1) **Crystalline Polymers:** These polymers do not always form perfect crystalline materials, but are semi-crystalline having crystalline as well as amorphous regions. In such polymers, the crystalline phase is distinguished by their melting temperature (T_m).
2) **Amorphous Polymers:** These polymers are distinguished by their glass transition temperature [Tg, temperature at which they undergo sudden transformation from glass state (hard) to the rubbery state (soft)]. This transition resembles to the onset of chain motion.

2.1.2.9. Based on the Tacticity

Tacticity is the geometric arrangement or orientation of the individual group of monomer unit with respect to the backbone (main chain) of the polymers. Based on the structure, polymers are classified into the following three types:

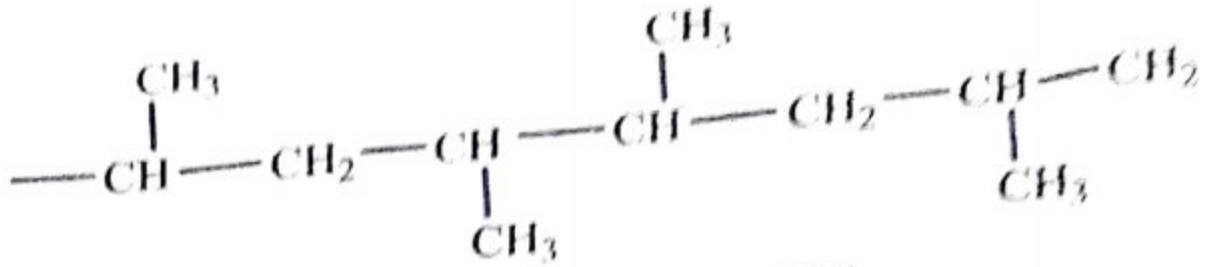
1) **Isotactic Polymers:** In these polymers, the characteristic or side groups are arranged on the same side of the main chain.



Isotactic Polypropene

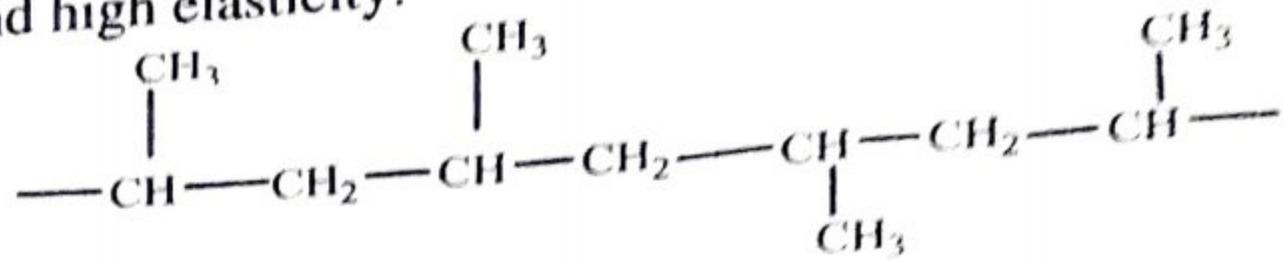
2) **Syndiotactic Polymers:** In these polymers, the characteristic or side groups are alternately arranged.

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Syndiotaic Polypropene

3) **Atactic Polymers:** In these polymers, the characteristic or side groups are randomly arranged around the main chain. Atactic polymers have proper strength and high elasticity.



Atactic Polypropene

2.1.3. Properties

Many materials are used for controlling the release of drugs and other active agents. Initially the earliest of these polymers were designed for other non-biological uses, and were chosen due to their desirable physical properties. Some examples are:

1) Poly(urethanes) for elasticity,
2) Poly(siloxanes) or silicones for insulating ability,
3) Poly(methyl methacrylate) for physical strength and transparency,
4) Poly(vinyl alcohol) for hydrophilicity and strength,
5) Poly(ethylene) for toughness and lack of swelling, and
6) Poly(vinyl pyrrolidone) for suspension capabilities.

A material can be effectively used in controlled drug delivery formulations if it is inert, free of leachable contaminants, readily processable, have a suitable physical structure, and have minimum undesired aging. An **ideal polymer** should have the following **properties**:

1) It should be inert and compatible with the environment,
2) It should be non-toxic,
3) It should be easy to administer,
4) Its fabrication should be easy and inexpensive, and
5) It should have a good mechanical strength.

2.1.4. Advantages

Polymers have the following advantages:

1) It delivers drug at a constant rate of controlled release for a prescribed time period.
2) The carrier of polymer degrades into non-toxic and absorbable sub-units that get metabolised lately.
3) The system is biocompatible, does not exhibit dose dumping at any time period, and the polymer retains its properties until after drug depletion.
4) Biodegradable systems remove the need for surgical removal of implanted device after drug depletion.
5) They breakdown into biologically acceptable molecules which get metabolised and eliminated from the body via normal metabolic pathways.

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The following three advantages are offered by polymeric drug delivery products are:

1) **Localised Drug Delivery:** The product can be implanted straight to the site where drug action is required, thereby decreasing the systemic exposure of the drug, particularly for toxic drugs that are associated to many systemic side effects.
2) **Sustained Drug Delivery:** The encapsulated drug is released for prolonged time period, and thus eliminates the necessity for multiple injections. This improves patient compliance for drugs used for chronic signs and requiring frequent injection.
3) **Stabilisation of the Drug:** The polymer can guard the drug from physiological surrounding, and thus improves *in vivo* drug stability. Due to this property, this technology is attractive for the delivery of labile drugs (such as proteins).

The drugs are constantly released from polymer matrix by diffusion or by erosion of polymer or by combination of both.

2.1.5. Disadvantages

Polymers have the following disadvantages:

1) They cannot tolerate extreme temperature; **for example,** plastics immediately melt down on coming in contact with heat.
2) Biodegradable polymers show substantial dose dumping at some points after implantations.
3) A burst effect or high early drug release shortly after administration occurs in most of the systems.
4) Biodegradable systems administered via injection of a particulate form are non-retrievable.

2.1.6. Application of Polymers in Formulation of Controlled Release Drug Delivery Systems

1) **Controlled Release Dosage Forms:**
   i) Reservoir systems,
   ii) Ocusert system,
   iii) Matrix systems,
   iv) Swelling controlled release systems,
   v) Biodegradable systems,
   vi) Osmotically controlled drug delivery,
   vii) Progestasert system,
   viii) Reservoir designed transdermal patches,
   ix) Matrix systems,
   viii) Stimulus responsive drug release,
   ix) Ultrasound responsive drug release,
   x) Temperature responsive drug release,
   xi) pH responsive drug release,
   xii) Electric current responsive drug release, and
   xiii) Polymer-drug conjugates.

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2) **Immediate Release Dosage Forms**

i) **Tablets:** Polymers are being used since many years as excipients in conventional immediate-release oral dosage forms. They either assist the manufacturing process or provide protection to the drugs from degradation upon storage. Microcrystalline cellulose is used as a diluent (as a substitute to carbohydrates) in tablet formulations of highly potent low-dose drugs. Starch and cellulose are used as disintegrants in tablet formulations as they swell in water and result in tablet bursting, which increases the exposed surface area of the drug and improves its dissolution. Polyvinyl-pyrrolidone and hydroxypropyl methylcellulose polymers are used as binders to aid in the formation of granules, which improve the flow and compaction properties of tablet formulations before tableting. Sometimes, dosage forms should be coated with a non-functional polymeric film, which protects the drug from degradation, masks the unpleasant taste of any drug or excipients, and also improves the external appearance of the formulation without affecting the drug release rate.

ii) **Capsules:** These dosage forms are used as an alternative to tablets, to formulate poorly compressible materials, to mask the bitter taste of certain drugs, or to increase bioavailability. Nearly same polymeric excipients are used to bulk out capsule fills as used in immediate release tablets. Gelatin is used as a shell material for hard (two-piece) and soft (one-piece) capsules. HPMC is used as an alternative material for manufacturing hard (two-piece) capsules.

2) **Modified Release Dosage Forms:** It is known that many therapeutic drug delivery using immediate release dosage forms results in sub-optimal therapy and/or systemic side effects. Pharmaceutical scientists have made efforts to develop modified release dosage forms so that the limitations of conventional oral dosage forms can be overcome.

3) **Extended Release Dosage Forms:** The drugs having short biological half-lives are formulated as extended or sustained release dosage forms in order to enhance their therapeutic effect. Extended and sustained release dosage forms extend the time for which systemic drug levels remain within the therapeutic range. This reduces the number of doses the patient needs to take to exert a therapeutic effect, and thus increases patient compliance. Ammonium methacrylate copolymers (Eudragit RS and RL), cellulose derivatives (ethylcellulose and cellulose acetate), and polyvinyl derivative (polyvinyl acetate) are the **examples** of most commonly used water-insoluble polymers for extended release systems. The proportion of quaternary ammonium groups in Eudragit RS and RL is different, due to which water permeability of Eudragit RS is comparatively low. Ethylcellulose is available in different grades of different viscosity, and those with higher viscosity grades form stronger and more durable films.

4) **Gastroretentive Dosage Forms:** These dosage forms offer an alternative strategy to achieve extended release profile, in which the formulation remains in the stomach for prolonged time periods, releases the drug *in situ*,

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which dissolves in the liquid contents and slowly passes as into the small intestine. A drug from conventional extended release dosage form is gradually released during transit along the GIT. Such a delivery system overcome the problems of drugs that are absorbed from specific sites in the GIT and produce non-uniform plasma time profile delivery systems; **for example**, many drugs undergo poor absorption from the distal gut, where an extended release dosage form remains for prolong time. To achieve gastroretention, the ability of mucoadhesive and low-density polymers to extend gastric residence time by bonding to the mucus lining of stomach and floating on top of the gastric contents, respectively have been evaluated.

2.2. SUMMARY

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

1) The compounds having high molecular masses and formed by monomers are termed **polymers**. The term **polymer** is derived from the Greek words, ***poly*** means **many** and ***meros*** means **unit** or **parts**.
2) **Addition polymers** are made from olefinic, diolefnic, vinyl and associated monomers by polymerisation process in which monomer molecules are added to one another in a fast series via chain mechanism.
3) Addition polymers produced by the polymerisation of a single monomeric species are termed **homopolymers**.
4) **Condensation polymers** are produced by condensation polymerisation process in which intermolecular reactions occur between bifunctional or polyfunctional monomer molecules which have reactive functional groups.
5) Polyethene Vinyl Acetate (PVA), Polyethene Vinyl Chloride (PVC), Polydimethyl Siloxam (PDS), Polyether Urethane (PEU), Ethyl Cellulose (EC), Cellulose Acetate (CA), and polyethylene are the **examples** of **non-biodegradable polymers**.
6) Polycaprolactone (PCL), Polylactic Acid (PLA), Polyglycolic Acid (PGA), Poly(Lactic-co-Glycolic) Acid (PLGA), etc. are the **examples** of **biodegradable polymers**.
7) Buna-S, buna-N, neoprene, etc. are the **examples** of **elastomers**.
8) **Thermoplastic polymers** have intermolecular forces between elastomers and fibres. They can be softened on heating and toughened on cooling **at** room temperature.
9) **Thermosetting polymers** are hard and become infusible on heating. They do not soften on heating under pressure and they cannot be remoulded.
10) In **isotactic polymers**, the characteristic or side groups are arranged on the same side of the main chain.
11) In **syndiotactic polymers**, the characteristic or side groups are alternately arranged.
12) In **atactic polymers**, the characteristic or side groups are randomly arranged around the main chain. Atactic polymers have proper strength and high elasticity.
13) **Hydrophobic polymers** are water-insoluble due to the presence of non-polar functional groups.

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CHAPTER 3

Microencapsulation

3.1. MICROENCAPSULATION

3.1.1. Introduction and Definition

The process in which solids, liquids or even gases are enclosed within microscopic particles by forming thin coatings of wall material is termed **microencapsulation**.

A **microcapsule** formed as a result of microencapsulation is a small sphere having a uniform wall surrounding it. The material enclosed within a microcapsule is the **core** (or internal phase or fill); while the wall around the microcapsule is the **coating** (or shell or membrane). The diameter of microcapsules usually ranges between a few micrometres to a few millimetres.

Microencapsulation can also be defined as the process in which individual particles or droplets of solid or liquid material (i.e., the core) are surrounded with a continuous film of polymeric material (i.e., the coating) to produce microcapsules (in micrometre to millimetre range) (**figure 3.1**).

Core Material

It is the material to be enclosed, and should possess the following properties:

1) It should be a liquid or solid.
2) Liquid core should be a dissolved or dispersed material.
3) Its composition should be of the coating material.
4) It should be the drug or the active constituent.
5) It should enhance the rate of release.

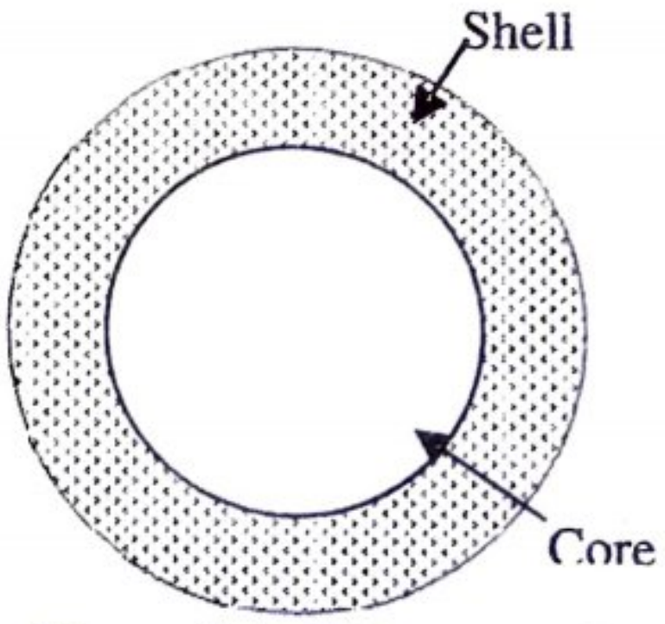


Figure 3.1: Microcapsule with Core and Coat

Coating Material

It is the material to be coated on the core, and should possess the following properties:

1) It should be inert towards the core material.
2) It should be compatible with the core material.
3) It should stabilise the core material.
4) It should have a controlled release under specific conditions.
5) It should form a flexible, brittle, hard, and thin coating.
6) It should be available in abundance.
7) It should be inexpensive.

Examples of Coating Materials

1) **Gums:** Gum Arabic, sodium alginate, and carrageenan.
2) **Carbohydrates:** Starch, dextran, and sucrose.
3) **Celluloses:** Carboxymethylcellulose and methylcellulose.
4) **Lipids:** Bees wax, stearic acid, and phospholipids.
5) **Proteins:** Gelatin and albumin.

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3.1.2. Advantages

Microencapsulation method has the following advantages:

1) It converts liquid into free-flowing and pseudo solids, thus improve th handling and storage of certain drugs, **e.g.,** eprazinone, clofibrate, castor o cod-liver oil, etc.
2) It reduces the volatile nature of some substances, **e.g.,** methyl salicyla peppermint oil, flavours, perfumes, etc.
3) It avoids incompatibilities in drug combinations, **e.g.,** aspirin an chlorpheniramine maleate, eutectic combinations, etc.
4) It masks the unpleasant taste of some drugs, **e.g.,** penicillin derivatives lik ampicillin, aminophylline, prednisolone, cod liver oil, etc.
5) It also masks the unpleasant or unacceptable odour of certain core material **e.g.,** castor oil, cod liver oil, methionine, cysteine, etc.
6) It reduces the GIT irritation caused by some drugs, **e.g.,** ferrous sulphat potassium chloride, paracetamol, phenylbutazone, indomethacin nitrofurantoin, etc.
7) It reduces the hygroscopic nature of some core materials, **e.g.,** sodiu chloride, etc.
8) It provides sustained, prolonged, delayed, or controlled release of drug.
9) It reduces operation hazards while using toxic chemicals, **e.g.,** insecticide pesticides, and sensitisers (like penicillins, etc.).
10) It improves the flowability, compactibility, and compressibility of the cor materials, **e.g.,** vitamins, etc.
11) It causes immobilisation of enzymes, thus improving their stability an retention of activity.
12) It also allows combining the chemically incompatible ingredients in a singl form, **e.g.,** aspirin, citric acid, etc.

3.1.3. Disadvantages

Microencapsulation method has the following disadvantages:

1) It is expensive.
2) It cannot be used for all the core materials.
3) Sometimes it leads to incomplete and discontinuous coating.
4) It does not use a single technique for all the core materials.
5) Sensitive pharmaceuticals cannot be used because the product has inadequat stability and shelf-life.
6) Individual design approach is required for different core materials.
7) The coated products have non-reproducible and unstable release characters.
8) Limited number of safe, approved, biocompatible, and biodegradabl materials can be used.
9) Mechanical stress, like compression, compaction, packaging, transpor handling, etc., may damage the coat or the product.
10) Microparticles due to size restrictions cannot be used for parenteral applications
11) There may be difficulties in scale up and large scale manufacturing.

3.1.4. Microparticles

Solid particles or particulate dispersions of 1-1000µm size range are termed microparticles. In a microparticles matrix, the drug molecules are dissolved, entrapped, encapsulated, or attached.

Microparticles, microspheres, or microcapsules can be prepared by various methods depending on the size of particles. **Microparticles** are spherical-shaped micrometric matrix system. They are polymeric entities in which drug molecules are dispersed physically and uniformly.

Microcapsules are spherical or non-spherical micrometric reservoir systems. They are small particles of 100-150µm size range. They contain an active agent or core material covered by a coating or shell. In microcapsules, the drug remains confined to a cavity surrounded by a polymer membrane. **Microspheres** are monolithic sphere in which the drug remains distributed throughout the matrix as a molecular dispersion of particles. They are of 1-1000µm size range.

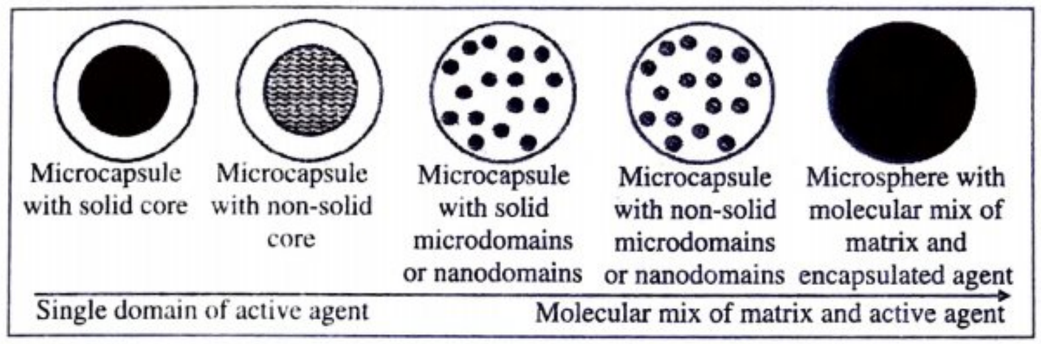


Figure 3.2: Different Categories of Microparticles

3.1.4.1. Advantages

Microparticles have the following advantages:

1) They increase the drug bioavailability.
2) They decrease the local and systemic side effects; **for example,** gastrointestinal irritation caused by some drugs on oral ingestion is reduced.
3) They mask the unpleasant taste and odour of drugs.
4) They provide protection from environmental factors.
5) They prevent the fluctuations of plasma drug concentration.
6) They improve the powder flow.
7) They improve treatment efficiency and patient compliance.
8) They provide chemical and physical storage stability to the drug as well as the carrier.
9) They utilise biodegradable lipids.
10) They allow the incorporation of hydrophilic and hydrophobic drugs.
11) They allow safe handling of toxic substances.
12) Due to their reduced particle size, the solubility of poorly soluble drugs increases.
13) They offer targeted release of the encapsulated drug material.
14) They allow the separation of incompatible components, such as excipients, buffers, and other drugs.

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15) They help in dispersing the water-insoluble substances in aqueous media.
16) They effectively deliver the substances that are insoluble or sparingly solub in water.
17) Smaller microparticles can be applied to other sites, such as eyes, lungs, and join
18) They are used in the form of microcapsules to deliver drugs and vaccines a diagnostic agents and in surgical procedures.
19) They are used to administer effervescent drugs in those who cannot che like in elderly patients and debilitated patients who face difficulty i swallowing solids.
20) In microparticles, high concentration of drug can be loaded and drugs can b incorporated into the systems without any chemical reaction to preserve th drug activity.

3.1.4.2. Disadvantages

Microparticles have the following disadvantages:

1) These formulations are costly because the materials used and the processin costs of the controlled release preparations are higher than those of th standard preparations.
2) The degradation and by-product of polymer matrix produce an undesirabl effect on the environment.
3) The degradation and by-product of polymer additives (**e.g.,** plasticiser stabilisers, antioxidants, and fillers) also produce undesirable affects.
4) Their reproducibility is low.
5) The stability of core materials to be encapsulated is affected by the proces conditions (**e.g.,** temperature change, pH, solvent addition, an evaporation/agitation).
6) The environmental effects after the degradation of polymer matrix an products obtained after heat treatment, hydrolysis, oxidation, solar radiatio or biological agents and the cost, is need to be registered by government.
7) The environmental impact of degradation products of polymer matri produced in response to heat, hydrolysis, oxidation, solar radiation, o biological agents, and the cost, time probability of success in securin government registration of the product, if required.

3.1.4.3. Microspheres

Microspheres are small, spherical, free-flowing particles, having diameter of 1- 1000µm. They consist of biodegradable proteins or synthetic polymers Microspheres are of two types, i.e., **microcapsules** and **micromatrices**. I microcapsules, the entrapped substance is surrounded by a distinct capsule wall while in micromatrices, the entrapped substance remains dispersed throughou the matrix. Often, microspheres are termed as microparticles.

Various natural and synthetic materials are used for manufacturing microspheres They are used to enhance the bioavailability of conventional drugs and also t reduce side effects.

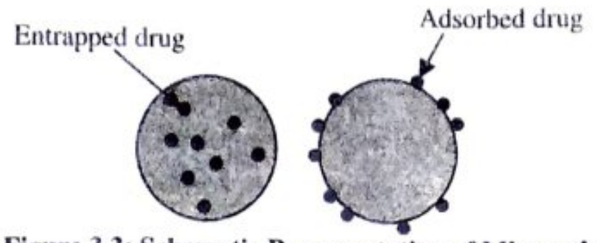


Figure 3.3: Schematic Representation of Microspheres

An **ideal microsphere** has the following **characteristics**:

1) It should be able to incorporate a high concentration of drug.
2) The synthesised formulation should have a high stability and a clinically acceptable shelf-life.
3) It should have a controlled particle size.
4) It should have a controlled dispersibility in aqueous vehicles for injection.
5) The drug should be released with a good control over a wide time scale.
6) It should have biocompatibility with a controlled biodegradability.
7) It should be susceptible to chemical modification.

Microspheres are of the following **types**:

1) **Bioadhesive Microspheres:** Sticking drug to the membrane with the aid of sticking property of water-soluble polymers is termed as **adhesion**; and adhesion of drug delivery system to mucosal membrane (like buccal, ocular, rectal, nasal, etc.) is termed as **bioadhesion**. These microspheres remain at the application site for a prolonged time period, cause intimate contact with the absorption site, and thus results in better therapeutic action.
2) **Magnetic Microspheres:** These microspheres are particularly used when the drug is to be localised on the diseased site. In this delivery system, large amount of freely circulating drug is replaced with small amount of magnetically targeted drug. The incorporated materials (**e.g.,** chitosan, dextran etc.), used for magnetic microspheres, send magnetic responses to magnetic carriers through a magnetic field. Magnetic microspheres are of the following **two types**:
   i) **Therapeutic Magnetic Microspheres:** These are used for delivering chemotherapeutic agents to liver tumours. They can also be used for targeting proteins and peptides.
   ii) **Diagnostic Microspheres:** These are used for diagnosis purposes. **For example,** for imaging liver metastases and to distinguish bowel loops from other abdominal structures by forming nano-sized supramagnetic iron oxide particles.
3) **Floating Microspheres:** The bulk density of these microspheres is less than the gastric fluid; therefore, they remain buoyant in stomach and do not affect the gastric emptying rate. The drug is released gradually at the desired rate, the microsphere system floats in the gastric content, and thus the gastric residence and fluctuation in plasma concentration increases. These systems also reduce the possibility of dose dumping, result in prolonged therapeutic effect, and thus reduce the dosing frequency. **For example**, ketoprofen can be delivered as a floating microsphere.

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4) **Radioactive Microspheres:** The microspheres used in **radio embolisation therapy** are 10-30nm size (larger than the diameter of capillaries). They ge trapped in the first capillary bed they come across. Radioactive microsphere are injected in the arteries, from where they reach the target site (tumour) t deliver high radiation dose to the targeted areas, without damaging the normal surrounding tissues. This system of drug delivery differs from othe systems as the radioactive substance is not released from the microsphere but acts from within a radioisotope. **Examples** of different radioactive microspheres are α emitters, β emitters, and γ emitters.

5) **Polymeric Microspheres:** These are grouped into the following **two classes**:
   i) **Biodegradable Polymeric Microspheres:** Biodegradable, biocompatible, and also bioadhesive natural polymers (**e.g.,** starch) are used in these microspheres. These polymers have high degree of swelling property with aqueous medium; thus, they prolong the residence time on coming in contact with mucous membrane and form a gel-like substance.

   The rate and extent of drug release depends on polymer concentration and the release pattern in a sustained manner. The major **advantage** of this system is that it can be used for a wide range of application in microsphere-based treatment. However, the major **disadvantage** is that in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release.

   iii) **Synthetic Polymeric Microspheres:** These microspheres are mainly used in clinical applications as bulking agents, fillers, embolic particles, drug delivery vehicles, etc. Synthetic polymeric microspheres are safe and biocompatible; however, their major **drawback** is that they move away from the injection site and cause potential risk, embolism, and subsequent organ damage.

3.1.4.4. Microcapsules

Microcapsules, formed as a result of microencapsulation, are small spheres having a uniform wall surrounding them. The material enclosed within a microcapsule is **the core** (or internal phase or fill); while the wall around the microcapsule is **the coating** (or shell or membrane). The diameter of microcapsules usually ranges between a few micrometres to a few millimetres.

An **ideal microcapsule** should have the following **characteristics**:

1) It should have the ability to incorporate drug in high concentrations.
2) It should impart stability to the preparation, along with a clinically acceptable shelf-life.
3) It should provide controlled particle size and dispersibility in aqueous vehicles for injection.
4) It should release the active ingredient in a controlled manner for a prolonged period.
5) It should be biocompatible with a controllable biodegradability.
6) It should be susceptible to chemical modifications.

On the basis of morphology, microcapsules are grouped into the following **three classes**:

1) **Mononuclear (Core-Shell) Microcapsules:** These have the shell around the core material.
2) **Polynuclear Capsules:** These have many core materials enclosed within the shell.
3) **Matrix Encapsulation:** In these, the core material is homogeneously distributed into the shell material.

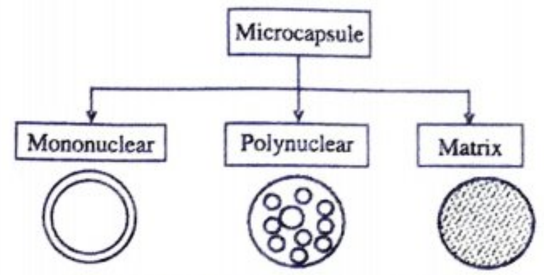


Figure 3.4: Types of Microcapsules

Apart from these three basic morphologies, microcapsules can also be mononuclear with multiple shells or may form clusters of microcapsules.

3.1.5. Formulation

Microparticles can be prepared using various polymers of biodegradable and non-biodegradable nature. These polymers may be of natural and synthetic origin and also modified natural substances. The polymers used for manufacturing microspheres are classified as follows:

1) **Synthetic Polymers**
   i) Non-biodegradable polymers:
      a) PMMA (Polymethylmethacrylate),
      b) Acrolein,
      c) Glycidyl methacrylate, and
      d) Epoxy polymers.
   ii) Biodegradable polymers:
      a) Lactides and glycosides and their copolymers,
      b) Polyalkyl cyanoacrylates, and
      c) Polyanhydrides.
2) **Natural Materials**
   i) Proteins:
      a) Albumin,
      b) Gelatin, and
      c) Collagen.
   ii) Carbohydrates:
      a) Starch,
      b) Agarose,
      c) Carrageenan, and
      d) Chitosan.
3) **Chemically-Modified Carbohydrates**
   i) DEAE cellulose,
   ii) Poly(acryl)dextran, and
   iii) Poly(acryl)starch.

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3.1.6. Methods of Microencapsulation

Microencapsulation process is of the **following types**:

1) Air suspension technique,
2) Coacervation-phase separation,
3) Multiorifice-centrifugal process,
4) Pan coating,
5) Spray drying and congealing,
6) Fluidised-bed technology,
7) Solvent evaporation,
8) Polymerisation,
9) Rapid expansion of supercritical fluids,
10) Salting out process, and
11) Complex emulsion based method.

3.1.6.1. Air Suspension Technique

Air suspension technique (or **Wurster** or **fluidised bed coating**) involv dispersion of the solid core materials in an air stream, and then spray coating these air suspended particles (**figure 3.5**). The particles to be coated a suspended in an upward moving air stream. The chamber design and its operatin parameters are such that the particles circulate repeatedly through the coatin zone of the chamber. In this zone, the suspended particles are applied with th polymeric coating material in the form of a spray.

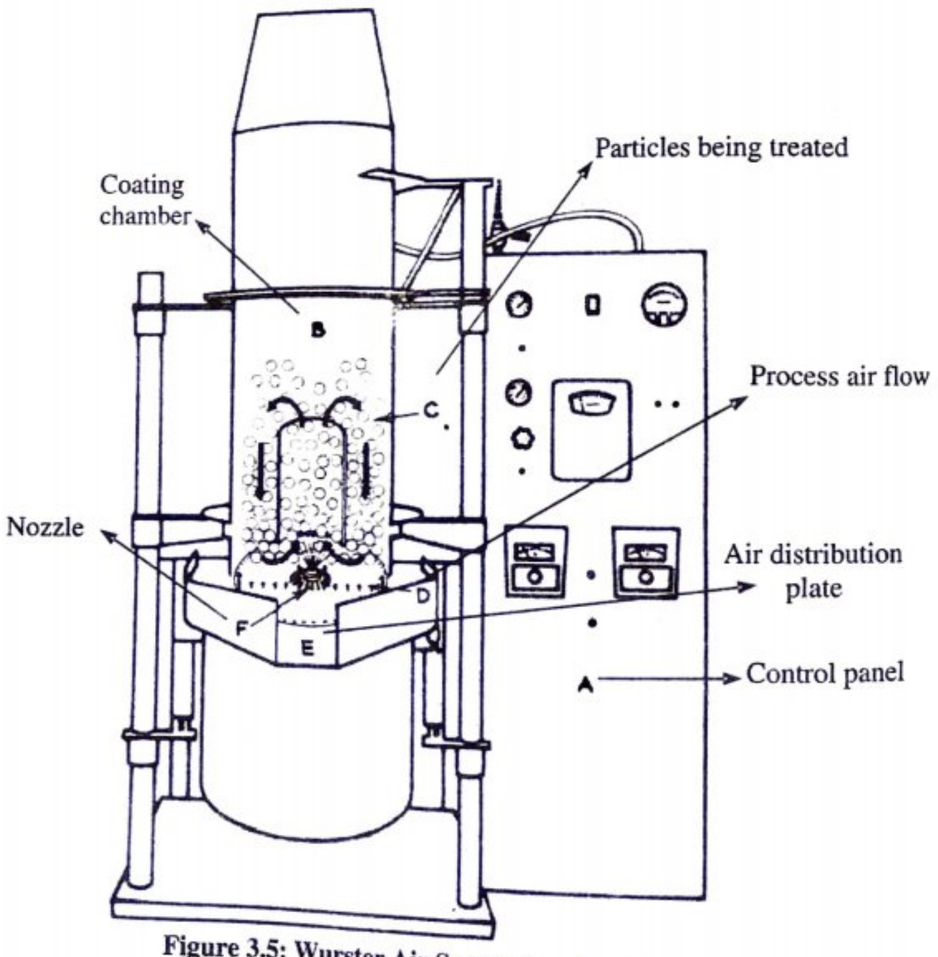


Figure 3.5: Wurster Air Suspension Apparatus

When the core material passes through the coating zone, it receives a significa amount of coating material; this amount increases with each time the co material passes. This cyclic process is repeated for around several hundred time however the number of repetitions depends on the desired coating thickness, th

purpose of microencapsulation, and whether or not the core material is completely encapsulated. The air stream introduced in the chamber also dries the microcapsules formed. The rate of drying and the volume temperature of the air stream are directly proportional.

Merits

1) It is a rapid coating method.
2) It is an easy method, thus skilled labours are not required.
3) It can be used for most of the solid core material, regardless of their size, shape, and the coating material used.
4) It can be effectively used for very fine core materials.
5) It provides superior coating quality.
6) It requires less coating material.
7) Coating material can be applied in the form of a solution, suspension, emulsion, or melt.
8) Both aqueous and non-aqueous coatings can be used.
9) Very less amount of coating material is lost that can be even recovered.
10) It provides total environmental protection, thus there are neither any related hazards to the operators nor any contamination risk.
11) The equipment can also be used for granulation, drying, mixing, etc.

Demerits

1) It cannot be used for heat-sensitive core materials.
2) It can be used only for solid cores.
3) It offers reduced versatility.
4) The equipment used is costly.
5) The particles of core material should have a size greater than 50mm.
6) The core material should be non-volatile in nature.

3.1.6.2. Coacervation-Phase Separation Method

A tiny spherical droplet in which various organic molecules (lipid molecules particularly) are held together by hydrophobic forces from a surrounding liquid is termed a **coacervate**. The method, by which a solution of hydrophilic polymer(s) is separated into two phases, i.e., small droplets of a dense polymer-rich phase and a dilute liquid phase, is termed **coacervation**.

This coacervation process is induced by the following **factors**:

1) By changing the system temperature,
2) By changing the pH,
3) By changing the electrolyte balance,
4) By adding non-solvents, and
5) By adding materials which are incompatible with the polymer solution.

Based on the number of polymers, **coacervation method** is of the following **types**:

1) **Simple Coacervation:** In this type, only one polymer (**e.g.,** cellulose, gelatin, polyvinyl alcohol, and carboxymethyl) is used. The phases undergo separation on addition of water-miscible non-solvents (**e.g.,** acetone, isopropanol, ethanol, dioxane, or propanol), addition of inorganic salts (**e.g.,**

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sodium sulphate), or changing of temperature. These conditions cause desolvation (or dehydration) of the polymer phase.

2) **Complex Coacervation:** In this type, two oppositely charged hydrophilic polymers are used. Polymer-polymer interaction occurs in this process. For **example,** in gelatin-gum Arabic system, the pH should lie below gelatin's isoelectric point so that it can maintain the positive charge. After the formation of embryonic coacervates around the dispersed oil or solid phases, the polymer complexes become stable by cross-linking with glutaraldehyde.

Steps in Coacervation-Phase Separation Technique

Step 1: Formation of Three Immiscible Chemical Phases: In this step, the following three different chemical phases are formed:

1) The liquid manufacturing phase (i.e., the solvent for the coating material),
2) The core material phase (insoluble in the solvent), and
3) The coating material phase (made by separating the polymer from the solvent).

This step involves dispersion of the core material (i.e., drug) in the liquid manufacturing phase, consisting of the dissolved coating material (i.e., polymer or colloid), followed by separation of the polymeric coating material into the third phase using a suitable phase separation-coacervation technique like:

1) Changing the temperature,
2) Adding salt,
3) Adding an incompatible polymer,
4) Adding a non-solvent, and
5) Polymer-polymer interaction.

Table 3.1 enlists the techniques of coacervation-phase separation, along with the core and coating:

Table 3.1: Techniques of Materials Used in Coacervation-Phase Separation

Techniques	Core Materials	Coating Materials
Non-Solvent Addition	Gelatin	Acetone and ethanol
	Agar and methyl cellulose	Acetone
	Pectin	Isopropyl alcohol
Salt Addition	5% gelatin gel	25% sodium sulphate salt solution
Temperature Change Method	Ethyl cellulose	Cyclohexane
Incompatible Polymer Addition	Polybutadiene to ethyl cellulose solution	Toluene
Polymer-Polymer Interaction	Acacia	Acidic solution of gelatin

Step 2: Deposition of Coating Material Around the Core Material: In this step, the phase separated polymeric coating material deposits around the core material (**figure 3.6**) only if the interfacial tension of the coat is less than that of the core. The deposition rate can be controlled by the regulation of mixing conditions (**e.g.,** viscosity, speed, temperature, etc.).

Step 3: Rigidisation of the Coat: In this step, with the beginning of coacervation a gradual gelation of the colloid occurs (**figure 3.6**). Consequently, the viscosity of the core material phase increases and the microcapsules obtained undergo cohesion or aggregation; however, these microcapsules can be stabilised

by using shock preventing agents or polyelectrolytes (**e.g.,** sodium CMC, sodium carboxy methyl starch, acrylic acid-methacrylate copolymer, anionic or cationic surfactants, silica dioxide, etc.), which reduce the gel viscosity by charge repulsion.

Since these agents are associated with moisture, residual solvent, and porous, permeable coats, they fail to reduce the mechanical fragility of the walls; thus walls can be hardened by treating with a solvent withdrawing liquid. A compact and non-porous coat can be formed by chemical cross linking with wall-hardening chemical cross linkers (**e.g.,** aldehydes like glutaraldehyde and formaldehyde). Hardening of walls can also be increased by raising the temperature to 40-60°C for a short period.

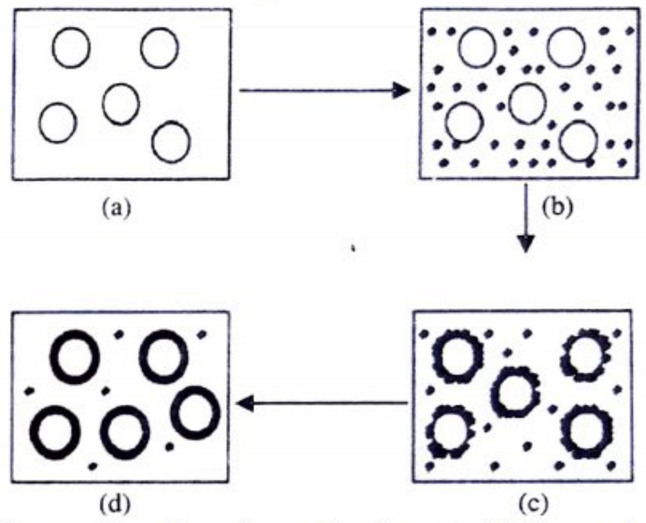


Figure 3.6: Coacervation-Phase Separation Process; (a) Core material dispersion in solution of shell polymer; (b) Separation of coacervate from solution; (c) Coating of core material by microdroplets of coacervate; (d) Coalescence of coacervate to form a continuous shell around the core particles.

3.1.6.3. Multiorifice-Centrifugal Process

Multiorifice-centrifugal method was developed by the **Southwest Research Institute (SWRI)**, and is a mechanical process for producing microcapsules using centrifugal forces. In this method, a particle of core material is passed through an enveloping microencapsulation membrane. Rotational speed of the cylinder, flow rate of the core and coating materials, and concentration, viscosity and surface tension of the core material are the process variables involved. This method can microencapsulate various sizes of liquids and solids using different coating materials. The encapsulated product can be supplied in the hardening media either as slurry or as a dry powder.

Figure 3.7 represents the cross-sectional view of the apparatus used. The major part of the apparatus is the rotating cylinder (**1**), within which three circumferential grooves (**2**, **3**, and **4**) are present. Countersunk in the intermediate groove (**3**) are closely packed orifices arranged circumferentially around the cylinder. The upper and lower grooves are also present circumferentially around the cylinder. These grooves carry the coating material (in molten or solution form) to the respective grooves via coating inlet (**5**). The ridges on the coating

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material grooves (**2** and **4**) serve as a barrier. When the volume of the upper ... lower grooves is surpassed by the volume of material pumped into the syste... the coating material overflows this barrier. The coating material (**6**) experienc... centrifugal force due to the rotating cylinder flows along the side of ... immediate groove into the countersunk portion, thereby forming a film across ... orifice. The core material is introduced through the centrally located inlet (**7**)... counter rotating disc (**8**) within the cylinder atomises the core material liq... droplets or solid particles, and throws them towards the orifices. The c... material arrives at the orifices and encounters the coating material membra... The rotating cylinder generates centrifugal force which pushes the core mater... through the enveloping coating membrane (**9**) which is immediately regenera... by the continually overflowing coating material.

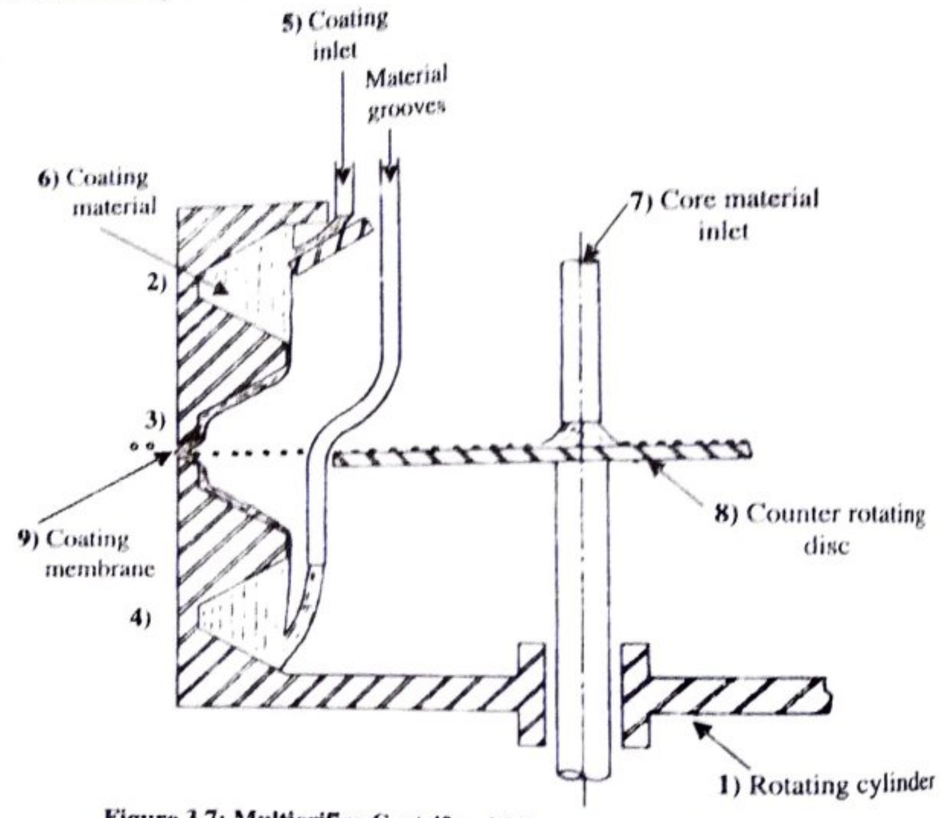


Figure 3.7: Multiorifice-Centrifugal Microencapsulation Apparatus

3.1.6.4. Pan Coating

Pan coating is the oldest and widely used industrial method for forming sma... coated particles or tablets. In this method, the particles of core material a... dropped in a pan and the coating material is either sprayed (to provide unifor... coverage and avoid unwanted localised over wetting) or poured (to reduc... undesirable water vapour permeability of the film and give superior coatin... uniformity) on the moving particles. Spray pattern, pressure, orifice siz... temperature, distance between the atomiser and the load, rotation speed, angl... and geometry of the pan, feed nature, coating solution viscosity, evaporation rat... application rate, etc. are the process variables which can be regulated to contr... the product quality. Hydraulic or airless atomisers are mostly preferred for p... coating.

Merits

1) Coating pans are widely used in many industries.
2) This coating method can be suitably used for core and coating materials.
3) The method offers process flexibility.

Demerits

1) The method demands skilled operators.
2) It is a time-taking process.
3) A large amount of coating material is required for achieving the desired thickness and uniformity.
4) The tablets gain 10-20% of weight due to coating.
5) Since large numbers of not so easy to control process variables are involved, technical difficulties arise in obtaining satisfactory coating.
6) The method lacks consistency and reproducibility.
7) It is expensive.
8) It is not suitable for particles of size <500µm.
9) Risk of particle atomisation in the atmosphere increases.
10) The quality of coating declines if roughness, irregularity, and size distribution increase.

3.1.6.5. Spray Drying and Spray Congealing

Spray drying for microencapsulation is an economic process used for encapsulating fragrances, oils, and flavours. In this method, the feed in a fluid state is sprayed into a hot drying medium and gets continually transformed to a dried particulate state. The core material (an oil or active ingredient immiscible with water) is dispersed in a concentrated solution of wall material to obtain an emulsion (slurry) having oil droplets of desired size (**figure 3.9**).

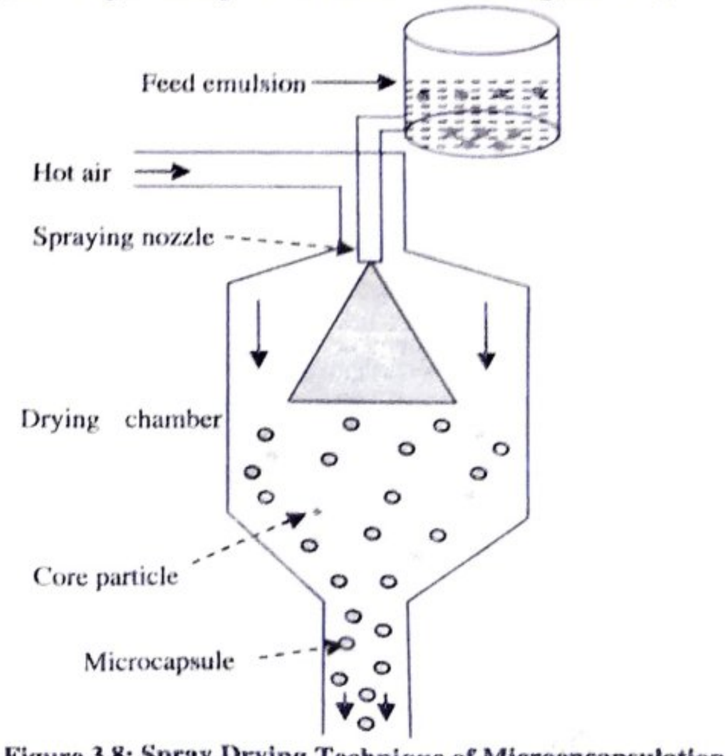


Figure 3.8: Spray Drying Technique of Microencapsulation

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This emulsion is atomised or sprayed in the form of droplets into the hea compartment of a spray dryer by pumping through a rotating disc. Inside t compartment, the water portion of the emulsion evaporates leaving behind dr capsules of various shapes and containing scattered drops of core material. The capsules are collected by continuous discharge from the spray drying chamb Spray drying method can also be used for drying small microencapsulat materials from aqueous slurry produced by chemical means.

Spray congealing can be performed using the spray dryer applied with protective coating as a melt. In this method, the core material is dispersed in t coating material melt (not in the coating solution). The hot coating mater solidifies when sprayed in a cool air stream. Materials which remain solid room temperature but melt at high temperatures (**e.g.,** waxes, fatty acid alcohols, and polymers) are used for spray congealing.

3.1.6.6. Fluidised-Bed Technology

Fluid bed coating for preparing microcapsules is of the following **three types**:

1) **Top Spray Coating:** With top spray coating in the fluid bed (batch a continuous), particles are fluidised in the flow of heated air introduced in the product container through the base plate (**figure 3.9**).

   The fluid bed is sprayed with the coating liquid through a nozzle from abo against the air flow (counter-current). The particles dry as they continue move upwards in the air flow. The coating liquid distributes uniformly owi to the small size of the droplets and low viscosity of the spray medium.

   Coating in the continuous fluid bed is suitable for protective or colo coatings where the product throughput rates are high. In this method, t product is continuously fed into one side of the machine and by means of a flow is transported forward via the sieve bottom. The dry coated particles a extracted continuously.

2) **Bottom Spray Coating (Wurster Coating):** This process is used when controlled release of active ingredients is required. In the Wurster coatin process (**figure 3.9**), the surface is sealed completely by less using the coatin substance. The spray nozzle is fitted in the base plate resulting in a spra pattern concurrent with the air feed. By using a Wurster cylinder and a ba plate with different perforations, the particles to be coated are accelerated the Wurster tube and concurrently fed through the spray cone.

   As the particles move upwards, they dry and fall outside the Wurster tub back towards the base plate. They are guided from the outside back to th inside of the tube, where they are again accelerated by the spray, thu producing a highly uniform film even on different sized particles.

3) **Bottom Spray Coating (Continuous Fluid Bed):** This process is suitable f protective or colour coatings where the products throughput rates are high. Th product is continuously fed into one side of the machine and is transporte forward via the sieve bottom by means of air flow. Depending on th application, the system is sub-divided into pre-heating zones, spray zones, a

drying zones where coating liquid is sprayed from below in the form of a bottom spray. The dry and coated particles are continuously extracted.

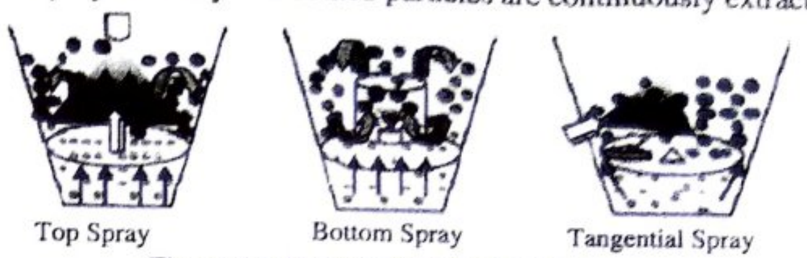


Figure 3.9: Fluidised-Bed Technology

3.1.6.7. Solvent Evaporation

Solvent evaporation is widely used in pharmaceutical industries for microencapsulation. This technique facilitates controlled drug release, which is clinically beneficial. Water-insoluble polymers are employed as encapsulation matrix, and PLGA (Poly Lactic-co-Glycolic Acid, a biodegradable polymer) is used as an encapsulation material in this technique. Many hydrophobic drugs (**e.g.,** cisplatin, lidocaine, naltrexone, and progesterone) and hydrophilic drugs (**e.g.,** insulin, proteins, peptides, and vaccines) have been encapsulated by solvent evaporation.

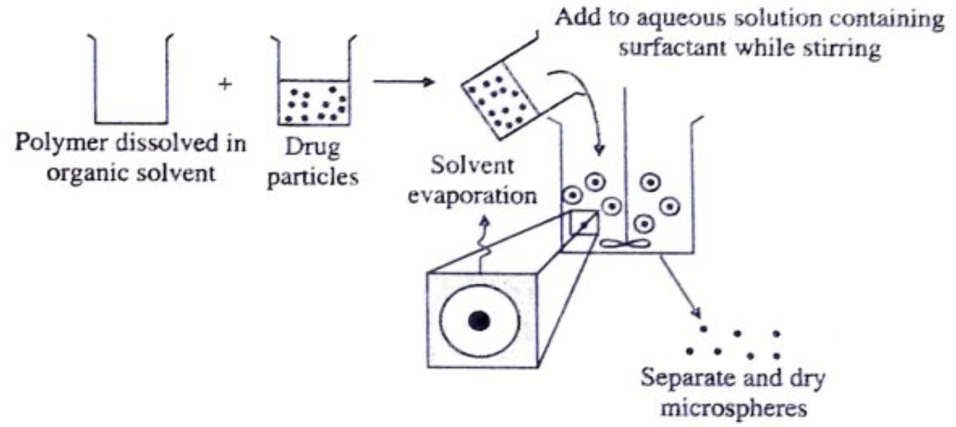


Figure 3.10: Solvent Evaporation Technique of Microencapsulation

In this method (**figure 3.10**), an aqueous solution of the drug (containing a viscosity enhancer or stabiliser) is prepared and added to an organic phase (consisting of the polymer solution in solvents, like dichloromethane or chloroform) with vigorous stirring. The resultant solution is the primary water in oil emulsion, which is added to a large volume of water containing a surfactant or emulsifier (like PVA or PVP) to form the multiple emulsion (w/o/w). This obtained double emulsion is then stirred till most of the organic solvent evaporates to form solid microspheres, which are finally washed and dried.

3.1.6.8. Polymerisation

In polymerisation method, the monomeric units present at the interface between a core material phase and a continuous phase (in which the core material is dispersed) react. Since the continuous or core material supporting phase is either a gas or liquid, polymerisation reactions occur at liquid-liquid, liquid-gas, solid-liquid, or liquid-solid interface.

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Polymerisation technique of microencapsulation is of the following **three type**

1) **Interfacial Polymerisation:** In this technique (**figure 3.11**), a capsule sh is formed on the droplet or particle surface by polymerisation of the reacti monomers. Usually, multifunctional monomers (like multifunctio isocyanates and multifunctional acid chlorides) are used either alone or combined form. This monomer is dissolved in the liquid core material a dispersed in the aqueous phase, containing a dispersing agent. A co-reacta multifunctional amine is also added to the mixture for rapid polymerisation the interface and for formation of capsule shell. In reaction of isocyana with amine, a polyurea shell is formed, similarly in reaction of acid chlori with amine, a polynylon or polyamide shell is formed.

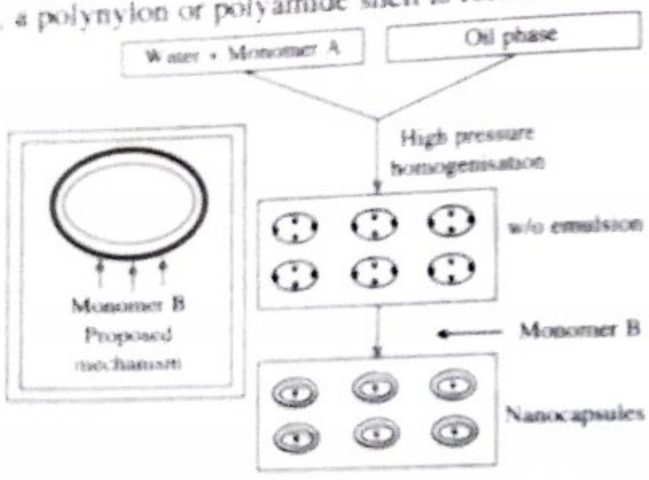


Figure 3.11: Interfacial Polymerisation Technique

2) **Matrix Polymerisation:** In this technique, the core material is embedded a polymeric matrix during the formation of particles. Spray drying is a simp method of this type, in which the particles are formed when the solve evaporates from the matrix material. However, matrix solidification can al occur due to a chemical change.

3) ***In Situ* Polymerisation:** In this technique, a single monomer is direct polymerised on the particle surface; **for example,** cellulose fibres a encapsulated in polyethylene while immersed in dry toluene. The deposition ra is normally 0.5µm/min, and the coating thickness ranges between 0.2-75µm.

3.1.6.9. Rapid Expansion of Supercritical Fluids

Supercritical fluids are highly compressed gases possessing some properties both liquids and gases. The density of supercritical fluids changes significant with a small change in temperature or pressure. Supercritical CO_2 (carbo dioxide) and N_2O (nitrous oxide) are most widely used. Supercritical CO_2 basically used due to its low critical temperature value; it is also non-toxic, no flammable, readily available, highly pure, and economic. Rapid expansion supercritical fluids can also be used for preparing nanoparticles.

Supercritical fluid contains the active ingredient (core material), and the she material maintained at high pressure is released through a small nozzle atmospheric pressure. This sudden drop in pressure results in desolvation of th shell material, which then deposits on the core material forming a coating laye (**figure 3.12**).

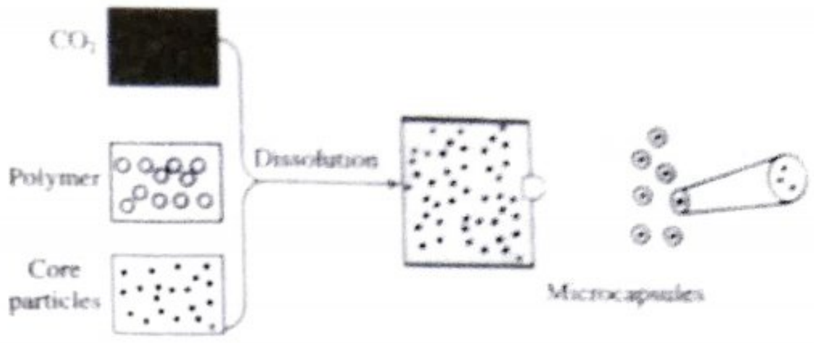


Figure 3.12: Rapid Expansion of Supercritical Fluids

Different core materials, **e.g.,** pesticides, pigments, vitamins, flavours, and dyes are encapsulated with this method. Various shell materials, **e.g.,** paraffin wax and polyethylene glycol, are used for encapsulating the core material.

A **limitation** of this method is that both the core and the shell material should be highly soluble in supercritical fluids.

3.1.6.10. Salting-Out Process

In the salting-out method (**figure 3.13**), an aqueous phase saturated with electrolytes (**e.g.,** magnesium acetate and magnesium chloride) and containing a stabiliser and viscosity enhancer (**e.g.,** PVA) is added to an acetone solution of polymer with vigorous stirring. Since the aqueous phase is saturated with electrolytes, miscibility of both the phases is prevented. The aqueous phase is continued to be added till a phase inversion occurs yielding an o/w emulsion.

In salting-out process, a salt is added to an aqueous polymer solution; as a result of which the polymer phase separates from the aqueous phase. A **drawback** of this process is that there may be a need to add high concentrations of salt in the final capsule wall, and these salts may affect the drug release from capsules.

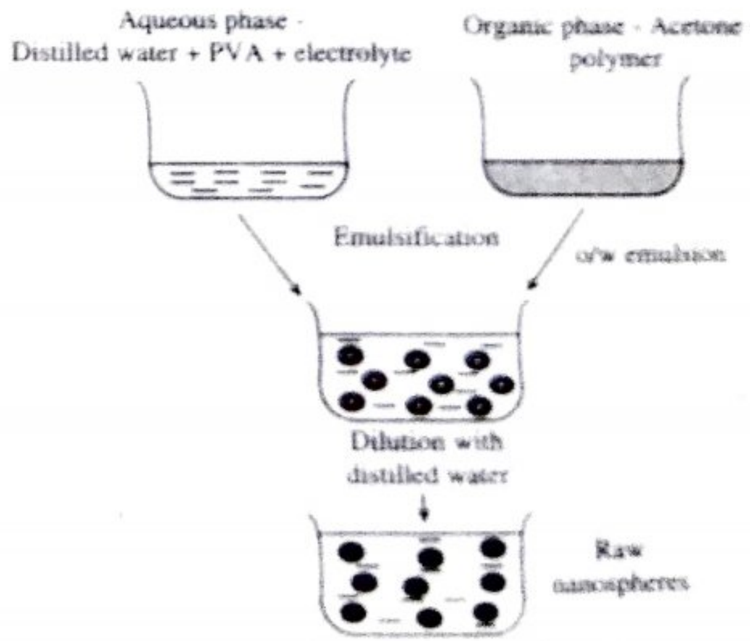


Figure 3.13: Salting-Out Process

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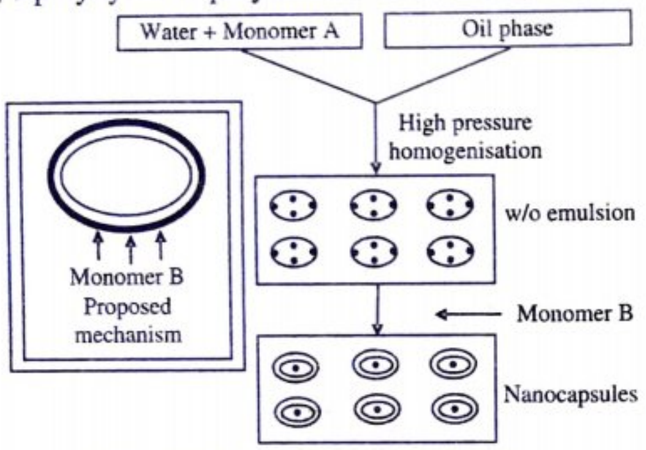


Figure 3.11: Interfacial Polymerisation Technique

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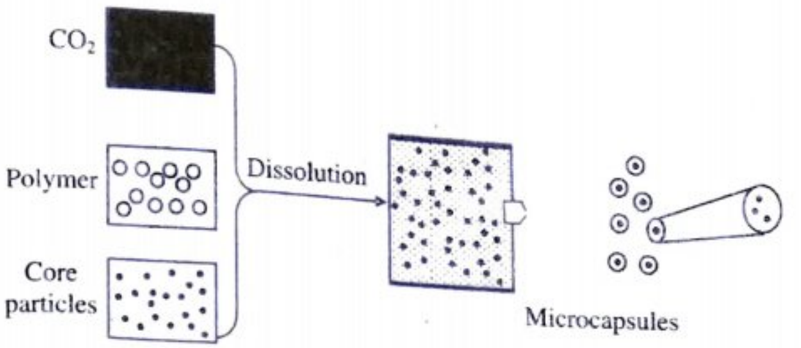


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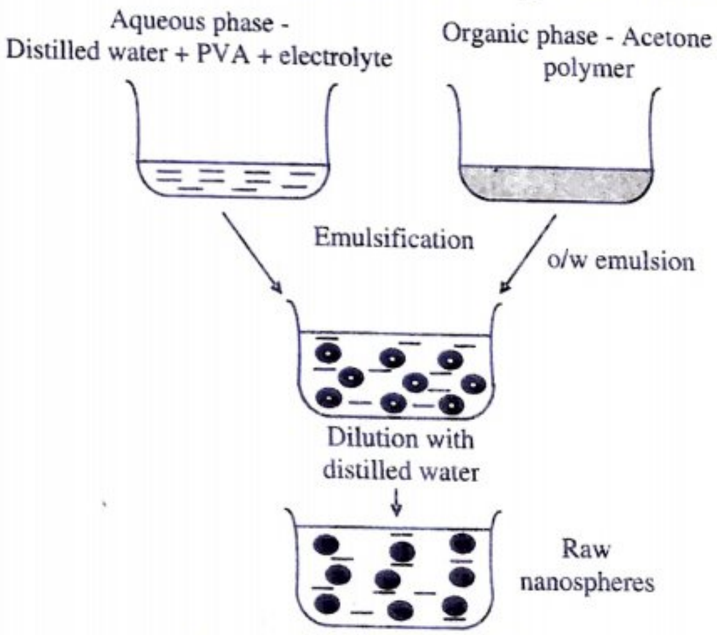


Figure 3.13: Salting-Out Process

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3.1.6.11. Complex Emulsion-Based Method

Complex emulsion based methods are of the following types:

1) Simple emulsion-based method (**figure 3.14**), and
2) Double emulsion-based method (**figure 3.15**).

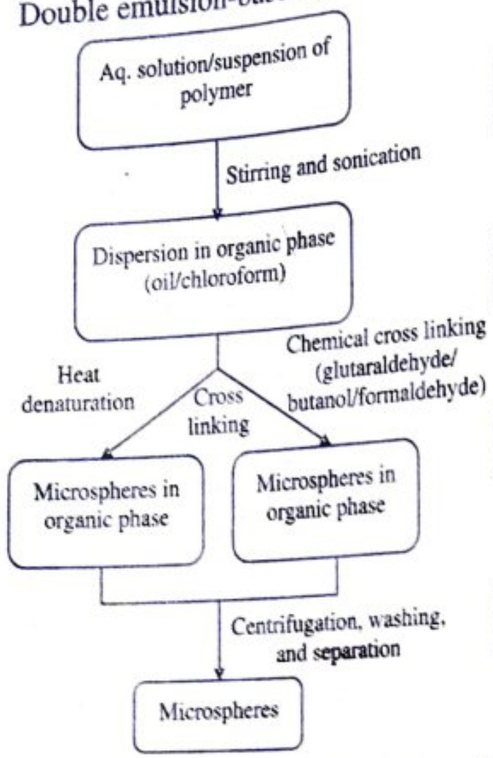


Figure 3.14: Simple Emulsion-Based Method

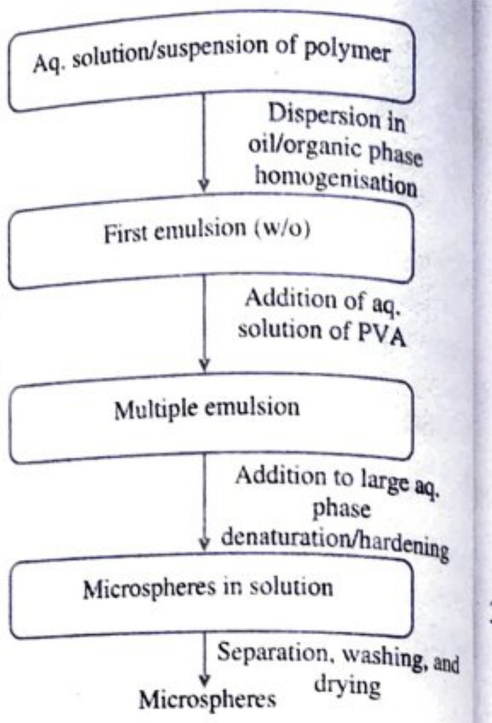


Figure 3.15: Double Emulsion-Based Method

3.1.7. Evaluation

The parameters and methods followed for the evaluation of microspheres a discussed below:

1) **Microsphere Recovery/Yield:** It determines the amount of microsphe obtained at the end of preparation, and the amount of polymer and drug us in the preparation. Microsphere recovery/yield can be calculated as follows

$$\text{Percentage Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

$$\text{Practical Yield of Microspheres} = \frac{\text{Amount of Encapsulated Drug}}{\text{Amount of Added Drug}}$$

2) **Drug Entrapment Efficiency:** It is evaluated by calculating the amount drug entrapped in the microsphere and the amount of drug adsorbed on polymer surface or its interior. The amount of free, adsorbed and entrapp drug should be measured separately to evaluate the efficacy of the produc microsphere in terms of its active ingredients.

Determination of Free Drug in Microspheres (Unentrapped Drug): I beaker, accurately weighed microspheres are taken and added with sali This mixture is shaken well to release the free drug present in the polym matrix. The quantity of free drug is calculated using a suitable analyti method. It is calculated by:

$$\text{Percentage loading of microsphere} = \frac{\text{Quantity of free drug present}}{\text{Weight of microsphere}}$$

The quantity of drug at the surface is calculated by digesting the microsphere with saline (0.9%w/v) at room temperature, soliciting the solution for 5 minutes in an ultrasonic bath, and centrifuging for 2 minutes at 3000rpm. A filter of 0.45µm is used to filter the supernatant, and the drug is quantified by a suitable analytical method.

$$\text{Percentage loading of microsphere} = \frac{\text{Quantity of drug present}}{\text{Weight of the microsphere}}$$

Entrapped Drug in Microsphere: The leftover residue obtained after the extraction of free and adsorbed drug is mixed with 5ml of 0.1M glacial acetic acid. This sample is centrifuged for 10 minutes at 5000rpm, and the supernatant is filtered using a 0.45µm sized filter. The quantity of drug entrapped is calculated by an appropriate analytical method.

$$\text{Percentage of encapsulated drug} = \frac{\text{Quantity of drug encapsulated (gm)}}{\text{Quantity of drug added for encapsulation}}$$

3) **Surface Morphology:** It offers crucial information regarding the porosity and microstructure of microspheres. The most common technique used for studying the surface morphology is **Scanning Electron Microscopy (SEM)**. For this purpose, the prepared sample is dehydrated as SEM requires a vacuum field for generating image. Electron dense coating materials (**e.g.,** gold, palladium, or a combination of both) are used to coat the samples (by sputter coating or thermal vacuum evaporation method), before loading them to take photomicrograph.

4) **Particle Size Analysis:** Analysis of particle size is important to ensure that the particle size of the formulation lies within the optimal range. Following methods, employing different physical principles, are used for determining particle size:

i) Manual Methods:
   a) Optical microscopy,
   b) Electron microscopy:
      - Transmission electron microscopy, and
      - Scanning electron microscopy.
   c) Sieving, and
   d) Sedimentation (Anderson pipette method).

ii) Automated Methods:
   a) Particle counters:
      - Optical particle counting,
      - The counter principle,
      - Permeability, and
      - Impaction and inertial techniques.
   b) Light scattering:
      - Dynamic light scattering, and
      - Enhance laser diffraction.
   c) Flow cytometry, and
   d) Field flow fractionation.

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5) ***In vitro* Release Studies:** These studies are performed to analyse the behaviour of these systems in terms of drug release and their efficacy. In an *in vitro* environment, drug release from the polymer takes place through a diffusion process because microsphere is a heterogeneous system. Thus, the drug and polymer matrix are phase separated, and form a biphasic system. Drug release is determined by the extent of degradation of polymeric microsphere.

For the *in vitro* release experiment, **dialysis method** is used, in which weighed quantity of the microsphere is placed in a dialysis bag. This bag is placed in a larger volume of continuous phase acceptor fluid and the compartment is stirred. The drug used diffuses out of the microspheres into the continuous phase, and is periodically sampled and assayed.

6) **Differential Scanning Calorimetry (DSC):** This technique is used to obtain qualitative and quantitative information about the physicochemical status of the drug in the microsphere. DSC includes an endothermic or exothermic process and the related thermal transitions, such as melting, re-crystallisation, decomposition, out gassing, or a change in heat capacity of the listed material. This method is used for monitoring different samples of the same materials to analyse their similarities/differences or the effects of additives on the thermal properties of material.

7) ***In vivo* Tissue Distribution Studies:** *In vivo* studies are important as they provide tangible evidence of the efficacy of microspheres. Also, the properties of microsphere are critical for understanding the functional characteristics of formulation in a biological system.

For *in vivo* analysis of the formulation properties, adult albino mice/Wistar rats/rabbits, etc. of specified weight are used. Each animal is given a measured dose of the drug as dispersion in saline with 1% of Tween 80. Microsphere is injected to the animals through the tail route vein at scheduled time intervals, and then they are sacrificed by cervical dislocation. Lungs, liver, kidneys, heart, and spleen are removed for targeted action studies, and HPLC method is used to determine the drug concentration in each organ.

Animal models are used to conduct *in vivo* tissue distribution studies and to prove the hypothesis of targeting microsphere/formulation to the organs and comparing them with conventional dosage forms of the drug.

3.1.8. Applications

Drugs and related chemicals are microencapsulated due to various reasons. Microencapsulation technique is used widely for the following purposes:

1) It is used to design controlled release, sustained release and prolonged release dosage forms.
2) It is used to mask the bitter taste of certain drugs (**e.g.,** paracetamol, nitrofurantoin, etc.).
3) It is used to reduce the gastric and GIT irritations caused by certain drugs. **For example**, it has been reported that sustained release preparations of aspirin cause comparatively less gastrointestinal bleeding than conventional formulations.

4) It is used to convert a liquid to a pseudo-solid to ease handling and storage, **e.g.,** eprazinone.
5) It is used to protect the core materials (**e.g.,** vitamin A palmitate) against atmospheric effects.
6) It is used to separate incompatible substances.
7) It is used to prepare enteric-coated dosage forms, in which the drug gets selectively absorbed in the intestine (and not in the stomach).
8) It is also used to formulate oily medicines into tableted dosage forms to overcome the problems caused by producing tablets from otherwise tacky granulations and in direct compression to tablets.
9) It provides protection to drugs from environmental effects, like humidity, light, oxygen, or heat. However, it does not provide complete protection to the drug formulations from degradation caused by oxygen, moisture, or heat.
10) It is also used to reduce the volatility of drug because an encapsulated volatile substance can be stored for longer times without evaporation.
11) It is used to microencapsulate various substances, like carbon tetrachlorides, to reduce their odour and volatility.
12) It is used to reduce the potential danger of handling toxic or noxious substances. Microencapsulation has significantly reduced the toxicity caused by handling of fumigants, herbicides, insecticides, and pesticides.
13) It is used to reduce the hygroscopic properties of many core materials.
14) It is also used to prepare intrauterine contraceptive devices.
15) It is used in the fabrication of multi-layered tablet preparations for controlled release of drug present in medial layers of tableted particles.

3.1.9. Examples of Some Microencapsulated Drugs

Table 3.2 enlists the **examples** of some microencapsulated drugs:

Table 3.2: Examples of Some Microencapsulated Drugs

Active Moieties	Characteristics	Property Purposes of Encapsulation	Final Product Forms
Aspirin	Slightly water-soluble	Taste masking, sustained release, and reduced gastric irritation.	Tablet or capsule
Paracetamol	Slightly water-soluble	Taste masking	Tablet
Islet of Langerhans	Viable cells	Sustained normalisation of diabetic condition.	Injection
Isosorbide dinitrate	Water-soluble	Sustained release	Capsule
Progesterone	Slightly water-soluble	Sustained release	Varied
Menthol	Volatile solution	Reduced volatility and sustained release.	Lotion
Potassium chloride	Highly water-soluble	Reduced gastric irritation.	Capsule
Urease	Water-soluble enzyme	Permselectivity of enzyme, substrate and reaction.	Dispersion
Vitamin A Palmitate	Non-volatile liquid	Stabilisation to oxidation	Dry powder
Nifedipine	Practically water-insoluble	Prevent photoinstability	Dry powder

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Urease	Water-soluble enzyme	Permselectivity of enzyme, substrate and reaction.	Dispersion
Vitamin A Palmitate	Non-volatile liquid	Stabilisation to oxidation	Dry powder
Nifedipine	Practically water-insoluble	Prevent photoinstability	Dry powder

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CHAPTER 4

Mucosal Drug Delivery System

4.1. MUCOSAL DRUG DELIVERY SYSTEM

4.1.1. Introduction

In order to produce a systemic pharmacological effect, a drug can be administered through different routes. A drug is most commonly administered through oral route in which when the drug is swallowed it reaches the systemic circulation through small intestine membrane. Thus, drug administration via oral route is the most significant for producing systemic effect. The parenteral route is not routinely used for self-administration of medication. It may be possible that 90% of all drugs used to produce systemic effects are administered orally.

It is known since centuries that drug solutes administered through buccal and sublingual route get rapidly absorbed into the reticulated vein (lying below the oral mucosa), transported through the facial veins, internal jugular vein and brachiocephalic vein, and ultimately reaches the systemic circulation. Thus, the buccal and sublingual administration routes can be used for bypassing the hepatic first-pass drug elimination. The buccal region in the oral mucosal cavity is the most significant administration route for delivering drugs to the systemic circulation. The oral mucosa has a rich blood supply, is relatively permeable, and the lack of Langerhans cells makes it tolerant to potential allergens.

Ideal Properties/Characteristics of Mucosal Drug Delivery System

1) It should adhere to the attachment site for a few hours.
2) It should release the drug in a controlled manner.
3) It should release the drug towards the mucosa in a unidirectional way.
4) It should facilitate the rate and extent of drug absorption.
5) It should not cause any irritation or inconvenience to the patient.
6) It should not interfere with normal functions, such as talking drinking, etc.

4.1.2. Advantages

Drug administration through mucosal drug delivery has the following advantages:

1) Drugs are administered easily and elimination of therapy in emergency can be facilitated.
2) Drugs are released for a prolonged time period.
3) Drugs can be administered to unconscious and traumatised patients.
4) The bioavailability of drugs increases, since first pass metabolism is bypassed.
5) Drugs unstable in acidic environment of stomach can be administered.
6) Drugs get absorbed by passive diffusion.
7) Drugs administered are in close contact with the absorbing membrane, thus their absorption rate is maximum.
8) Drugs show rapid onset of action.

4.1.3. Disadvantages

Drug administration through mucosal drug delivery has the following disadvantages:

1) Drugs unstable at buccal pH cannot be administered.
2) Drugs having a bitter or unpleasant taste, obnoxious odour, or those which irritate the mucosa cannot be administered.
3) Drugs required in small doses can only be administered.
4) Drugs absorbed by passive diffusion can only be administered.
5) Eating and drinking may become restricted.

4.1.4. Principles and Concepts of Bioadhesion/Mucoadhesion

The concept of mucosal adhesives/mucoadhesives was introduced in controlled drug delivery area in the early 1980s. It is the ability of synthetic or biological materials to adhere to a biological tissue for a prolonged time period. For drug delivery purposes, the term **bioadhesion** refers to the attachment of a drug carrier to a specific biological system. The term **mucoadhesion** refers to the adherence of drug to a mucus coat. Mucoadhesive drug delivery provides a close prolonged contact between the drugs and absorbing tissues, i.e., ocular, nasal, buccal, vaginal, GIT, and rectal.

4.1.4.1. Principles of Bioadhesion

In conventional chemistry, it is believed that for adhesion the molecules should bind across the interface through the following bonds:

1) **Ionic Bonds:** These strong bonds are formed when two oppositely charged ions attract each other through electrostatic interactions (**e.g.,** in a salt crystal).
2) **Covalent Bonds:** These strong bonds are formed when electron pairs are shared between the bonded atoms to fill the orbitals in both.
3) **Hydrogen Bonds:** These bonds are generally weaker than ionic or covalent bonds. Hydrogen atom is slightly positively charged, thus is attracted to and covalently binds to electronegative atoms (such as oxygen or nitrogen).
4) **Van der Waals Bonds:** These are some of the weaker forms of interaction. They arise from dipole-dipole and dipole-induced dipole attractions in polar molecules, and dispersion forces with non-polar substances.
5) **Hydrophobic Bonds (Hydrophobic Effect):** These are also some of the weakest interactions. Indirect bonds (such groups only attract to each other) occur when non-polar groups are present in an aqueous solution. Water molecules adjacent to non-polar groups form hydrogen bonded structures that lower the system entropy. Thus, the tendency of non-polar groups to associate with each other increases to minimise this effect.

4.1.4.2. Theories of Bioadhesion

The process of bioadhesive can be complex and involves more than one of the following theories:

1) **Wetting Theory:** This theory is applied to liquid systems and takes into account surface and interfacial energies. It involves the ability of a liquid to spontaneously spread on a surface as a pre-requisite for adhesion development.

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Spreading coefficient (S_{AB}) can be calculated from the surface energies of the solid and liquids using the equation: .....(1)

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$$

Where, γ_A = Surface tension (energy) of the liquid A.

γ_B = Surface energy of the solid B.

γ_{AB} = Interfacial energy between the solid and liquid.

The value of S_{AB} should be positive for the liquid to spread spontaneously over the solid. **Work of adhesion** (W_A) is the energy required to separate the two phases, and is given by the equation: .....(2)

$$W_A = \gamma_A + \gamma_B - \gamma_{AB}$$

Greater the individual surface energies of the solid and liquid relative to the interfacial energy, greater is the work of adhesion.

2) **Electronic Theory:** As per this theory, electron transfer occurs across contacting adhering surfaces due to differences in their electronic structure. This results in the formation of an electrical double layer, which is adhered to the interface due to attractive forces.

3) **Adsorption Theory:** This theory defines the attachment of adhesives due to hydrogen bonds and Van der Waal forces. These forces mainly contribute to the adhesive interaction. As per the chemisorption theory (a sub-section of adsorption theory), an interaction across the interface occurs due to strong covalent bonds.

4) **Diffusion Theory:** This theory defines the inter-diffusion of polymer chains across an adhesive interface driven by concentration gradients. This is affected by the available molecular chain lengths, the compatibility of two polymers and their mobilities. The diffusion coefficient and the contact time influence the depth of inter-penetration. If the penetration depth is sufficient, a semi-permanent adhesive bond is formed.

5) **Mechanical Theory:** As per this theory, adhesion arises from an interlocking of a liquid adhesive (on setting) into irregularities on a rough surface. Rough surfaces also provide an increased surface area for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure which are important in the adhesion process.

6) **Fracture Theory:** This theory relates the adhesive strength to the force required for detaching the two involved surfaces after adhesion. This theory assumes that the failure of adhesive bond occurs at the interface. However failure occurs at the weakest component, which is a cohesive failure with one of the adhering surfaces.

4.1.4.3. Mechanism of Mucoadhesion

The mucoadhesion process due to relative complexity cannot be described by a one of these theories. The mechanism of mucoadhesion involves a whole ran 'scenarios' for *in-vivo* mucoadhesive bond formation (**figure 4.1**) including:

1) Dry or partially hydrated dosage forms contacting surfaces with substan mucus layers (particulates administered in the nasal cavity).

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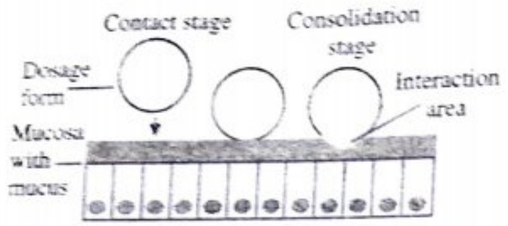


Figure 4.2: Two Stages in Mucoadhesion

The consolidation stage can be principally explained by two theories:

i) **Diffusion Theory:** According to this theory, the mucoadhesive molecules and the mucus glycoproteins interact by inter-penetration of their chains and build-up of secondary bonds. This happens as the mucoadhesive device exhibits features that favour chemical and mechanical interactions.

ii) **Dehydration Theory:** According to this theory, when the materials that can readily form into gels in an aqueous environment, are placed in contact with the mucus, they undergo dehydration due to the difference of osmotic pressure.

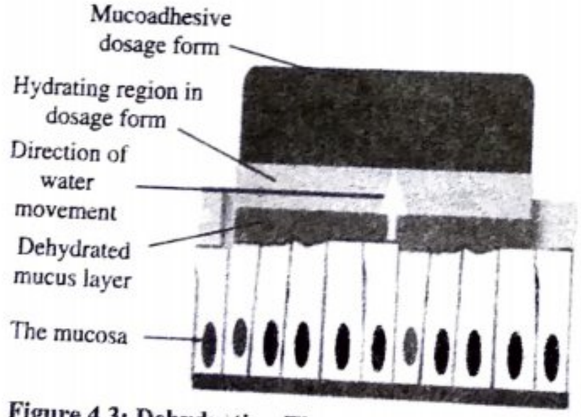


Figure 4.3: Dehydration Theory of Mucoadhesion

4.1.5. Factors Affecting Mucosal Adhesion

The given factors affect mucoadhesion as follows:

1) **Polymer-Related Factors:** These include the following:

i) **Molecular Weight:** Inter-penetration of polymer molecule is favourable for low molecular weight molecules, while entanglements are favoured for high molecular weight polymers. Optimum molecular weight for maximum bioadhesion depends on the polymer types. Their nature dictates the degree of swelling in water, which in turn determines inter-penetration of polymer molecules in the mucus. Bioadhesive forces increase with the molecular weight (up to 100,000 and not much effect is produced beyond this level). For chain inter-penetration, the polymer should be of adequate length, and its size and configuration are also important factors.

ii) **Concentration of Active Polymer:** An optimum concentration of polymer is required for achieving the best bioadhesion. In highly concentrated system, the adhesive strength decreases; while in concentrated solutions, the coiled molecules become solvent poor and

not many chains are available for inter-penetration. These results are, however, for liquid bioadhesive forms. For solid dosage forms (such as tablets), higher the polymer concentration, stronger is the bioadhesion.

iii) **Flexibility of Polymer Chains:** This factor is important for inter-penetration. The water-soluble polymers become cross-linked, and this reduces the mobility of individual polymer chain. With the increase in cross-linking density, the effective chain length that can penetrate the mucus layer decreases more, and mucoadhesive strength is thus reduced.

iv) **Spatial Conformation:** This factor, along with molecular weight or chain length, is also significant. Despite a high molecular weight of 1,95,00,000, the adhesive strength of dextran is similar to that of PEG, having a molecular weight of 200,000. The helical conformation of dextran, unlike PEG polymers having a linear conformation, shields numerous adhesively active groups that are responsible for adhesion.

2) **Environment-Related Factors:** These include the following:

i) **pH:** It has a significant effect on mucoadhesion. pH influences the charge present on the surface of mucus as well as polymers. Mucus carries a different charge density depending on pH because of differences in dissociation of functional groups on the carbohydrate moiety and amino acids.

ii) **Applied Strength:** A solid bioadhesive system can be maintained by applying a defined strength. The adhesion strength increases optimally with the applied strength or with the duration of its application, irrespective of the polymer.

The pressure initially applied to the mucoadhesive tissue contact site affects the inter-penetration depth. If high pressure is applied for an extended time period, the polymers become mucoadhesive even though they are not attractively interacted with mucin.

iii) **Initial Contact Time:** It is the time between mucoadhesive, and the mucus layer determines the extent of swelling and the inter-penetration of polymer chains. The initial contact time, along with the initial pressure, can affect the system performance. Mucoadhesive strength increases with the increase in initial contact time. Initial contact time is critical in case of mucoadhesive that need to be polymerised at the application site.

iv) **Swelling:** This factor is related to the polymer, and its environment. Since the polymer chains are disentangled and free of interactions, their inter-penetration is easier. Swelling depends on polymer concentration and presence of water.

When swelling is more, bioadhesion decreases. This phenomenon should not occur too early to result in a sufficient action of bioadhesive system. Its appearance allows easy detachment of bioadhesive system after the discharge of active ingredient.

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3) **Physiological Variables:** These include the following:
   i) **Mucin Turnover:** The natural turnover of mucin molecule from the mucus layer is important for two reasons:
      a) Mucin turnover limits the residence time of the mucoadhesives on the mucus layer, thus detaching the mucoadhesives from the surface.
      b) Mucin turnover results in extensive amounts of soluble molecules that interact with mucoadhesives before they interact with the mucus layer. This type of surface fouling does not favour mucoadhesion to the tissue surface.
   ii) **Diseased State:** Physicochemical properties of mucus alter during diseased conditions, such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract, and inflammatory conditions of eye. If mucoadhesives are to be used in the diseased states, its mucoadhesive property should be evaluated under the same condition.

4.1.6. Transmucosal Permeability

Two routes are involved in drug permeation across epithelial membranes, i.e., the **transcellular route** and the **paracellular route**. In the studies of mechanisms of trans-membrane permeation, the epithelial membrane structure is simplified to consist of a lipoidal pathway and an aqueous pore pathway (**figure 4.4**).

Skin and gastrointestinal mucosa are considered lipoidal barriers, in which the drug absorption is determined by the magnitude of its partition coefficient and molecular size, till the diffusion through aqueous diffusion layer (P_a) becomes a rate-limiting step in trans-membrane permeation. Several researchers have observed lack of a linear correlation between penetrant lipophilicity (indicated by the partition coefficient magnitude) and permeability. This implies that these membranes are not simple lipoidal barriers.

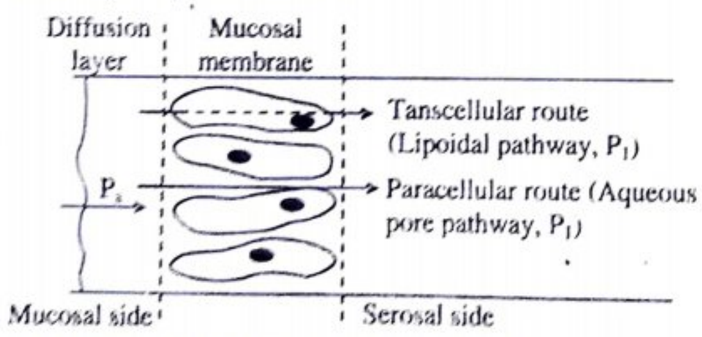


Figure 4.4: Physical Model for Trans-Membrane Permeation across a Mucosal Membrane consisting of Lipoidal and Aqueous Pore Pathways in Parallel, which is in series with an aqueous diffusion layer on the mucosal surface. P's are the permeabilities across the aqueous diffusion layer (P_a), the lipoidal pathway (P_l), and the aqueous pore pathway (P_l)

For nasal mucosal membrane an experiment was performed to prove the existence of a lipoidal and an aqueous pore pathway. The rate and extent of nasal absorption of β-adrenoreceptor-blocking drugs in humans were related to the lipophilicity of drugs (the most lipophilic propranolol achieved the highest absorption). The rate constant for *in situ* absorption of progesterone, testosterone,

and hydrocortisone in rats and the lipophilicity of steroids were found to be proportional. However, several studies indicate that a permeant's absorption is affected by its lipophilicity, still it does not alone determines the rate and extent of nasal absorption.

It has been suggested that the nasal mucosa serves as a modified lipoidal barrier for lipophilic permeants. The pH-partition theory (absorption depends on the concentration of undissociated species of a permeant molecule) is not applicable for many hydrophilic drugs. It has also been reported that the logarithm of nasal absorption and the logarithm of drug molecular weights are linearly correlated for many water-soluble compounds. This indicates the presence of aqueous pore channels in the nasal mucosa for the absorption of hydrophilic drugs.

Transmucosal permeation of polar molecules (such as peptide-based pharmaceuticals) occurs through paracellular route; however, the following **barriers** exist during the **paracellular permeation**:

1) The barrier function of **basal lamina** depends on the molecular weight of the permeant molecule, its reactivity with the barrier, and the structural and functional factors of the barrier.
2) **Membrane-coating granules** extrude into the intercellular region of keratinised and non-keratinised oral epithelium and prevent the transmucosal penetration of water-soluble peptide or protein, such as horseradish peroxidase.
3) The barrier function of **keratin layer** in oral mucosa is not as well-defined as in the skin. The permeation rate of water was shown to be greater in non-keratinised than in keratinised oral epithelium, but the permeation of horseradish peroxidase was found to be similar in both mucosae.
4) The permeability coefficients of 19 solutes across the rabbit lingual frenulum and attached gingiva were determined under *in vitro* conditions. They were found correlated, suggesting that the epithelia from different regions of the oral mucosa are similar in mechanisms and rates of trans-mucosal permeation.

In comparison to the complexity of nasal and oral mucosae, drug absorption through rectal mucosa follows the pH-partition theory. It has been established that ionic and lipid-insoluble drugs are poorly absorbed and the lipid-soluble drugs are rapidly absorbed on rectal administration. It was reported that the rectal mucosa of rats have a poorer distribution of aqueous pore channels than other regions of the GIT, including the jejunum. The correlation between rectal absorption of drugs and their partition coefficients implies that rectal mucosa can be considered as a simple lipoidal barrier.

The vaginal mucosal membrane, similar to the nasal mucosa, comprises of a lipoidal pathway and an aqueous pore pathway. In the vaginal mucosa of rabbits, the permeability coefficient of aliphatic alcohols increases with the increase in their lipophilicity; thus, indicating the importance of lipoidal pathway in vaginal permeation. The aqueous diffusion layer on the rabbits' vaginal mucosal surface was estimated to be approximately 310μm thick.

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Hwang *et al.* studied the absorption of a homologous series of straight-chain alkanoic acids in the vaginal mucosa of rabbits. Results indicated the importance of aqueous pore pathway for the transmucosal permeation of alkanoic acids with a short alkyl chain. Permeability coefficient of acids was found to be increasing with the alkyl chain length, but was not in linear correlation with their partition coefficient. This indicates that just like the nasal membrane, the vaginal membrane also has semi-polar regions that are neither purely lipophilic nor purely hydrophilic.

A few studies in rhesus monkeys indicate the presence of intercellular lipids that restrict vaginal absorption of water-soluble compounds having large molecular weight. In estrous (cycling) animals, absorption of hydrophilic compounds increases during the proestrus and diestrus stages of the estrous cycle due to the loosening of epithelial cell junctions.

4.1.7. Formulation Considerations of Buccal Delivery Systems

Following are the basic formulation requirements of buccal drug delivery system:

1) **Drug:** Before mucoadhesive drug delivery systems are formulated, it should be decided that whether the intended action is for rapid release, prolonged release, local effect, and/or systemic effect. A suitable drug should be selected based on its pharmacokinetic properties for designing buccoadhesive drug delivery systems.

   The drug should have the following **characteristics**:
   i) The conventional single dose of the drug should be small.
   ii) The drugs with biological half-life of 2-8 hours are good candidates for controlled drug delivery.
   iii) The drug t_{max} shows wider-fluctuations or higher values on oral administration.
   iv) The drug may undergo first pass effect or pre-systemic drug elimination on oral administration.
   v) The drug undergoes passive absorption on oral administration.

2) **Bioadhesive Polymers:** Selection and characterisation of appropriate bioadhesive polymers is the first step in the development of buccoadhesive dosage forms. These polymers are important in buccoadhesive system of drug delivery. Polymers are also used in matrix devices, in which the drug is embedded in the polymer matrix, which control the duration of drug release. Bioadhesive polymers are from the most diverse class and substantially benefit the patient health care and treatment. The drug is released in the mucous membrane via rate controlling layer or core layer. Bioadhesive polymers adhered to the mucin/epithelial surface are effective and significantly improve the oral drug delivery.

   The **ideal characteristics** for a **polymer** and its degradation products for buccoadhesive drug delivery systems are:
   i) It should be inert and compatible with the environment.
   ii) It should be non-toxic and absorbable from the mucus layer.
   iii) It should allow easy incorporation of drug in the formulation.

   iv) It should quickly adhere to moist tissue surface and should possess site specificity.
   v) It should not decompose on storage or during the shelf-life of the dosage form.
   vi) It should be economical and easily available in the market.

Examples of some commonly used mucoadhesive polymers in pharmaceutical applications are enlisted in **table 4.1**:

Table 4.1: Mucoadhesive Polymers used in the Oral Cavity

Criteria	Categories	Examples
Source	Semi-natural/Natural	Agarose, chitosan, gelatin, hyaluronic acid, and various gums (guar gum, xanthan, gellan, carrageenan, pectin, and sodium alginate).
	Synthetic	1) **Cellulose Derivatives:** CMC, thiolated CMC, NaCMC, HEC, HPC, HPMC, and MC.
		2) **Poly (Acrylic Acid)-Based Polymers:** CP, PC, PAA, polyacrylates, poly (methyl vinyl ether-co-methacrylic acid), poly (2-hydroxy ethyl methacrylate), poly (acrylic acid co-ethyl hexyl acrylate), poly (methacrylate), poly (isobutyicyanoacrylats), copolymer of acrylic acid, and PEG.
		3) **Other:** Polyoxyethylene, PVA, PVP, and thiolated polymers.
Aqueous Solubility	Water-soluble	CP, HEC, HPC, HPMC (cold water), PAA, NaCMC, and sodium alginate.
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, and PC.
Charge	Cationic	Aminodextran, Chitosan, (DEAE)-dextran, and TMC.
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, NaCMC, and xanthan gum.
	Non-ionic	Hydroxy ethyl starch, HPC, poly (ethylene oxide), and PVA.
Potential	Covalent	PVP and scleroglucan.
	Hydrogen bond	Cyanoacrylate.
Bioadhesive Forces	Electrostatic Interaction	Acrylates [hydroxylated methacrylate, poly (methacrylic acid)], CP, PC, PVA, and chitosan.

3) **Backing Membrane:** It plays an important role in the attachment of bioadhesive devices to the mucus membrane. Inert materials should be used as a backing membrane. These materials should also be impermeable to the drug and penetration enhancer. The resultant impermeable membrane on buccal bioadhesive patches prevents drug loss and improves patient compliance. Carbopol, magnesium stearate, HPMC, HPC, CMC, polycarbophil, etc. are the **examples** of some commonly used backing membrane material.

4) **Plasticisers:** These are used for achieving softness and flexibility of thin films of polymers. They also act as permeation enhancers. Glycerol, PEG200, PEG400, castor oil, etc. are the **examples** of some commonly used plasticisers. A suitable plasticiser is selected depending on the ability of

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plasticiser material to solvate the polymer and alters the polymer-polymer interactions. If the plasticiser is used in correct proportion to the polymer, it relieves molecular rigidity and imparts flexibility.

5) **Permeation Enhancers:** These substances facilitate permeation through buccal mucosa. A suitable permeation enhancer is selected based on the physicochemical properties of the drug, administration site, nature of the vehicle and other excipients. The **mode of action** of penetration enhancers is as follows:
   i) They alter the mucus rheology by reducing the viscosity of the mucus and saliva overcomes this barrier.
   ii) They increase the fluidity of lipid bilayer membrane, disturb the intracellular lipid packing by interacting with either lipid or protein components.
   iii) They act on the components at tight junctions by inhibiting various peptidases and proteases present in the buccal mucosa, thus overcoming the enzymatic barrier. They also change membrane fluidity, which in turn alters the enzymatic activity.
   iv) They increase the thermodynamic activity of drugs by increasing their solubility, thereby altering their partition coefficient.

Table 4.2 enlists the common **examples** of permeation enhancers, along with their mechanisms:

Table 4.2: Examples of Permeation Enhancers with their Mechanism

Categories	Examples	Mechanism(s)
Surfactants and Bile Salts	Surfactants and bile salts, sodium dodecyl sulphate, sodium lauryl sulphate, and polysorbate 80.	Act on the components at tight junctions; increase the fluidity of lipid bilayer membrane.
Fatty Acids	Oleic acid, cod liver oil, capric acid, and lauric acid.	Increase the fluidity of lipid bilayer membrane.
Polymers and their Derivatives	Chitosan, trimethyl chitosan, and chitosan–4–thiobutylamide.	Increase the fluidity of lipid bilayer membrane; Increase the retention of drug at mucosal surface.
Others	Ehanol, azone, octisalate, padimate, and menthol.	Act on the components at tight junctions; Increase the fluidity of lipid bilayer membrane.

6) **Preservatives:** Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA, and benzoyl alcohol are the **examples** of some commonly used preservatives.

4.1.8. Manufacturing Methods of Buccal Patches

The manufacturing processes for mucoadhesive buccal patches/films are discussed below:

1) **Solvent Casting:** In this method, the drug and the patch excipients are dispersed in an organic solvent and coated on a sheet of release liner. After the solvent evaporates, a thin layer of protective backing material is laminated on the sheet of coated release liner. This forms a laminate that is die-cut to form patches of desired size and geometry.

2) **Direct Milling:** In this method, patches are manufactured without using solvents. The drug and excipients are mechanically mixed by direct milling or by kneading in the absence of any liquid. After mixing, the obtained material is rolled on a release liner to obtain the desired thickness. Then the backing material is laminated as in the solvent casting method. There are minor or no differences at all in the patch performance between the patches fabricated by solvent casting and direct milling, thus the solvent-free process is preferred as residual solvents are not formed and solvent-related health issues do not occur.

3) **Hot Melt Extrusion of Films:** In this method, a blend of pharmaceutical ingredients is molten and forced through an orifice to obtain a homogeneous material in the form of granules, tablets, or films. The method of hot melt extrusion has been used for manufacturing controlled release matrix tablets, pellets, granules, and oral disintegrating films.

4.1.9. Evaluation

The mucoadhesive buccal patches/films can be evaluated as follows:

1) **Surface pH:** Buccal patches are kept on an agar plate surface for 2 hours and allowed to become swollen. The surface pH is measured by placing a pH paper on the swollen patch surface.

2) **Thickness Measurements:** Thickness of each patch is measured at five different locations (centre and four corners) using an electronic digital micrometer.

3) **Swelling Study:** Each patch is weighed individually (designated as W1), placed in separate 2% agar gel plates, incubated at 37±1°C, and examined for any physical changes. At regular intervals of 1 hour until 3 hours, the patches are removed from the gel plates and excess surface water is removed using a filter paper. The swollen patches are reweighed (designated as W2) and the Swelling Index (SI) is calculated as follows:

$$SI = \frac{(W2 - W1)}{W1} \times 100$$

4) **Folding Endurance:** This is determined by folding the patches at the same point without breaking.

5) **Thermal Analysis Study:** This study is performed using Differential Scanning Calorimeter (DSC).

6) **Morphological Characterisation:** Morphological characters are studied using Scanning Electron Microscope (SEM).

7) **Water Absorption Capacity Test:** Circular patches (having a surface area of 2.3cm^2) are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38gm Na_2HPO_4, 0.19gm KH_2PO_4, and 8gm NaCl per litre of distilled water adjusted to pH 6.7 with phosphoric acid), and incubated at 37±0.5°C. At time intervals of 0.25, 0.5, 1, 2, 3, and 4 hours, samples are weighed (wet weight) and allowed to dry for a week in desiccators over anhydrous calcium chloride at room temperature. After a week the final constant weights are recorded, and water uptake (%) is calculated as follows:

$$\text{Water uptake } (\%) = \frac{(W_w - W_i)}{W_f} \times 100$$

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Where,
W_w = Wet weight and
W_f = Final weight.

8) ***Ex-vivo* Bioadhesion Test:** Fresh sheep mouth is separated and washed with phosphate buffer (maintained at pH 6.8). A piece of gingival mucosa is tied in the open mouth of a glass vial containing phosphate buffer. This vial is tightly fitted inside a glass beaker, containing phosphate buffer (maintained at pH 6.8 and temperature 37±1°C), such that it touches the mucosal surface.

Using cyanoacrylate adhesive, the patch is stuck to the lower side of a rubber stopper. The two pans of the balance are balanced with a 5gm weight. This weight is removed from the left pan, and the patch over the mucosa is attached to the pan. The balance is kept in this position for 5 minutes of contact time. Water is slowly added to the right pan at the rate of 100 drops/minute until the patch detaches from the mucosal surface. The weight (in grams) required to detach the patch from the mucosal surface indicates the mucoadhesive strength.

9) ***In-vitro* Drug Release:** The USP XXIII-B rotating paddle apparatus is used for studying drug release from the bilayered and multilayered patches. The dissolution medium comprises of phosphate buffer (maintained at pH 6.8). The release is performed at a temperature of 37±0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material.

The disk is allocated to the bottom of the dissolution vessel. Samples of 5ml are withdrawn at pre-determined time intervals and replaced with the same amount of fresh medium. The samples are filtered through Whatman filter paper and analysed for drug content after appropriate dilution.

The *in-vitro* buccal permeation through the buccal mucosa (of sheep and rabbit) is performed using Keshary-Chien/Franz type glass diffusion cell at 37±0.2°C. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together.

10) **Permeation Study of Buccal Patch:** The receptor compartment is filled with phosphate buffer (maintained at pH 6.8), and the hydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at pre-determined time intervals and analysed for drug content.

11) ***Ex-vivo* Mucoadhesion Time:** This time is determined by applying the buccal patch on a freshly cut buccal mucosa of sheep and rabbit. The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with a drop of phosphate buffer (maintained at pH 6.8) and pasted to the buccal mucosa by forcing lightly with fingertip for 30 seconds. Then the glass slide is put in the beaker filled with 200ml of phosphate buffer (pH 6.8), maintained at 37±1°C temperature. After 2 minutes, stirring is

done at 50 rpm rate to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hours. The time at which the colour and shape of the patch changes, the patch collapses, and the drug content at that time are noted.

12) **Measurement of Mechanical Properties:** Tensile strength and elongation at break are the mechanical properties of the patches, which are evaluated with a tensile tester. Patch strip with dimensions of 60 × 10mm and having no visual defects are cut and positioned between two clamps separated by 3cm distance.

Clamps are so designed that they secure the patch and do not crush it during the test. The lower clamp is held stationary and the strips are pulled apart by the upper clamp moving at a rate of 2mm/sec, until the strip breaks. The force and elongation of the patch at the point when it breaks is recorded.

The tensile strength and elongation at break values are calculated as follows:

$$T = \frac{m \times g}{b \times t} kg/mm^2$$

Where, m = Mass (gm)
g = Acceleration due to gravity (980cm/sec^2).
b = Breadth of the specimen (cm).
t = Thickness of specimen (cm).

Tensile strength (T) measures the strength of patches as diametric tension or tearing force. It is measured in gm or N/m^2. It represents the strength of patches to various stresses and can be measured using simple calibrated vertical spring balance.

13) **Stability Study in Human Saliva:** The stability study of optimised bilayered and multilayered patches is performed in saliva collected from humans of 18-50 years of age. Buccal patches are placed in separate petri dishes, each containing 5ml of human saliva. Then the dishes are kept for 6 hours in a temperature controlled oven at 37±0.2°C. At regular time intervals of 0, 1, 2, 3, and 6 hours, the dose formulations with better bioavailability are needed.

Improved methods of drug release through transmucosal and transdermal methods are important, as these routes completely eliminate the pain factor related to the parenteral routes of drug administration. Buccal adhesive systems are beneficial in terms of accessibility, administration, withdrawal, retainability, low enzymatic activity, economy, and high patient compliance.

Adhesion of buccal adhesive drug delivery devices to mucosal membranes increases drug concentration gradient at the absorption site, and thus improves the bioavailability of systemically delivered drugs. Buccal adhesive dosage forms also target local disorders at the mucosal surface (**e.g.,** mouth ulcers) to reduce the dose required as well as the side effects associated with systemic drug administration.

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CHAPTER 5

Implantable Drug Delivery System

5.1. IMPLANTABLE DRUG DELIVERY SYSTEM (IDDS)

5.1.1. Introduction

Lafarge introduced the implantable system concept for sustained release drug administration in **1861**. It was first introduced to produce steroid hormones-containing solid implants for long-term delivery.

Implantable drug delivery systems are designed to be placed under the skin and release drugs into the blood circulation without repetitive insertion of needles. Therefore, IDDS is defined as "**a sterile drug delivery device for subcutaneous implantation having the ability to deliver drugs at a controlled rate over a prolonged time period, comprising a rod-shaped polymeric inner matrix with an elongated body and two ends**".

Ideal Properties of an Implantable Drug Delivery System

1) It should be environmentally stable.
2) It should be biocompatible.
3) It should be easy to manufacture and sterilise.
4) It should enable rate controlled drug release.
5) It should improve patient compliance by reducing the drug dosing frequency throughout the treatment period.
6) It should be relatively inexpensive.
7) It should have a good mechanical strength.
8) It should be free from surgical procedure.

5.1.2. Advantages

Implantable drug delivery system has the following advantages:

1) **Convenience:** With implantation therapy, the patients can be provided with medication outside the hospital with nominal medical surveillance.
2) **Compliance:** Reduction or complete abolition of patient-involved dosing increases compliance significantly.
3) **Improved Drug Delivery:** An implantable drug delivery system delivers the drug locally or in the blood circulation with negligible intervention from biological or metabolic barriers.
4) **Potential for Controlled Release:** An implantable drug delivery system delivers the drug by zero-order controlled release kinetics, thereby reducing the dosage frequency and increasing patient compliance.

5) **Potential for Intermittent Release:** Extremely programmable pumps enable intermittent release of drugs in response to factors, like cardiac rhythm, metabolic needs, etc.
6) **Flexibility:** Various types of flexibilities, like materials, method of manufactures, etc., are available in implants. They permit controlled delivery of hydrophilic as well as lipophilic drugs.

5.1.3. Disadvantages

Implantable drug delivery system has the following disadvantages:

1) **Invasive:** For inserting implants, the patients have to undergo a major or a minor surgical process.
2) **Termination:** Non-biodegradable polymeric implants need to be surgically removed from the body at the end of the treatment.
3) **Danger of Device Failure:** If the device fails to operate properly during the treatment due to any reason, the device should be surgically removed from the patient's body.
4) **Limited to Potent Drug:** Only potent drugs (effective even in very small amount) can be used since the device is of very small size to reduce patient's discomfort.
5) **Adverse Reaction:** Since a high concentration of drug is delivered to the implantation site via device, a chance of adverse reaction due to this local high concentration always exists.

5.1.4. Mechanism of Drug Release from Implantable Therapeutic System

A large number of mechanisms are being designed since many years to obtain controlled release delivery of drugs for a prolonged time period using implantable drugs. Currently, these approaches are designed as follows:

1) **Polymer Membrane Permeation Controlled Drug Delivery System**
   i) In this controlled drug delivery device, drug reservoir is encapsulated within a capsule-shaped or spherical compartment.
   ii) This system is covered with a rate controlling polymeric membrane.
   iii) The drug reservoir can be either solid particles or solid particles dispersed in a liquid or solid dispersing medium.
   iv) The drug reservoir system is encapsulated within the polymeric membrane by encapsulation, microencapsulation, moulding, extrusion, etc.
   v) **For example,** Norplant sub-dermal implant.
2) **Polymer Matrix Diffusion Controlled Drug Delivery System**
   i) In this controlled drug delivery device, the reservoir is formed by dispersing the solid particles in a lipophilic or hydrophilic polymer matrix.
   ii) This dispersion can be obtained by dispersing the solid drug dosage form in the liquid or semi-solid polymer matrix at room temperature and then by cross-linking of polymer chains.
   iii) The drug-polymer dispersions are then moulded or extruded to form drug delivery devices of various shapes.

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iv) It can also be prepared by dissolving the drug solid or the polymer in an organic solvent and then by conservation or solid evaporation at an elevated temperature under vacuum to form microsphere.

v) **For example**, Compudose implant.

3) **Membrane-Matrix Hybrid Type Drug Delivery System**

i) This device is a hybrid of polymer membrane permeation and polymer matrix permeation controlled drug delivery systems.

ii) Alike the polymer membrane permeation controlled drug delivery system, this device follows the constant drug release kinetics. Therefore, it reduces the chances of dose dumping from the reservoir compartment.

iii) Alike the matrix diffusion system, the drug reservoir of this device is prepared by homogeneous dispersion of solid drug particles in a polymer matrix.

iv) However, the total reservoir in this device is encapsulated in a rate controlling polymeric membrane.

v) Thus, membrane-matrix hybrid type drug delivery system is a sandwich type implantable device.

vi) **For example**, Norplant II sub-dermal implant.

4) **Microreservoir Partition Controlled Drug Delivery System**

i) In this controlled release drug delivery device, the drug reservoir is a suspension of drug crystals in an aqueous solution of water-miscible polymer and it also forms a homogeneous dispersion.

ii) Microdispersion is obtained by high energy dispersion technique.

iii) By extrusion and molding methods, these drug delivery devices can be obtained of different sizes and shapes.

iv) As per the physicochemical properties of the drug, this device can be coated with a layer of biocompatible polymer to modify the mechanism and rate of drug release.

v) **For example**, Syncromate implant.

5) **Osmotic Pressure-Activated Drug Delivery System**

i) In this controlled release drug delivery device, osmotic pressure is the main source of energy to activate and modulate drug delivery at the implantation site.

ii) In this system, the drug reservoir is either a solution or a semi-solid state within a semi-permeable compartment with controlled water permeability.

iii) **For example**, Alzet osmotic pump.

6) **Vapour Pressure-Activated Drug Delivery System**

i) In this controlled release drug delivery device, vapour pressure is the main source of energy to activate controlled drug delivery.

ii) In this system, the drug reservoir is a solution contained in an infusate chamber.

iii) Infusate chamber is separated from the vapour pressure chamber via freely movable bellows.

iv) Vapour pressure chamber contains a vaporisable fluid, **e.g.,** fluorocarbon, which vaporises at body temperature and creates vapour pressure that forcefully moves the bellows in upward direction.

7) **Magnetically-Activated Drug Delivery System**

i) In this controlled release drug delivery device, electromagnetic energy is the main source of energy to activate controlled drug delivery and to control the rate of drug delivery.

ii) This drug delivery device is incorporated with a magnetic wave triggering mechanism.

iii) A sub-dermally implantable, magnetically-modulated hemispherical drug delivery device was fabricated by positioning a tiny donut-shaped magnet at the center of a polymer matrix.

iv) This matrix contains a homogeneous dispersion of a drug with low polymer permeability at a rather high drug-polymer ratio to form hemispherical pellet.

v) The external surface of hemispherical pellet is covered with a pure polymer, **e.g.,** ethylene vinyl acetate copolymer.

vi) By applying an external magnetic field, the drugs are activated by the electromagnetic energy to release from the pellet at a much higher rate of delivery.

vii) **For example**, Bovin Serum Albumin (BSA) is given via this device.

5.1.5. Concept of Implants

An implant is a medical device that is used as a replacement of a missing biological structure to support a damaged biological structure or enhance the functioning of an existing biological structure. Medical implants are man-made devices in contrast to a transplant (a transplanted biomedical tissue). The surface of implants in contact with the body is made up of a biomedical material, **e.g.,** titanium, silicone, and apatite, whichever is the most functional. Sometimes, implants contain electronics, **e.g.,** artificial pacemaker and cochlear implants. Some implants, like subcutaneous drug delivery devices in the form of implantable pills or drug-eluting stents, are bioactive.

5.1.5.1. Non-Degradable Systems

Several types of non-degradable implantable drug delivery systems are available in the market, of which the non-degradable matrix systems and reservoir systems are the most common forms (**figure 5.1**).

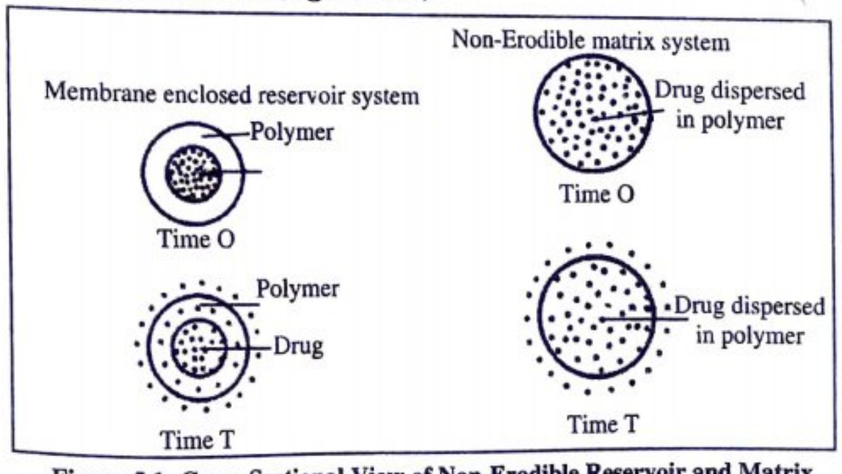


Figure 5.1: Cross-Sectional View of Non-Erodible Reservoir and Matrix Systems, Showing Diffusion of the Drug across the Polymer

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In the **polymeric matrix system**, the drug is homogeneously dispersed within the matrix material. The polymeric matrix material enables slow diffusion of the drug to provide sustained drug release from the delivery system. In the **reservoir-type system**, a compact drug core is surrounded by a permeable non-degradable membrane whose thickness and permeability properties can control the diffusion of drug into the body. The release kinetics of drug from this system suggests that if a constant equilibrium exists between the drug concentration in the reservoir and the inner surface of the enclosed membrane, the driving force for diffusional release of the agent is constant and zero-order release kinetics of the drug from the delivery system is obtained. However, this system has a few **disadvantages**:

1) Since these systems have a non-degradable outer membrane, a minor surgical process is required to remove the delivery system from the body after the release of drug.
2) Membrane rupture may also occur that leads to drug dumping, which depending on the type of drug involved in the reservoir gives rise to toxic side effects from drug plasma concentrations that exceed maximum safety levels. Thus, due to the chances of drug dumping, the reservoir system has become a less popular drug delivery method.

Matrix systems are also used as non-degradable implants, consisting of homogeneously distributed drug in a solid non-biodegradable polymer. Alike the reservoir systems, matrix systems also enable diffusion of drug particles through the non-degradable fibrous network of the polymer to obtain sustained drug release. However, the release kinetics of drug is not constant and depends on the volume fraction of the agent in the matrix. **Greater the concentration of the dissolved agent in the matrix, greater is the release from the system.**

Magnetically controlled release system is another type of non-degradable system, in which small magnetic beads are uniformly dispersed in a polymer (**figure 5.2**). When this system is exposed to a biological system, the drug undergoes normal diffusion due to a concentration gradient. On the other hand, when this system is exposed to an external oscillating magnetic field, larger quantities of drug are released quickly. This type of drug delivery system has a major **advantage** of controlling the release kinetics of drug by using external magnetic stimuli.

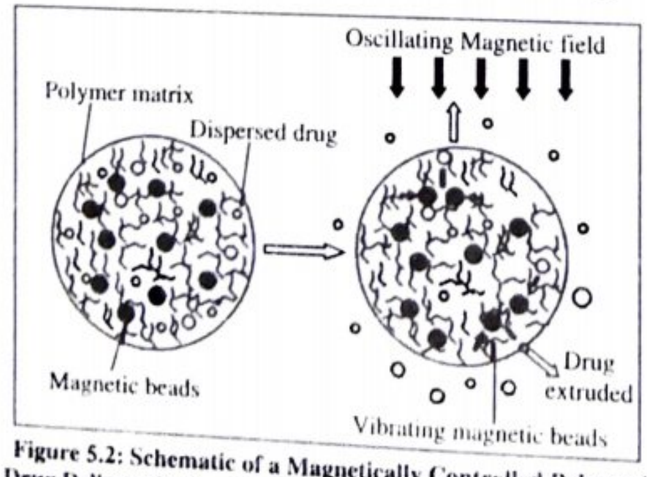


Figure 5.2: Schematic of a Magnetically Controlled Polymeric Drug Delivery System Illustrating Increased Drug Release from the System after Exposure to an Oscillating Magnetic Field

5.1.5.2. Biodegradable Systems

Biodegradable delivery systems are more popular than the non-degradable systems. The major **advantages** of biodegradable systems are that inert polymers are used for fabricating the delivery system, and these polymers ultimately get absorbed or excreted by the body. This eradicates the need for surgical removal of the implant after the end of treatment, and thus patient acceptance and compliance are enhanced.

Development of biodegradable systems is more complicated than formulating non-degradable systems. Many variables should be considered during the fabrication of new biodegradable systems. Degradation kinetics of the polymer (*in vivo*) should remain constant to maintain sustained drug release. The degradation rate of polymer in the body is also affected by many factors. Any change in body pH or temperature can also transiently increase or decrease the degradation rate of the system. The surface area of delivery system also plays an important role in its degradation. Surface area of the implantable system decreases with its erosion. Thus, the change in shape of the drug delivery system should be considered during the formulation design. A more uniform and constant release can be attained by using geometrical shapes whose surface area does not change with time when the system gets eroded. A flattened slab-type shape with no edge erosion gives a zero-order release kinetic profile.

Some manufactures have designed systems consisting of a bioerodible inert core coated with the active drug matrix to minimise the problem of change in surface area that occurs during system erosion. Another problem of bioerodible systems is that drug diffusion from the polymer matrix occurs at a rate slower than that of the bioerosion of the system. Diffusion of the drug also depends on the chemical nature of the polymeric substance used in the formulation of the drug delivery system. This problem should be overcome during the development of bioerodible systems as they are intended to be used for extended release of drug or when the drug has a narrow therapeutic index.

At present, there are two different types of biodegradable delivery systems. The **first type** is a **reservoir system**, which is similar to the non-degradable reservoir system in structure and also in drug release mechanism. These bioerodible systems consist of an exterior polymeric membrane that degrades at a slower rate than the expected rate of drug diffusion through the membrane. Therefore, the membrane remains intact and the drug is completely released. In the end, the exterior polymeric membrane degrades (*in vivo*) and gets excreted.

The **second type** of bioerodible system is **monolithic type**, in which the drug dispersed in a polymer, gets slowly eroded (*in vivo*) by biological processes at a controlled rate.

The most popular **biodegradable polymers** under investigation are polyglycolic acid, polylactic acid, polyglycolic-lactic acid, polyaspartic acid, and polycaprolactone. Ethyl vinyl acetate copolymer matrices for the delivery of macromolecular drugs (such as insulin) have also been studied.

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5.1.6. Applications

Some applications of IDDS are:

1) **Ocular Disease:** Different implantable systems, including membrane-controlled devices implantable silicone devices and implantable infusion systems, have been investigated to provide prolonged ocular drug delivery. **Ocusert**, containing pilocarpine base and alginic acid in a drug reservoir surrounded by a release-rate controlling ethylene-vinyl acetate membrane, is an **example** of membrane-controlled system.

   This system provides an initial burst followed by a near zero-order delivery of pilocarpine at 20-40µg/hr for a week. Ocusert is well-tolerated in adults, and gives a satisfactory control of intraocular pressure with negligible side effects; but, it is poorly tolerated in geriatrics where most of the therapeutic need exists.

2) **Contraception:** FDA has recently approved the marketing of **Norplant**, a sub-dermal implant for long-term delivery of levonorgestrel (contraceptive agent). This device consists of six silicone membrane capsules, each containing 36mg of levonorgestrel, which are placed sub-dermally on the inside of the upper arm or forearm in a fan-shaped pattern through a trocar from a single trocar entry point.

   Cumulatively these capsules deliver 70µg/day (*in vitro*) and 90µg/day (*in vivo*) for the first 100 days with a steady decrease to 30µg/day at about 800 days. This delivery rate continues for five years.

   Other polymer-based systems being studied for contraception include **vaginal ring** of silicon rubber, which is used for 3-6 months with a removal period of one week monthly during menstruation; **progestasert**, an intrauterine drug-releasing device of ethylene vinyl acetate copolymer, which lasts for a year; and suspensions of injectable microspheres or rods of biodegradable polymers.

3) **Dental Application:** Polymeric implants have been studied for dental applications involving local prolonged administration of fluoride anti-bacterials and antibiotics. **Stannous fluoride** was incorporated in different dental cements to evaluate sustained-release fluoride delivery. Another dispersed in the **hydroxyethyl methacrylate** and **methyl methacrylate copolymer hydrogel** coated with an outer layer of same copolymers in different proportion to be rate-limiting in drug release.

   The 8mm long device contains 42mg of fluoride in the core and is attached to the buccal surface of the maxillary first molar to release fluoride for 30 days at the rate of 0.5mg/day. Increased fluoride concentration in the saliva of the subject was found to cause erythema or small ulcers in the buccal mucosal opposite to the device.

   Ethylcellulose slabs containing polyethylene glycol and chlorhexidine (antibacterial) have also been evaluated. These slabs can be cut to fit the periodontal pocket and can be quickly inserted with minimal discomfort to

the patient. **Acrylic polymers** have also been evaluated for such a system. **Sustained-release implants of hollow cellulose fibres**, containing 20% chlorhexidine gluconate solution, have also been studied. This device is placed in periodontal pockets and significantly relieves discomfort, reduces gingival flow, and lessens bleeding on probe.

Matrix systems of ethylene-vinyl acetate copolymer and **releasing tetracycline** (on site therapeutic system) are also being clinically evaluated to treat periodontal disease.

4) **Immunisation: Polymeric implants** are being tested for enhanced immune response to antigens to provide pulsatile or continuous administration of the antigen over a prolonged time period. Immunisation efficacy of **ethylene-vinyl acetate copolymer pellets** containing bovine serum albumin as model antigen was also evaluated, and the immune response was comparable to that achieved by two injections of bovine serum albumin in Freund's adjuvant (an o/w suspension containing bacteria).

5) **Cancer: Silicone rod implants** (similar to those used for delivering levonorgestrone) have been tested for delivery of testosterone propionate or ethinyl estradiol in prostate cancer patients. **Lupron depot** is an implantation system used for providing one month depot release of leuprolide acetate [a synthetic analogue of Gonadotropin-Releasing Hormone (GnRH)].

   This implant consists of biodegradable microspheres prepared from polylactic-glycolic copolymer at 50:50 compositions. **Zoladex** is an implantation system used for providing one month depot release of goserelin acetate from a biodegradable implantable rod for treating prostate cancer.

6) **Narcotic Antagonists: Naltrexone** has been evaluated in implant from long-term delivery of narcotic antagonists. Naltrexone freebase, its hydrochloride or the pamoate acid salt has been prepared in various polymers and dosage forms for prolonged narcotic antagonist activity. Though *in vitro* delivery of up to 50 days has been achieved by some of the systems, *in vivo* duration of release was found to be shorter.

   Polylactide, polylactic glycolide and polycaprolactone-co-lactide polymers were evaluated in biodegradable polymer-coated microspheres, containing naltrexone base. Diffusion-controlled, linear naltrexone release was observed from the coated microspheres ,for about 50 days. These microspheres produced morphine antagonist response in implanted rats for 60 days.

7) **Other Applications:** Many insulin-delivery systems have been prepared and evaluated for a biofeedback approach. Biodegradable implantable delivery systems have been developed to provide prolonged release of antibiotic.

   These are biofeedback-controlled system, where the drug release rate depends on the body's need for the drug at a given time. Therapeutically, these systems may come closest to duplicating the release from a gland (like, the pancreas). Various mechanisms have been used to obtain self-regulated delivery.

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5.2. OSMOTIC PUMP DRUG DELIVERY SYSTEM

5.2.1. Introduction

Osmotic pump controlled release preparation is one of the most promising and effective dosage form as it is independent of all the physiological and physiochemical factors. This system also optimises the process and formulation parameters, **e.g.,** solubility, concentration and osmotic pressure of core component(s), size of delivery orifice, and nature of rate-controlling membrane, and thus modulates the rate and pattern of drug release.

A significant development made in the osmotic delivery devices is their capability to deliver drugs with moderate and extreme solubility. These devices also deliver drugs as liquids to enhance permeability and to deliver insoluble drugs that can dispense sub-saturated solutions of drugs. Osmotic pump drug delivery technology can be used to deliver high drug doses meeting high drug loading requirements.

5.2.2. Advantages

Osmotic pump drug delivery systems offer the following advantages:

1) They provide zero-order delivery rate.
2) They provide delayed or pulsed drug delivery.
3) The delivery rate is greater than that attained by diffusion-based system(s) of comparable size.
4) *In vitro* drug delivery rate can be predicted with accuracy using mathematical equations, which are highly correlated with *in vivo* drug delivery rate.
5) Their drug delivery rate is independent of pH variations in the environment, including in the GIT.
6) Their drug delivery rate is independent of agitation in the outside environment, including gastrointestinal motility.
7) The drug release rate is highly predictable and programmable.
8) Drug delivery occurs in the solution form ready for absorption, with osmotic pump stimulating as a liquid dosage form prepared *in situ*.
9) Their drug delivery rate is independent of delivery orifice size within limits.
10) They can be incorporated with drugs having varying solubility.
11) These devices can be easily fabricated using conventional pharmaceutical, manufacturing equipment.

5.2.3. Disadvantages

Osmotic pump drug delivery systems have the following disadvantages:

1) They are expensive as special equipment is required for making an orifice in the system.
2) Size of the pores is critical.
3) Dose dumping may occur due to the film defects, which might occur if the coating process is not well-controlled.

4) Retrieval therapy is not possible due to unexpected adverse events.
5) Residence time of the system in the body varies with the gastric motility and food intake.
6) They might cause irritation or ulcers due to release of saturated drug solution.

5.2.4. Principle of Osmosis

Abbenollet submitted the first report of osmotic effect in 1748. However, **Pfeffer** obtained the first quantitative measurement in 1877 in his experiment, in which he separated a sugar solution from pure water using a membrane (permeable to water but impermeable to sugar). A flow of water occurs into the sugar solution that cannot be halted until a pressure (π) is applied to the sugar solution. Pfeffer showed that this pressure is the osmotic pressure (π) of the sugar solution and is directly proportional to the solution concentration and absolute temperature. After a few years, **Vant Hoff** showed the analogy between these results and ideal gas laws by the following expression:

$$\pi = \Phi crt$$

Where, Φ = Osmotic coefficient of the solution.
c = Molar concentration of sugar in the solution.
r = Gas constant.
t = Absolute temperature.

Concentrated solution of soluble solutes (used in controlled release formulation) has an extremely high osmotic pressure that ranges from 30atm for sodium phosphate to 500atm for a lactose-fructose mixture. This is because their osmotic pressure can produce high water flow across semi-permeable membrane. The osmotic water flow through a membrane is given by the following equation:

$$dv/dt = AQ\Delta\pi/L$$

Where,

dv\dt = Water flow across the membrane of area A, thickness L, and permeability Q (cm^2).
$\Delta\pi$ = Osmotic pressure difference between the two solutions on either side of the membrane .

This equation is used for completely permeable selective membrane, which is permeable to water but completely impermeable to osmotic agent.

5.2.5. Basic Components of Osmotic Pumps

Osmotic pumps consist of the following components:

1) **Drug:** Osmotic pump systems can be incorporated with water-soluble as well as water-insoluble drugs. The drugs incorporated in the osmotically controlled drug delivery systems should have short biological half-lives of up to 2-6 hours, high potency, and should be required for chronic treatment. Some ideal drug candidates to be used for the formulation and evaluation of osmotic pump drug delivery systems include antihypertensive agents, **e.g.,** Nifedipine, Verapamil, Metoprolol, Captopril, Diltiazem hydrochloride, Carvedilol, Valsartan; anti-diabetic agents, **e.g.,** Glipizide, Glimpiperide; NSAIDs, **e.g.,** Ketorolac, Ibuprofen, Diclofenac sodium, Aceclofenac, etc.

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2) **Osmotic Agents:** These are ionic compounds that consist of either inorganic salts (**e.g.**, sodium chloride, potassium chloride, magnesium sulphate, sodium sulphate, potassium sulphate, and sodium bicarbonate) or hydrophilic polymers (**e.g.**, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethylcellulose, methylcellulose, polyethyleneoxide, and polyvinyl pyrrolidine).

Sugars, like glucose, sorbitol, sucrose and inorganic salts of carbohydrates can also be used as effective osmotic agents. These agents are used for fabricating the osmotic device so that concentration gradient can be maintained across the membrane by generating a driving force for the uptake of water and for maintaining drug uniformity in the hydrated formulation.

Table 5.1 enlists the classifications along with the examples of compounds that can be used as osmogens.

Table 5.1: Compounds that can be Used as Osmogens

Categories	Examples
Water-soluble salts of inorganic acids	Magnesium chloride or sulphate, chloride and sulphate salts of lithium, sodium or potassium, and sodium or potassium hydrogen phosphate.
Water-soluble salts of organic acids	Sodium or potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, and sodium ascorbate.
Carbohydrates	Arabinose, xylose, ribose, glucose, fructose, galactose, mannose, sucrose, maltose, raffinose, and lactose.
Water-soluble amino acids	Glycine, leucine, alanine, and methionine.
Organic polymeric osmogens	Sodium carboxy methyl cellulose, HPMC, hydroxyethyl methyl cellulose, cross-linked PVP, polyethylene oxide, carbopol, and polyacrylamides.

3) **Semi-Permeable Membrane:** This plays an important role in the modulation of drug release from the osmotic drug delivery system. The membrane should be stable to the outer and the inner environment of the device. It should be rigid, inert, and should maintain its dimensional integrity so that a constant osmotic driving force can be provided during drug delivery. This membrane should be selectively permeable to avoid the loss of osmogen by diffusion across the membrane during the passage of drugs and other ingredients present in the compartment.

This membrane should be biocompatible and should have sufficient water permeability to retain the desired water flux rate. The transmission rates of water vapour can be used for estimating water flux rates. Polymers that are permeable to water but impermeable to solute can be used as a coating material in osmotic devices, **e.g.,** cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate, and ethyl cellulose, and Eudragits. Semi-permeable membrane should exhibit sufficient wet strength (-105) and wet modulus to retain its dimensional integrity during drug delivery.

4) **Plasticisers:** These are used in the coating membrane of osmotic drug delivery system. They change the visco-elastic behaviour of the polymers, thus affect the permeability of the polymeric films. The changes in visco-elastic behaviour of the polymers can be controlled by using plasticisers of different types and in different amounts. Polyethylene glycols, ethylene glycol monoacetate, ethylene glycol diacetate for low permeability, triethyl citrate and diethyl tartrate or diacetin are the **examples** of some commonly used plasticisers.

5) **Flux Regulators:** These agents are added in the osmotic drug delivery systems to regulate the permeability of fluid. Hydrophilic substances, like polyethylene glycols (300-6000 Daltons), polyhydric alcohols, and polyalkylene glycols, can improve the flux; while the hydrophobic materials, like phthalates substituted with an alkyl or alkoxy (**e.g.,** diethyl phthalate or dimethoxy ethylphthalate), can reduce the flux. Insoluble salts or oxides are considerably water-impermeable, and thus can be used for this purpose.

6) **Wicking Agents:** These agents have the ability to draw water into the porous network of a delivery device. They are either swellable or non-swellable in nature. They can undergo physisorption with water (a type of absorption in which the solvent molecules loosely adhere to surfaces of the wicking agent via Van der Waals forces between the surface of wicking agent and the adsorbed molecule).

The wicking agents carry water to surfaces in the tablet core, and thus create channels or a network of increased surface area. Colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, Sodium Lauryl Sulphate (SLS), low molecular weight Poly Vinyl Pyrrolidone (PVP), m-pyrol, bentonite, magnesium aluminium silicate, polyester, and polyethylene are the **examples** of some commonly used wicking agents.

7) **Pore-Forming Agents:** These agents are used in the osmotic pumps for poorly water-soluble drugs and in the development of controlled porosity or multi-particulate osmotic pumps. A microporous membrane *in situ* is formed by the leaching of a pore-former during the operation of the system. The pore-formers can be inorganic or organic and solid or liquid in nature.

Alkaline metal salts, such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate, etc.; alkaline earth metals, such as calcium chloride and calcium nitrate; carbohydrates, such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol, and diols; polyols, such as poly hydric alcohols and polyvinyl pyrrolidone are the **examples** of some commonly used pore-forming agents.

8) **Coating Solvents:** Solvents are used for making polymeric solution that is used for manufacturing the wall of osmotic device. Inert inorganic and organic solvents that do not adversely affect the core, wall and other materials are typically used. Methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water, etc. are the **examples** of some commonly used solvents.

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Mixtures of solvents, such as acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3), etc., are also widely used as coating solvents.

5.2.6. Classification

Osmotic pumps are generally divided into oral and implantable systems (**figure 5.3**) and oral osmotic drug delivery systems are classified as shown in **figure 5.4**.

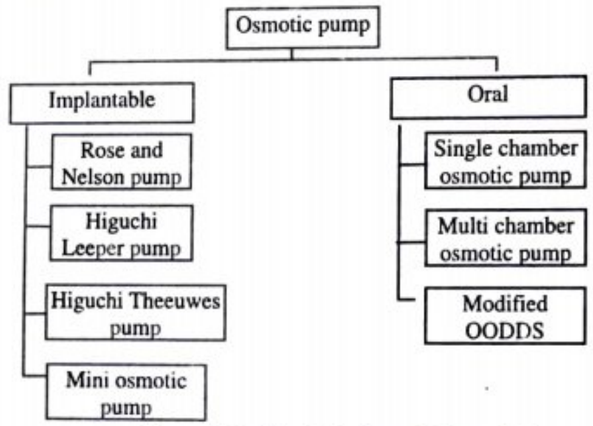


Figure 5.3: Classification of Osmotic Pumps

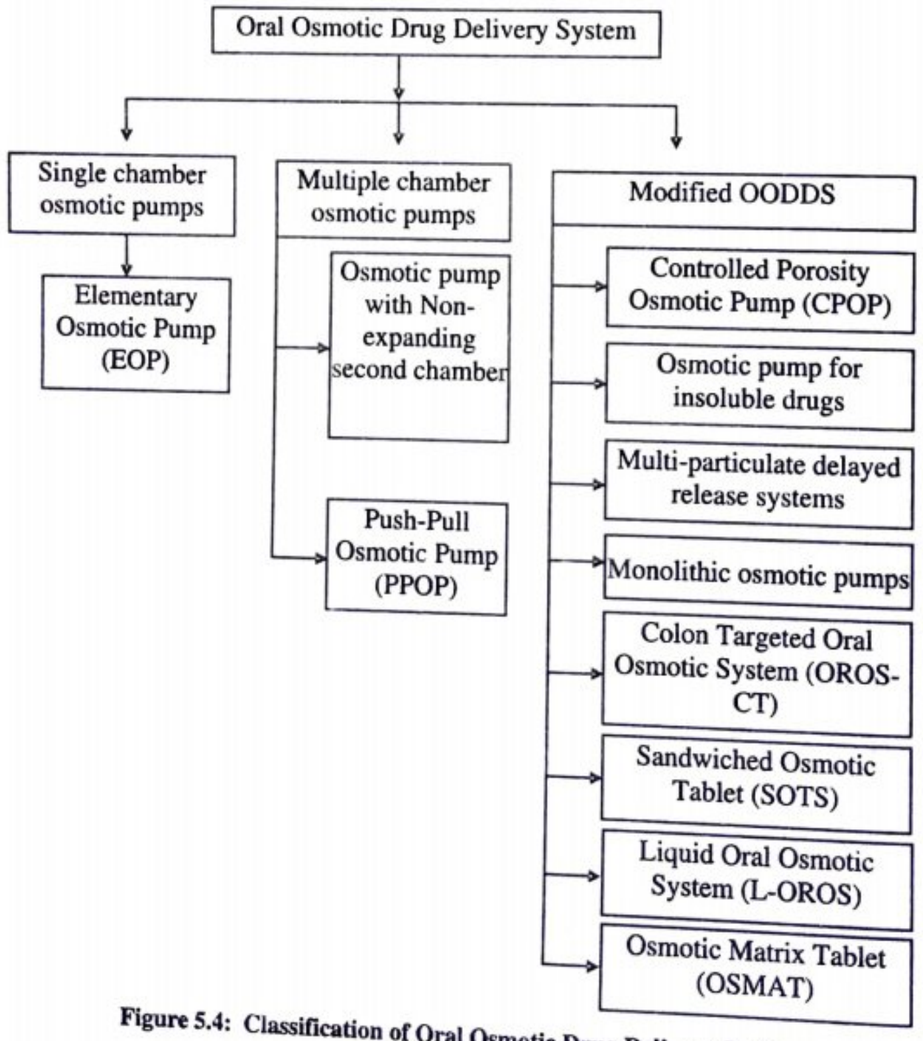


Figure 5.4: Classification of Oral Osmotic Drug Delivery System

5.2.6.1. DUROS Technology

DUROS technology (**figure 5.5**) provides a bi-compartment system separated by a piston. One compartment consists of osmotic engine formulated with excess of solid NaCl so that it remains present throughout the delivery and results in a constant osmotic gradient. One end of this compartment has a semi-permeable membrane through which water is drawn into the osmotic engine, and a large and constant osmotic gradient is established between the tissue water and the osmotic engine.

The other compartment consists of a drug solution with an orifice from which the drug is released due to the established osmotic gradient. This provides site-specific and systemic drug delivery when the pumps are implanted in human body. The pumps are preferably implanted subcutaneously in the inside of the upper arm. The delivery period ranges from a few days to a year.

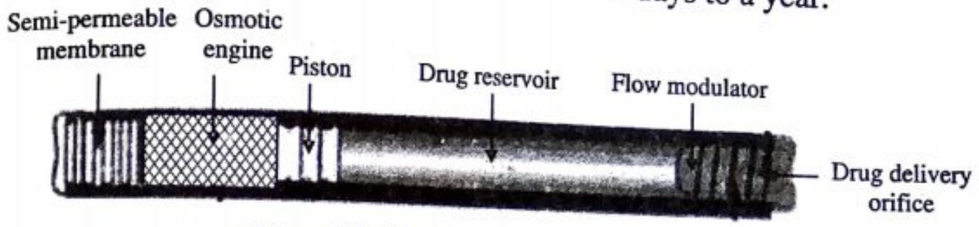


Figure 5.5: DUROS Infusion Implant

Materials used in this technology should be screened for compatibility, and should be biocompatible. The final drug product is sterilised by radiation sterilisation (gamma). In case the drug formulation cannot withstand sterilising doses of radiation, a DUROS sub-assembly is radiation sterilised and the drug formulation is added in the final aseptic operation. Henceforth, the system materials are also screened for their ability to withstand sterilising doses of radiation.

DUROS technology can potentially provide more flexibility than the competitive products regarding the types of drugs that can be administered, including proteins, peptides, and genes, because the drug dispensing mechanism does not depend on the drug substance.

5.2.6.2. ALZET Osmotic Pumps

ALZET osmotic pumps (**figure 5.6**) are miniature, implantable pumps used for research in mice, rats, etc. These infusion pumps can continuously deliver drugs, hormones, and other test agents at controlled rates from one day to six weeks without requiring external connections or frequent handling that eliminates the need for repeated night time or weekend dosing.

ALZET pumps are implanted subcutaneously or intraperitoneally, and can be used for systemic administration for targeted drug delivery. They can be attached to a catheter for localisation of the drug effect and for intravenous, intracerebral, or intra-arterial infusion to deliver different compounds, like antibodies, chemotherapeutic drugs, cytokines, growth factors, hormones, and peptides.

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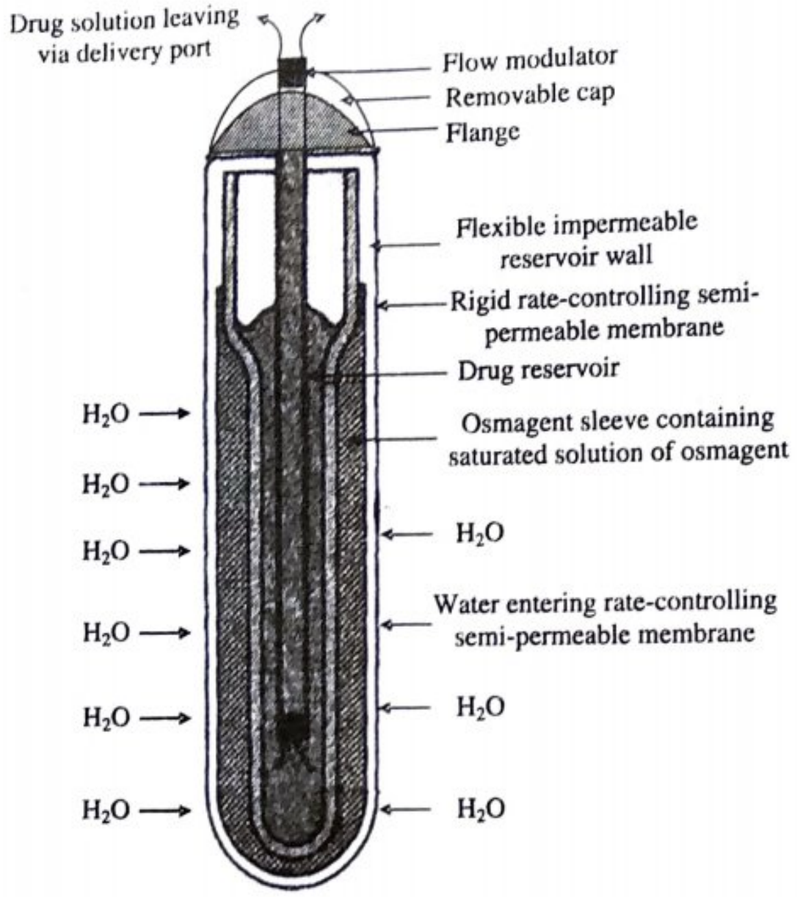


Figure 5.6: Cross Section of ALZET Osmotic Pump

ALZET pumps operate by osmotic displacement. An empty reservoir present in the core of the pump is filled with the drug or hormone solution to be delivered. This reservoir is separated via semi-permeable membrane from the chamber containing salt. The chamber surrounding the reservoir consists of a high concentration of salt; due to which water enters the pump through the semi-permeable membrane. Entry of water increases the volume in the salt chamber, thus compressing the flexible reservoir and delivering the drug solution into the animal through the exit port.

5.2.6.3. Rose and Nelson Pump

Rose and **Nelson** developed the first osmotic device in 1955. This device is the forerunner of the modern osmotically controlled drug delivery systems. The pump has three chambers, i.e., a drug chamber with an orifice, a salt chamber, and a water chamber (**figure 5.7**). The first two chambers (drug and salt chambers) are separated by the latex diaphragm and the latter two (salt and water chambers) are separated by semi-permeable membrane.

Osmotic pressure difference exists across the water and salt chamber; due to which, water flows unidirectionally from the water chamber to the salt chamber, thereby gradually increasing the volume of salt chamber. This increased volume in the salt chamber distends the latex diaphragm (that separates the salt and drug chambers), and thus pushes the drug through the orifice at a constant rate.

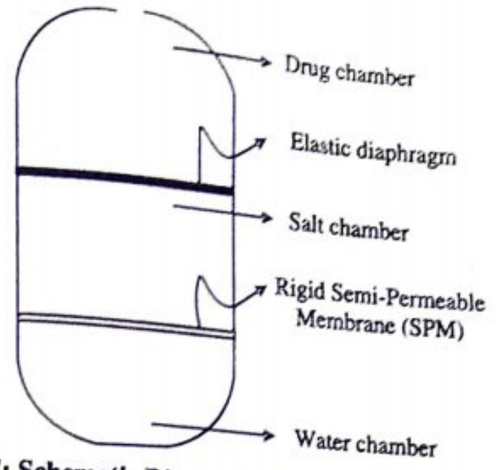


Figure 5.7: Schematic Diagram of Rose-Nelson Pump

This device was originally used for veterinary purposes for delivering drugs in the gut. One **disadvantage** of the Rose-Nelson pump is that the water chamber needs to be charged before every use. This problem was overcome with **Pharmetrix device** in which the water chamber was separated with an impermeable seal that was broken before administering the pump.

5.2.6.4. Higuchi-Leeper Pump

Higuchi-Leeper pump is the simplified form of three-chambered Rose-Nelson pump. The first series of Higuchi-Leeper pumps was launched by ALZA Corporation in 1970. It also consisted of three compartments, i.e., drug, salt and water compartments. The only difference between Rose-Nelson and Higuchi-Leeper pump is that the latter does not have a separate water chamber.

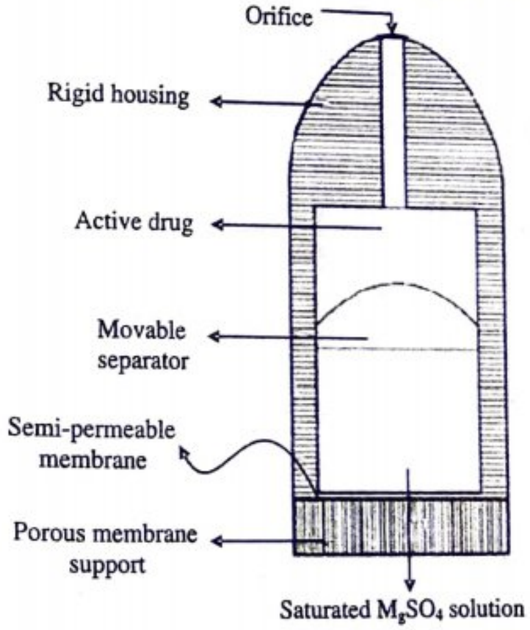


Figure 5.8: Schematic Diagram of Higuchi-Leeper Pump

Higuchi-Leeper pump (**figure 5.8**) is bullet-shaped, and has a rigid housing with an orifice at the top and a perforated support at the bottom. The inner surface of the porous membrane support has a fixed semi-permeable membrane. A movable separator is present that separates the housing into two chambers. The space between the movable separator and the semi-permeable membrane is filled with saturated solution of magnesium sulphate (having excess of solid magnesium

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sulphate). The front chamber is added with the drug and other required additives. When water, from the surrounding environment, enters through the semi-permeable membrane, the volume of lower chamber increases and the device gets activated. Due to the increased chamber volume, the movable separator shifts towards the orifice and releases the drug at a constant rate. Higuchi-Leeper pump can be stored for a few weeks to months.

Two most important modifications of Higuchi-Leeper pump are the use of closely fitting half shells to form the pump and a telescopic housing with expandable driving members. The most recent modification of Higuchi-Leeper pump is the use of pulsatile drug delivery. By producing a critical pressure at which the orifice opens and releases the drug, the pulsatile release of drug can be achieved.

5.2.6.5. Higuchi-Theeuwes Pump

Higuchi and **Theeuwes** developed the simplest version of Rose-Nelson pump in 1976, and named it the **Higuchi-Theeuwes** pump (**figure 5.9**). It consists of a rigid, rate-controlling, outer semi-permeable membrane surrounding a solid sodium chloride layer, below which elastic diaphragm is present for housing the drug. This device is a double-walled closed chamber, in which the outer wall is the semi-permeable membrane and the inner wall is made up of a flexible collapsible material. An osmotic agent is filled between the gap of outer and inner walls. The inner big chamber is filled with the drug, having direct access to the external environment through a narrow elongated tube. When the pump comes in contact with the aqueous environment, water imbibes into the chamber, containing an osmotic agent, through the semi-permeable membrane. As a result, the inner chamber containing the drug is compressed and it releases the drug through the orifice at a constant rate.

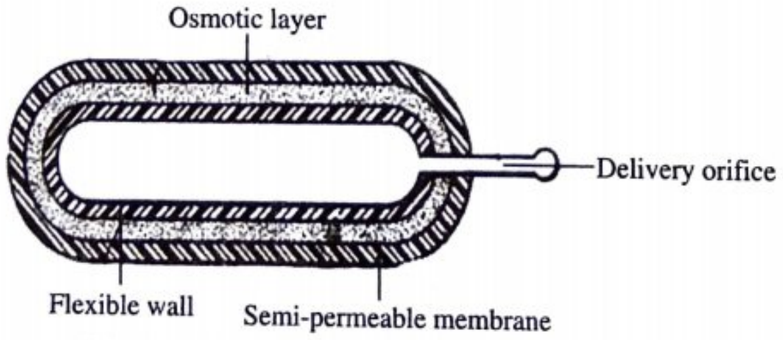


Figure 5.9: Higuchi-Theeuwes Pump

In one of the **modifications** of Higuchi-Theeuwes pump, carbon dioxide gas pressure is produced by adding a mixture of citric acid and sodium bicarbonate in the salt chamber.

5.2.6.6. Mini Osmotic Pumps

Mini osmotic implantable pump (**figure 5.10**) was first designed by the Alza Corp. for conducting experimental studies in animal models. Working of these pumps relies on the difference in osmotic pressure between a compartment within the pump (the salt sleeve) and the tissue environment in which the pump is

implanted. Due to the high osmolality of the salt sleeve, water flux into the pump through a semi-permeable membrane that forms the outer surface of the pump. The flexible reservoir becomes compressed as water enters the salt sleeve. This further displaces the test solution from the pump at a controlled, pre-determined rate. Mini osmotic pumps are designed for single use only as refilling of the compressed reservoir is not possible.

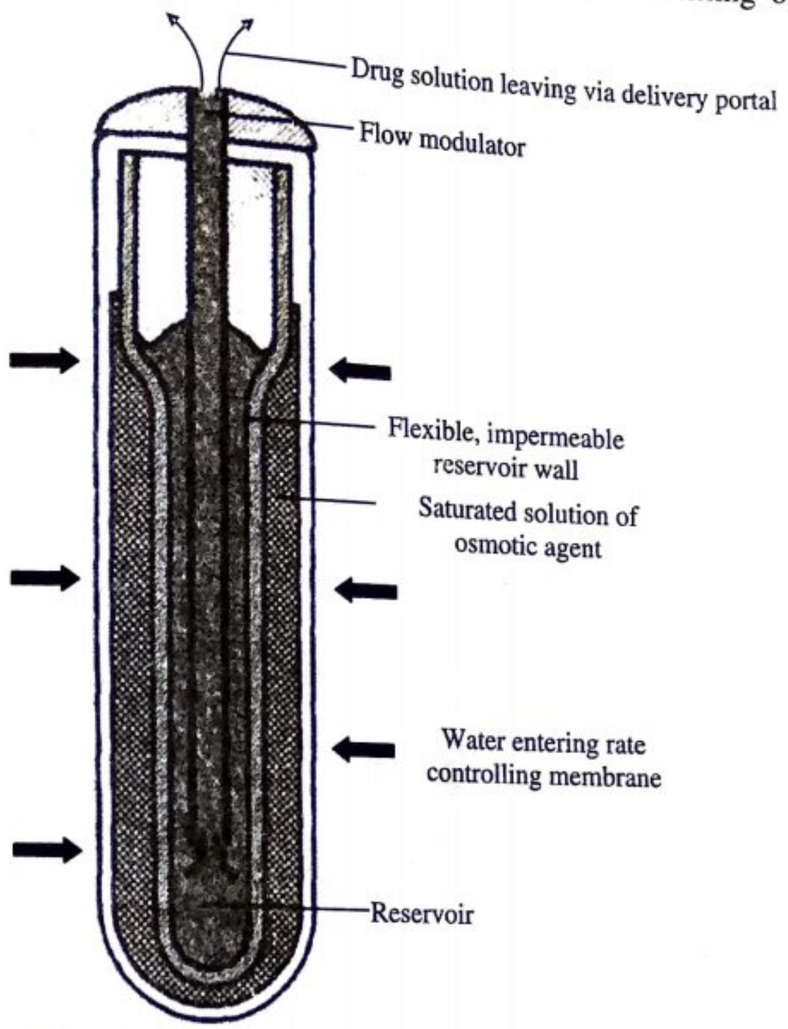


Figure 5.10: Mini Osmotic Pump

5.2.6.7. Elementary Osmotic Pump (EOP)

Elementary osmotic pump (**figure 5.11**) consists of an osmotically active agent coated with the rate controlling semi-permeable membrane, having an orifice of a critical size for drug delivery. In this system, drug release occurs in a controlled pattern due to the water permeation characteristics of a semi-permeable membrane surrounding the drug and osmotic properties of the osmogen in formulation. When the dosage form is exposed to the aqueous fluids, water imbibes from the surroundings at a rate determined by the fluid permeability of the membrane and osmotic pressure of the core formulation.

This osmotic imbibition of water forms a saturated solution of drug within the core, which is dispensed at a controlled rate from the delivery orifice in the membrane. Around 60-80% of drug is released at a constant rate from the EOP. The lag time for this process is around 30-60 minutes in most of the cases as the system hydrates before the beginning of zero-order delivery from the system. This system is preferred for the drugs that are moderately soluble in water.

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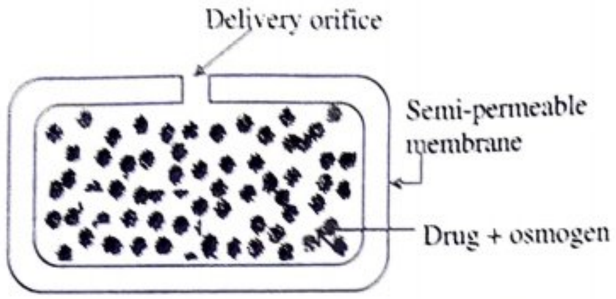


Figure 5.11: Elementary Osmotic Pump

5.2.6.8. Osmotic Pump with Non-Expanding Second Chamber

A non-expanding second chamber (**figure 5.12**) is used in the second category of multi-chamber devices. This group is further divided in two sub-groups based on the function of second chamber. In the first device, the second chamber is used for diluting the drug solution to be released in the body. The drug solution is diluted because if the drug is released in a concentrated form, it causes GIT irritation.

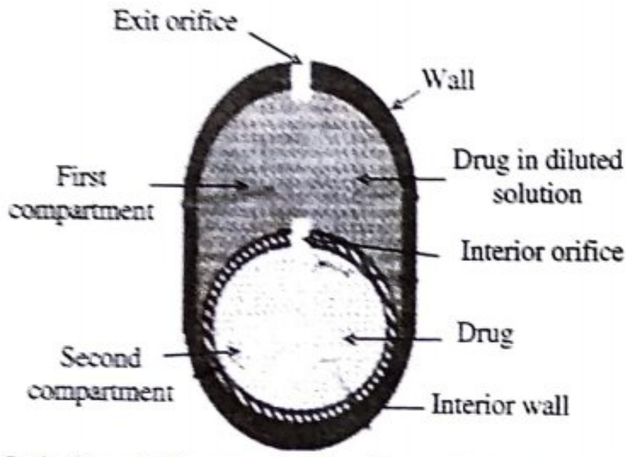


Figure 5.12: Osmotic Pump with Non-Expanding Second Chamber

In the second device, there are two rigid chambers. The first chamber contains a biologically inert osmotic agent (such as sugar or a simple salt, **e.g.,** sodium chloride), and the second one contains the drug. Water is drawn in both the chambers through the surrounding semi-permeable membrane. As a result, osmotic agent solution is formed in the first chamber, which then passes to the drug chamber through the connecting hole.

In the drug chamber, the osmotic agent solution mixes with the drug solution before leaving through the microporous membrane (forms a part of wall around the chamber). This device is preferred for delivering water-insoluble drugs.

5.2.6.9. Push-Pull Osmotic Pump (PPOP)

Push-pull osmotic pump is a modified form of elementary osmotic pump (**figure 5.13**). It is used to deliver poorly as well as highly water-soluble drugs at a constant rate. This system is similar to a standard bilayer coated tablet, in which the upper layer consists of the drug in a formulation of polymeric osmotic agent, and the other layer consists of tablet excipients. This polymeric osmotic agent may form an *in situ* drug suspension.

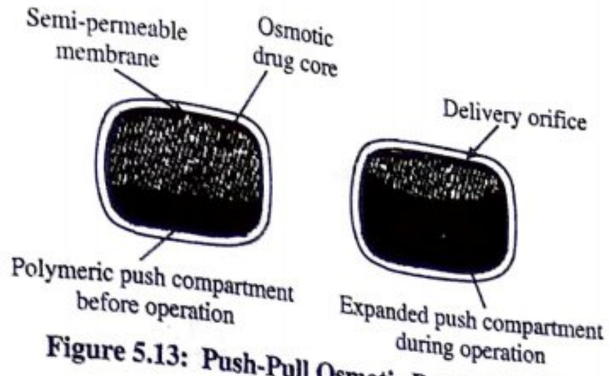


Figure 5.13: Push-Pull Osmotic Pump (PPOP)

When this tablet imbibes water, the other layer contains osmotic agent, colouring agents, polymer, and tablet excipients. These layers are formed and bonded by tablet compression to form a single bilayer core, which is then coated with a semi-permeable membrane. Once the coating has been done, a small hole is drilled through the membrane on the drug layer side of the tablet (using a laser or mechanical drill). On placing this system in aqueous environment, water gets attracted by an osmotic agent in both the layers of the tablet. This osmotic attraction in the drug layer attracts water into the compartment to form an *in situ* drug suspension.

In the non-drug layer, the osmotic agent simultaneously attracts water into that compartment, thus expanding its volume. Such expansion of non-drug layer releases the drug suspension through the delivery orifice.

5.2.6.10. Controlled Porosity Osmotic Pump (CPOP)

Controlled porosity osmotic pump contains water-soluble additives in the coating membrane, which dissolves on coming in contact with the aqueous environment. This results in the formation of microporous membrane *in situ* (**figure 5.14**).

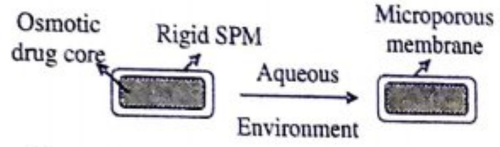


Figure 5.14: Controlled Porosity Osmotic Pump

A controlled porosity wall appears like a sponge, and is made up of materials producing 5-95% pores having 10A-100µm pore size. This membrane is permeable to water as well as to the dissolved solute. Water-soluble additives used in this pump are dimethyl sulphone, saccharides, amino acids, sorbitol, etc.

5.2.6.11. Osmotic Pump for Insoluble Drugs

In this osmotic pump device, the osmotic agent particles (osmogens) are coated with an elastic semi-permeable film. These particles are mixed with the insoluble drug and compressed into a tablet. This tablet is then coated with a semi-permeable membrane, in which an orifice is created.

When the tablet is exposed to the aqueous environment, water imbibes into the osmotic agent particles through the two membranes. As a result, the particles swell and push the insoluble drug hydrostatically through the delivery orifice.

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5.2.6.12. Multi-Particulate Delayed Release Osmotic System

The multi-particulate delayed release system (**figure 5.15**) uses pellets, containing drug with or without osmotic agent. These pellets are coated with an SPM, like cellulose acetate. On exposing the pellets to an aqueous environment, water penetrates the core and forms a saturated solution of soluble components. Water influx is induced by the osmotic pressure gradient, and this causes rapid expansion of the membrane, and subsequent formation of pores. Osmotic ingredient and the drug are released through these pores following the zero-order kinetics.

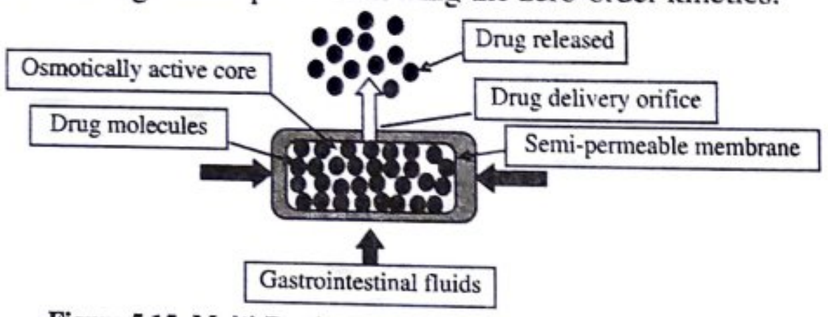


Figure 5.15: Multi-Particulate Delayed Release Osmotic System

Schultz and **Kleinebudde** conducted a study and reported that lag time and dissolution rates depend on the coating level and osmotic properties of the dissolution medium. They also stated that the dissolution characteristics depend on the membrane components, like plasticiser and its concentration and lipophilicity. Due to these semi-permeable walls, an osmotic device shows lag time before the beginning of drug delivery. This property is considered as a **disadvantage**; however, it can be used advantageously as some drugs (those for early morning asthma or arthritis) require delayed release.

5.2.6.13. Monolithic Osmotic System

The monolithic osmotic system includes a simple dispersion of water-soluble agent in polymer matrix (**figure 5.16**). On exposing the system to aqueous environment, water imbibes through the active agents, ruptures the polymer matrix capsule surrounding the drug, and subsequently releases the drug to the outside environment. In the starting phase, this process takes place in the outer environment of the polymeric matrix; but, slowly it proceeds towards the interior of the matrix. This system, however, fails if the device is incorporated with more than 20-30 units per litre of the active agents. This is because, above this level, leaching of the substance takes place.

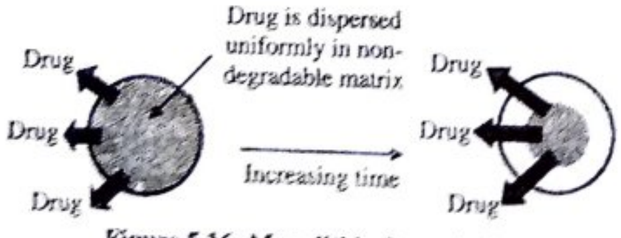


Figure 5.16: Monolithic Osmotic System

5.2.6.14. Colon Targeting Oral Osmotic System (OROS-CT)

The colon targeting oral osmotic system is used to formulate drugs prescribed for once or twice a day for targeted delivery of drugs to the colon. The OROS-CT (**figure 5.17**) either contains a single osmotic agent or five to six push-pull osmotic units filled in a hard gelatin capsule. The push-pull osmotic unit is

enteric coated. The gelatin capsule dissolves but the tablets remain intact on coming in contact with the gastric fluids. The enteric coating dissolves when the system enters the small intestine. As a result, water imbibes into the core and the push compartment swells. Simultaneously, flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate controlled by the rate of water transport across the semi-permeable membrane.

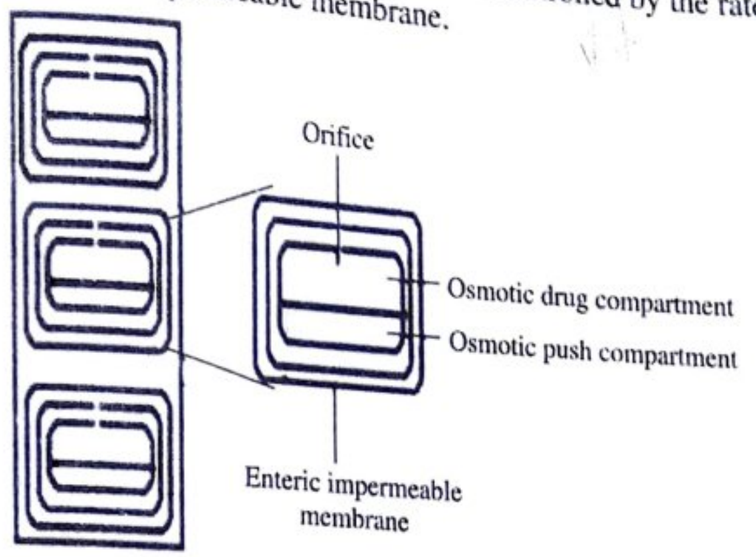


Figure 5.17: Cross-Sectional Diagram of OROS-CT

5.2.6.15. Sandwiched Osmotic Tablets (SOTS)

Sandwiched osmotic tablets (**figure 5.18**) consist of polymeric push layer sandwiched between two drug layers having two delivery orifices with a semi-permeable membrane coating on the tablet. On exposing the device to the aqueous environment, the middle push layer containing the swelling agents imbibes water from the surrounding areas through the semi-permeable membrane. As a result, the drug is released from the two orifices present on opposite sides of the tablet. Thus, SOTS are preferably used for drugs that may cause local irritation of the gastric mucosa.

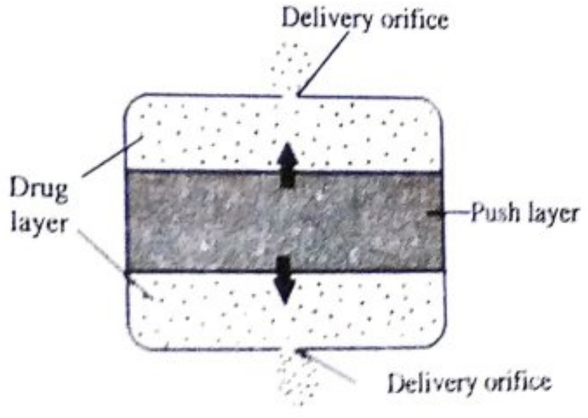


Figure 5.18: Sandwiched Osmotic Tablets

5.2.6.16. Liquid Oral Osmotic System (L-OROS)

Liquid oral osmotic system delivers drugs as liquid formulations and imparts the combined benefits of extended release with high bioavailability. Generally, this system is of **three types**, i.e., L-OROS hard cap, L-OROS soft cap, and delayed liquid bolus delivery system (**figures 5.19** and **5.20**).

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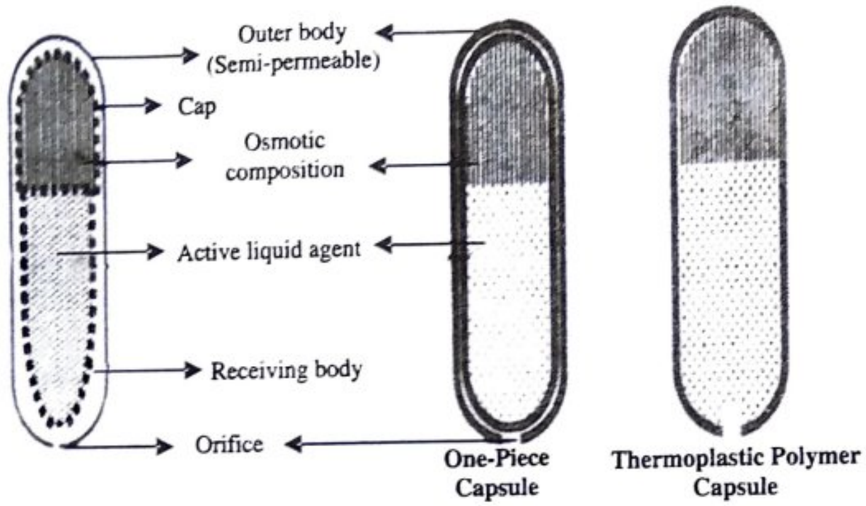


Figure 5.19: L-OROS – Hard Cap

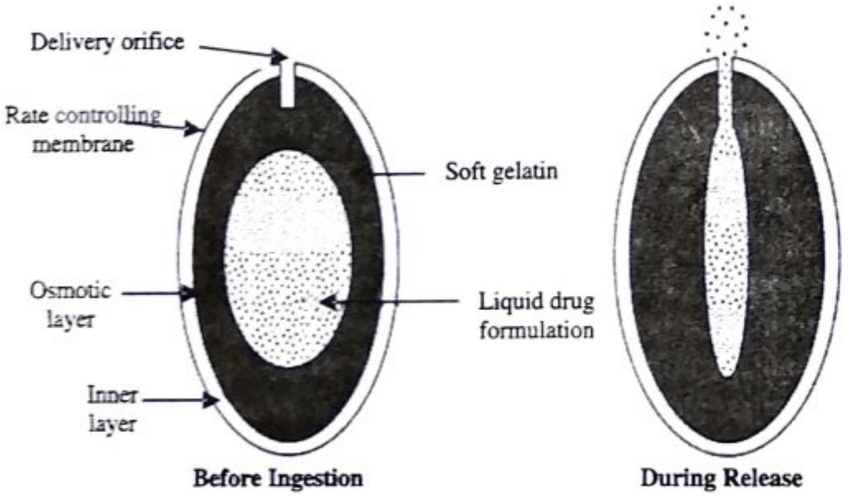


Figure 5.20: L-OROS – Soft Cap

Each system consists of a liquid drug layer, an osmotic engine or push layer, and a semi-permeable membrane coating. On exposing the system to the aqueous environment, water permeates across the rate controlling membrane, and thus the osmotic layer gets activated. The expanded osmotic layer develops a hydrostatic pressure inside the system. This pressure forces out the liquid formulation through the delivery orifice.

L-OROS hard cap and soft cap systems are designed for continuous drug delivery; whereas, the L-OROS delayed liquid bolus drug delivery system is designed for pulsatile drug delivery. The delayed liquid bolus delivery system has three layers, i.e., a placebo delay layer, a liquid drug layer, and an osmotic engine. All these three layers are surrounded by a rate controlling semi-permeable membrane.

A delivery orifice is drilled on the placebo layer, at end of the capsule-shaped device. Expansion of the osmotic engine first releases the placebo, and thus delays the release of drug layer. Release of drug can be extended up to 10 hours, and this depends on the permeability of the rate controlling membrane and thickness of the placebo layer.

5.2.6.17. Osmotic Matrix Tablet (OSMAT)

Osmotic matrix tablet is a novel system in which hydrophilic property of polymers are utilised so that the polymers swell and jellify in aqueous medium resulting to form a semi-permeable *in situ*. Drug release from such osmotically driven matrix system (containing an osmogen) is controlled by osmotic phenomenon. Thus, OSMAT uniformly combines the matrix and osmotic characteristics, and results in quantum improvement in drug delivery from swellable matrix systems. Manufacturing of osmotic matrix tablets is very simple and precludes the procedures of coating a semi-permeable membrane and drilling a delivery orifice. This technology is very economic and can be used for various drugs.

5.2.7. Evaluation

Evaluation of oral osmotic drug delivery systems includes the following range of studies:

1) ***In Vitro* Evaluation:** The oral osmotic drug delivery system, especially osmotic pump tablets are evaluated by:
   i) **Visual Inspection:** It includes visual inspection of the film for smoothness, uniformity of coating, edge coverage, and lustre.
   ii) **Coating Uniformity:** This parameter is evaluated by determining the weight, thickness and diameter of the tablets before and after coating.
   iii) **Coat Weight and Thickness:** This parameter is evaluated from depleted devices following careful washing and drying of the film, using standard analytical balance and screw gauge, respectively.
   iv) **Orifice Diameter:** A pre-calibrated ocular micrometer is used for microscopic study of the mean orifice diameter of osmotic pump tablet.
2) ***In Vitro* Drug Release:** Various methods, like vertically reciprocating shaker, conventional USP dissolution apparatus I and II, flow-through cell apparatus, etc. are used for determining the *in vitro* delivery rate of drugs from osmotic systems.
3) ***In Vivo* Evaluation:** In terms of pH and motility, the intestinal tract environment of humans is almost similar to that of dogs; therefore, dogs have been used for determining the *in-vivo* delivery rate of drug(s) from oral osmotic drug delivery systems and for establishing *in vitro-in vivo* correlation (IVIVC). However, *in vivo* evaluation can also be performed in healthy human volunteers, and various pharmacokinetic parameters (such as C_{max}, t_{max}, AUC, and MRT) and relative bioavailability are estimated.

5.3. SUMMARY

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

1) **Lafarge** introduced the implantable system concept for sustained release drug administration in **1861**. It was first introduced to produce steroid hormones-containing solid implants for long-term delivery.
2) **IDDS** is defined as "a sterile drug delivery device for subcutaneous implantation having the ability to deliver drugs at a controlled rate over a prolonged time period, comprising a rod-shaped polymeric inner matrix with

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CHAPTER 6

Transdermal Drug Delivery System

6.1. TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

6.1.1. Introduction

Transdermal Drug Delivery System (TDDS) involves the topically administered medications in self-contained, discrete dosage forms of patches, which on application to the skin deliver the drug into the bloodstream through the skin portal at a pre-determined and controlled rate over a prolonged time period to increase the therapeutic efficacy and reduce the side effect of drug.

A **transdermal** or **skin patch** is a medicated adhesive patch that is applied on the skin to deliver a specific dose of drug into the systemic circulation through the skin. TDDS maintains the drug concentration within the therapeutic window for prolonged time period to ensure that the drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration.

TDDS are preferred over injectables and oral routes as they increase patient compliance and avoid first-pass metabolism. Transdermal route has competed with oral route as the most successful innovative research area in drug delivery. This is because treatment through oral route aims to attain and maintain drug concentration in the body within a therapeutically effective range. This is done by introducing a fixed dose at regular intervals, due to which the drug concentration in body follows a peak and trough profile, and result in a greater chance of adverse effects or therapeutic failure; large amount of drug is lost in the surrounding area of the target organ and the therapy should be monitored to avoid overdosing.

6.1.2. Advantages

TDDS has the following advantages:

1) The gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug can be avoided.
2) Drugs to be given via oral route can be given as transdermal patches if the patient is vomiting or having diarrhoea.
3) It avoids first pass metabolism; **for example,** transdermal nitroglycerin gets rapidly metabolised by the liver when taken through oral route.
4) It is non-invasive, and avoids the inconvenience of parenteral therapy.
5) It provides extended therapy with a single application, thus improves compliance over other dosage forms requiring more frequent dose administration, **e.g.,** transdermal clonidine 7 day.

6) The activity of drugs having a short half-life is extended through the drug reservoir in therapeutic delivery system and its controlled release.
7) Drug therapy can be terminated rapidly by removal of the application from the skin surface.

6.1.3. Disadvantages

TDDS has the following disadvantages:

1) One or more components of the TDDS may cause contact dermatitis at the site of application in some patients, thus the treatment is discontinued.
2) Only potent drugs can be incorporated into transdermal patches because of the natural limits of drug entry due to the skin's impermeability.
3) Transdermal patches of some drugs, **e.g.,** scopolamine, need to be placed behind the ear, making it uncomfortable for the patients.
4) Transdermal patches do not provide long time adherence.

6.1.4. Permeation Through Skin

The TDDS aims to achieve systemic levels of medication through topical application on intact skin. Thus, the structural and biochemical features of the human skin and the features contributing to the barrier function and rate of drug access into the body via skin should be reviewed during the formulation of TDDS.

The skin is structurally divided into epidermis and dermis or corium (**figure 6.1**). These layers are penetrated by hair shafts and gland ducts. Skin is the most extensive organ in human body, as it covers an area of about $2m^2$ in an average human adult. From inside to outside the major skin layers include the fatty subcutaneous layer (hypodermis), the dermis of connective tissue, and the stratified avascular cellular epidermis; thus, making the skin a multi-layered organ.

Skin receives about $1/3^{rd}$ of all blood circulating through the body. **Epidermis,** having 150µm thickness, arises from an active epithelial basal cell population. It is the skin's outermost layer, and differentiation process results in migration of cells from the basal layer towards the skin surface. Since epidermis has no blood vessels, the nutrients and waste products diffuse across the dermal-epidermal junction to maintain its strength. Epidermis comprises of five layers, namely **stratum germinativum** (basal layer), **stratum spinosum** (spinous layer), **stratum granulosum** (granular layer), **stratum lucidium**, and **Stratum Corneum** (SC), from inside to outside. The SC cells are dead, and so the epidermis without SC layer is termed the **viable epidermis**. The SC layer is the rate-limiting barrier in transdermal permeation of most molecules. It comprises of 15-20 layers of keratin-filled corneocytes (terminally differentiated keratinocytes) anchored in a lipophilic matrix.

The lipids of this extracellular matrix are distinctive in many respects:

1) They provide only continuous phase (and diffusion pathway) from the skin surface to the base of SC.
2) The composition (ceramides, free fatty acids, and cholesterol) is unique among biomembranes, and phospholipids are also absent.

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3) Despite the shortage of polar bilayer-forming lipids, the SC lipids exist as multi-lamellar sheets.
4) The predominantly saturated, long-chain hydrocarbon tails facilitate a highly ordered, inter-digitated configuration and formation of gel phase membrane domains as opposed to the more fluid and permeable liquid crystalline membrane systems.

The SC layer in dry state is 10-15µm thick, and it swells to become 40µm thick upon hydration. The structure of SC layer is illustrated as a bricks and mortar arrangement, in which the keratin-rich corneocytes (bricks) are embedded in the intercellular lipid-rich matrix (mortar).

Dermis or corium is a firm connective tissue (of mesoderm origin) on which the epidermis is present. It comprises of a dense network of connective tissue, having bundles of collagen fibres mingled with elastic tissue in the superficial levels. Dermis contains fine plexuses of blood vessels, lymphatic, nerves, hair follicles, sweat glands, and sebaceous glands.

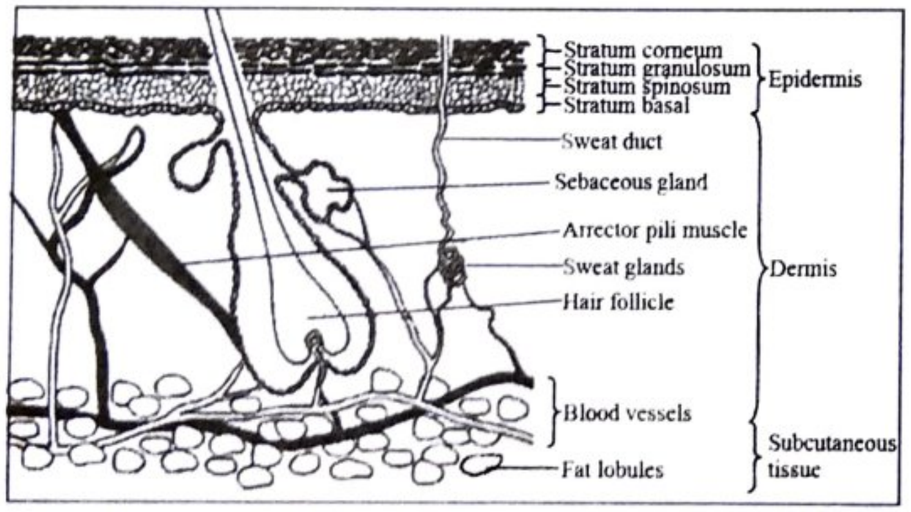


Figure 6.1: Cross-Sectional View of Human Skin Showing Different Cell Layers and Appendages

Kinetics of Transdermal Permeation

Skin permeation kinetics should be known for successful development of TDDS. Transdermal permeation of a drug involves the following steps:

1) Sorption by stratum corneum,
2) Penetration of drug through epidermis, and
3) Uptake of drug by the capillary network in the dermal papillary layer.

This permeation is possible when the drug possesses certain physiochemical properties. The **permeation rate** across the skin is given by:

$$dQ/dt = Ps\ (Cd - Cr) \quad \text{.....(1)}$$

Where, Cd and Cr = Concentration of skin penetrant in the donor compartment (i.e., on the stratum corneum surface) and in the receptor compartment (i.e., body), respectively; Ps = Overall permeability coefficient for the skin tissue to the penetrant. This **permeability coefficient** is given by:

$$Ps = Dss\ Ks/hs \quad \text{.....(2)}$$

Where, Dss = Apparent diffusivity for steady state diffusion of the penetrant molecule through thickness of skin tissues; Ks = Partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum; hs = overall thickness of skin tissues.

As Ks, Dss and hs are constants under given conditions, the permeability coefficient (Ps) for a skin penetrant is also considered a constant. **Equation (1)** indicates that a **constant rate of drug permeation can be obtained when Cd >> Cr**, i.e., drug concentration at the surface of stratum corneum (Cd) is consistently and substantially greater than the drug concentration in body (Cr). Thus, equation (1) becomes:

$$dQ/dt = Ps\ Cd \quad \text{.....(3)}$$

Rate of skin permeation is constant if the magnitude of Cd remains constant during the skin permeation. For Cd to be constant, the drug should be released from the device at a rate (Rr), either constant or greater than the rate of skin uptake (Ra), i.e., Rr >> Ra. Therefore, the drug concentration on skin surface (Cd) is maintained at a level equal to or greater than the equilibrium solubility of the drug in stratum corneum (Cs), i.e., Cd >> Cs. Thus, a maximum rate of skin permeation is obtained and is given by the equation:

$$(dQ/dt)m = Ps\ Cs \quad \text{....(4)}$$

Equation (4) indicates that the **maximum rate of skin permeation depends on the skin permeability coefficient** (Ps) and on **equilibrium solubility in stratum corneum** (Cs). Thus, skin permeation is limited to stratum corneum.

6.1.5. Factors Affecting Permeation

The transport mechanism across mammalian skin involves passive diffusion through the trans-epidermal route at steady state or through trans-appendageal route at non-steady state initially. Factors affecting the permeability of skin are of the following three categories (**figure 6.2**):

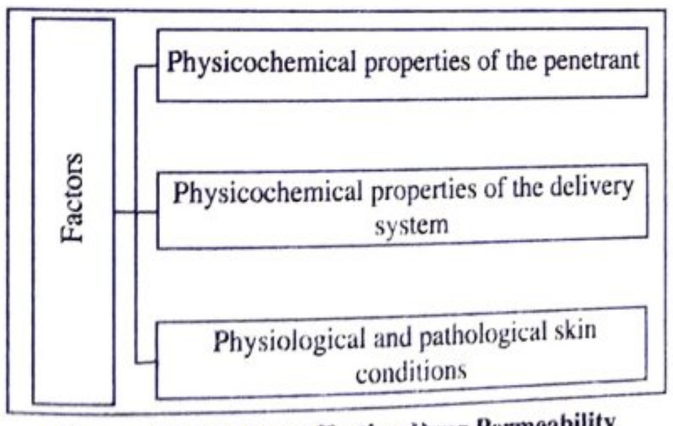


Figure 6.2: Factors affecting Drug Permeability

1) **Physicochemical Properties of the Penetrant:** These include:
   i) **Partition Coefficient:** Water- and lipid-soluble drugs are absorbed through the skin. Transdermal permeability coefficient is linearly dependent on partition coefficient. If the vehicle is changed, the

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lipid/water partition coefficient of a drug molecule may also alter. A drug molecule's partition coefficient can be changed by chemical modification without affecting its pharmacological activity.

ii) **pH Condition:** The rates of absorption of acidic and basic drugs are affected by pH, whereas the unchanged form of drug exhibits a better penetrating capacity. Transport of ionisable species from aqueous solutions is strongly dependent on pH.

iii) **Drug Concentration:** Transdermal permeability across mammalian skin is a passive diffusion process that depends on the concentration of penetrant molecule on the skin surface.

2) **Physicochemical Properties of the Drug Delivery System:** These include:

i) **Affinity of the Vehicle for Drug Molecules:** This affects the release of drug molecule from the carrier. Solubility in the carrier determines the release rate of drug. Mechanism of drug release depends on whether the drug is dissolved or suspended in the delivery/carrier system and on the interfacial partition coefficient of the drug from the delivery system to skin tissue.

ii) **Composition of Drug Delivery System:** This affects the rate of drug release and also the permeability of SC layer by hydration.

iii) **Enhancement of Transdermal Permeation:** Since the SC layer is dead in nature, the drug release from the dosage form is less. Penetration enhancers can cause physicochemical or physiological changes in the SC layer and increase drug penetration through the skin. Such drug penetration-enhancing property is found in many chemical substances.

3) **Physiological and Pathological Skin Conditions:** These include:

i) **Skin Age:** The permeability of foetal and infant skin is more than that of mature adult skin. Therefore, percutaneous absorption of topical steroids is rapid in children than in adults; but, water permeation is same in both.

ii) **Lipid Film:** Formation of a thin lipid film on skin surface occurs by the excretion of sebaceous glands and cell lipids, like sebum. Epidermal cell, containing emulsifying agent, may provide a protective film to prevent the removal of natural moisturising factor from the skin and also to maintain the barrier function of SC layer.

iii) **Skin Hydration:** Transdermal permeability can be increased by hydration of SC layer. Study of penetration rate of salicylic acid through skin with dry and hydrated corneum revealed that when the tissues were hydrated, the penetration rate of most water-soluble esters increased more than that of the other esters.

iv) **Skin Temperature:** Increase in skin temperature enhances the skin permeation rate. It also increases the vasodilation of blood vessels in contact with skin, thus increasing the percutaneous absorption.

v) **Cutaneous Drug Metabolism:** Some drugs cross the SC barrier and reach the general circulation in active form, while some reach in inactive

or metabolic form due to the presence of metabolic enzymes in the skin layers. It was reported that more than 95% of testosterone absorbed was metabolised as it present through the skin.

vi) **Species Difference:** Skin of different mammalian species shows various anatomical differences, like thickness of SC, number of sweat glands, and hair follicles per unit surface area.

vii) **Pathological Injury to Skin:** Injuries to skin can disturb the continuity of SC and increase skin permeability.

6.1.6. Basic Components of TDDS

Various components of TDDS are as follows:

1) Polymer matrix/drug reservoir,
2) Membrane,
3) Drug,
4) Permeation enhancers,
5) Pressure-Sensitive Adhesives (PSA),
6) Backing laminates,
7) Release liner, and
8) Other excipients.

6.1.6.1. Polymer Matrix/Drug Reservoir

Polymers form the backbone of TDDS, and control drug release from the device. A polymer matrix can be prepared by dispersing drug in a liquid or solid state synthetic polymer base. Polymers that are biocompatible and chemically compatible with the drug and other components of the system (like, penetration enhancers and PSAs) should be used in TDDS. Polymers should deliver the drug consistently and effectively throughout the intended shelf-life of the product, and should be safe. The following **criteria** should be considered **while selecting the polymer** for TDDS:

1) Molecular weight, glass transition temperature and chemical functionality of the polymer should favour the diffusion and release of drug through it.
2) The polymer should be stable, non-reactive with the drug, easy to be manufactured and fabricated into the desired product, and inexpensive.
3) The polymer and its degradation products should be non-toxic or non-antagonistic to the host.
4) The mechanical properties of the polymer should not depreciate on incorporation of large amounts of active ingredients.

Examples of some commonly used polymers for TDDS are:

1) **Natural Polymers:** Cellulose derivatives, zein, gelatin, shellac, waxes, proteins, gums and their derivatives, natural rubber, starch, etc.

2) **Synthetic Elastomers:** Polybutadieine, hydrin rubber, polysiloxane, silicone rubber, nitrile, acrylonitrile, butyl rubber, styrenebutadieine rubber, neoprene, etc.

3) **Synthetic Polymers:** Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinyl pyrrolidone,

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ii) **Thermophoresis:** A range of homeostatic controls maintain the skin temperature at 32°C. In the recent years, use of thermoregulation for improving the delivery profile of topical medicaments has been increased. It has shown a 2 to 3-fold increase in flux for every 7-8°C rise in temperature of skin surface. Increased permeation, heat treatment has been attributed to an increase in drug diffusivity in the vehicle and skin due to increased lipid fluidity. Similar to a homeostatic response to increase in skin temperature, the subcutaneous blood vessels also significantly enhance the transdermal delivery of topically applied compounds.

Iontophoresis: In this process, the oppositely charged ions are driven or repelled through the dermal layers into the area to be treated (either into the surrounding tissues for localised treatment or into the systemic circulation for systemic treatment). This is done with the application of electromotive force. Positively charged ions are driven into the skin at anode, and the negatively charged ions are driven into the skin at cathode. Study reports have shown increased skin permeation of drugs at anode or cathode, irrespective of predominant molecular ionic charge.

iii) **Microneedle-Based Devices:** One of the first patents was filed for a drug delivery device based on microneedle method for percutaneous drug administration. These microneedles (50-110mm long) penetrate the stratum corneum and epidermis to deliver drug from the reservoirs, containing drug. Various characterisations of the invention include separating the drug from the skin by using a membrane and controlling the drug release from its reservoir.

iv) **Needle-less Injection:** This is a pain-free method of administering drugs to the skin. Needle-less injection avoids the issues of safety, pain, and fear related to the use of hypodermic needles. Transdermal delivery by this approach can be achieved by applying the liquid or solid particles at supersonic speeds through the outer layers of skin by using a suitable energy source. This method has been reported to successfully deliver testosterone, lidocaine hydrochloride, calcitonin, and insulin.

6.1.6.5. Pressure-Sensitive Adhesives (PSAs)

PSAs are materials that adhere to a substrate (skin in TDDS) with the application of light force and leave behind no residue on removal. These materials form interatomic and intermolecular attractive forces at the interface, only when they are in intimate contact. This degree of contact can be obtained if the material is sensitive to pressure, i.e., it deforms under slight pressure. Adhesion involves a liquid-like flow, thus the adhesives make the skin surface wet on application of pressure; while the adhesive sets in that state on removal of pressure.

If a PSA's surface energy is less than that of the skin, it wets and spreads onto the skin. After initial adhesion, the PSA-skin bond can be built by stronger interactions (**e.g.,** hydrogen bonding) that depend on skin characteristics and other parameters. Polyisobutylene-based adhesives, acrylics and silicone-based PSAs, hydrocarbon resin, etc. are the **examples** of commonly used PSA

polymers in TDDS. PSAs can be placed around the edge of the TDDS or can be laminated as a continuous adhesive layer on the TDDS surface. PSAs should be compatible with the drug and excipients, or else the mechanical properties of the PSAs and the drug delivery rate will get altered.

6.1.6.6. Backing Laminates

Backings impart appearance, flexibility, and occlusion properties to TDDS. Due to this reason, chemical resistance of the material should be significantly considered while designing a backing layer. Excipient compatibility should also be considered as prolonged contact between the backing layer and the excipients may result in the leaching of excipients from the backing layer or may cause diffusion of excipients, drug or penetration enhancer through the layer. The most suitable backing is the one with lowest modulus or high flexibility, good oxygen transmission, and a high moisture vapour transmission rate. Vinyl, polyethylene, polyester films, aluminium and polyolefin films are some **examples** of backing materials.

6.1.6.7. Release Liner

The transdermal patch is covered by a protective liner during its storage period. This liner is removed and discarded before applying the patch to the skin. The liner should be chemically inert as it remains in intimate contact with the transdermal patch. A release liner is made up of a non-occlusive base layer (**e.g.,** paper fabric) or an occlusive base layer (**e.g.,** polyethylene, polyvinyl chloride) and a release coating layer of silicon or teflon. Polyester foil and metalised laminates are also used for TDDS release liners.

6.1.6.8. Other Excipients

Chloroform, methanol, acetone, isopropanol, and dichloromethane are the **examples** of solvents used for preparing drug reservoir. Dibutylphthalate, triethyl citrate, polyethylene glycol, and propylene glycol are the **examples** of plasticisers used for imparting plasticity to the transdermal patch.

6.1.7. Classification of TDDS

The TDDS can be classified into two major categories as follows (**figure 6.3**):

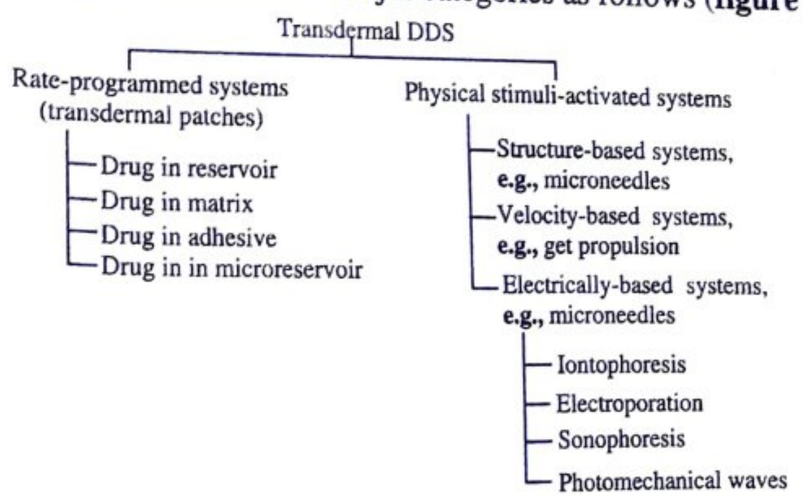


Figure 6.3: Classification of Transdermal DDS

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6.1.7.1. Rate-Programmed Transdermal DSS/Transdermal Patches

The developed patch-type TDDS can be described by three basic design principles (the fourth being a specialised design):

1) Drug in reservoir (membrane type),
2) Drug in matrix (monolithic type),
3) Drug in adhesive (matrix), and
4) Drug in microreservoir (reservoir in adhesive matrix).

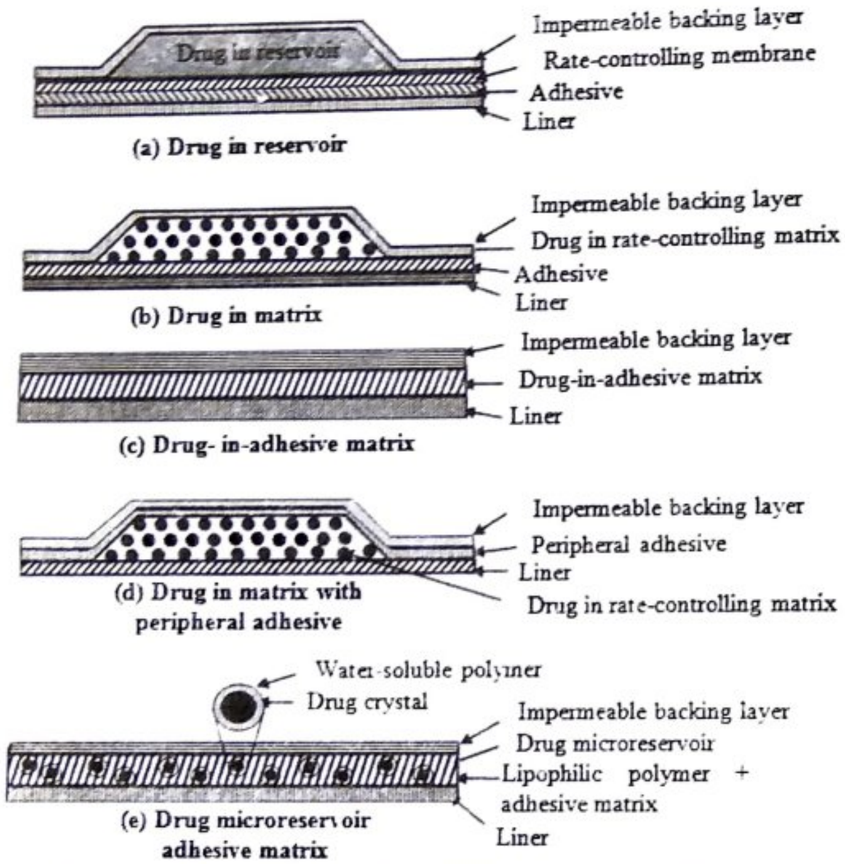


Figure 6.4: Types of Rate-Programmed Transdermal DDS

In the first case (**figure 6.4a**), the reservoir is separated from the skin via rate-controlling membrane. Designs in which the adhesive is remote from the drug delivery area of the system can also be developed (**figure 6.4d**). It is possible to combine the main types of patches by placing a membrane over matrix (hybrid system) (**figure 6.4b**) or by using drug-in-adhesive (**figure 6.4c**), along with a membrane-matrix device to deliver an initial bolus dose.

1) **Drug in Reservoir (Membrane Patch):** In membrane patches, a delivery rate-controlling membrane is present between the drug reservoir and skin. Microporous membranes (control drug flux by the size and tortuosity of pores in the membrane) or dense polymeric membranes (through which the drug permeates by dissolution and diffusion) can also be used. Ethylene-vinyl acetate copolymers, silicones, high-density polyethylene, polyester elastomers, and polyacrylonitrile are the **examples** of materials that can be used as rate-controlling membranes. An ideal membrane should be permeable to the drug and enhancer (if present) and should also retain other formulation excipients.

Drug reservoir can be composed of various materials, ranging from simple formulations (mineral oil) to complex formulations (aqueous-alcoholic solutions and gels, with or without co-solvents, and polymeric materials). A reservoir system should allow zero-order drug release over the delivery period, and for this the reservoir material is saturated with the drug over the period of product application, which can be achieved by formulating the drug as a suspension.

2) **Drug in Matrix:** The drug is uniformly dispersed in a polymeric matrix, through which it diffuses to the skin surface. The matrix is composed of silicone elastomers, polyurethanes, polyvinyl alcohol, polyvinyl pyrrolidones, and may be considered as the drug reservoir. The steps involved in drug delivery process from this system are:
   i) The drug molecules dissociate from the crystal lattice,
   ii) The drug molecules undergo solubilisation/partitioning in the polymer matrix, and
   iii) The drug molecules diffuse through the matrix to the skin surface.

   A drug can be released from a polymeric matrix under zero-order kinetics, if the drug is maintained at saturation level in the fluid phase of the matrix, and if its diffusion rate in the matrix is much greater than its diffusion rate in the skin.

3) **Drug-in-Adhesive Matrix:** These are the simplest systems in which the drug and enhancer are formulated in an adhesive mixture that is coated onto a backing membrane (**e.g.,** a polyester film) to produce an adhesive tape. However, these systems have a few **limitations**:
   i) They may undergo chemical interactions, which may interfere with adhesive performance, result in the breakdown of active species, or form new chemical entities.
   ii) Physicochemical characteristics of the drug and adhesive system may provide different release rates for hydrophilic and hydrophobic drugs, **e.g.,** lipophilicity of silicone adhesives limits the solubility of hydrophilic drugs in the adhesive matrix.
   iii) On adding other excipients (**e.g.,** skin permeation enhancers) into a drug-in-adhesive system, the drug release rates and adhesive properties may get altered.

4) **Drug in Microreservoir:** This TDDS is a combination of reservoir and matrix-dispersion systems. For preparing the drug reservoir in this system, the drug is suspended in an aqueous solution of water-soluble polymer and then the resultant solution is homogeneously dispersed in a lipophilic polymer to form numerous unleachable, microscopic spheres of drug reservoirs. The thermodynamically unstable dispersion is stabilised by immediately cross-linking the polymer.

6.1.7.2. Physical Stimuli-Activated Transdermal DDS

Transdermal delivery of drugs is not only possible through transdermal patches, but also through the use of methods involving physical stimuli, such as electrophoresis, electroporation, and sonophoresis.

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An **example** of structure-based system belonging to this class of TDDS is microneedles, developed by Alza and called **Macroflux**. This system consists of a thin titanium screen with 200µm long microprojections attached to the underside (**figure 6.5**). Such microneedles on application to the skin, create superficial pathways through the stratum corneum (which contains no nerves), without causing any pain to the receptors in the dermis as they are very short in length. Drugs can either be coated onto the micro-projections for bolus delivery or attached to a drug reservoir for continuous or iontophoretic application. This TDDS is suitable for delivering vaccines, small molecules, and biopharmaceuticals.

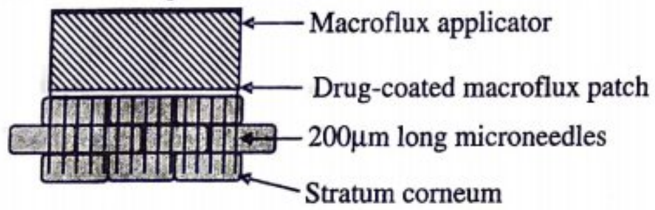


Figure 6.5: Macroflux (Microneedles) System for Transdermal Drug Delivery

6.1.8. Formulation Approaches

The formulation of TDDS involves the following approaches:

1) **Membrane Permeation-Controlled System:** This system can be multi-laminate process, **e.g.,** Transdermal Nitro. This TDDS consists of three substrates held together by two layers of drug-containing adhesive. The drug is first processed into the physical/chemical form in which it can be incorporated into the product. Thereafter, the drug adhesive components and excipients are mixed with a solvent to obtain a uniform solution, which is deposited as a thin film on moving substances.

   Later, the solvent is removed by drying these substances. Then lamination of the dried adhesive film and other layer is carried out to form a five layer product, consisting of release liner contact adhesive control membrane, drug reservoir, and backing substrate. Finally, the lamination is printed and die cut into the final dosage forms, which are packed in individual foil pouches. After inspection, the products are automatically inserted into a continuously moving web of pouch stock which is sealed around the dosage form.

2) **Adhesive Dispersion Type System:** This TDDS is prepared as follows (**figure 6.6**):
   i) **Preparation of Individual Matrix Solution:** The raw materials (i.e., polymer, tackifier, softening agent) are dissolved in an organic solvent to obtain a standard or stock solution. The matrix solution is prepared by mixing the stock solution with the specified ingredients, and adding the active ingredient and other non-soluble additives.
   ii) **Coating the Individual Matrix Layers:** The obtained solution is coated (by using coating machine) on smooth paper or film web to make individual layers. Later, the solvent is removed by drying. The coating machine has two units:
      a) **Coating Unit:** In this unit, the solvent-based formulations are coated onto the appropriate web, depending on the viscosity, solid contents, flowability, and surface tension of the matrix solution.

   b) **Drying Unit:** In this unit, the solvent is evaporated from the adhesive mass by running the coated web through a drying channel using a transport system (like cranked shaft or conveyor belt).

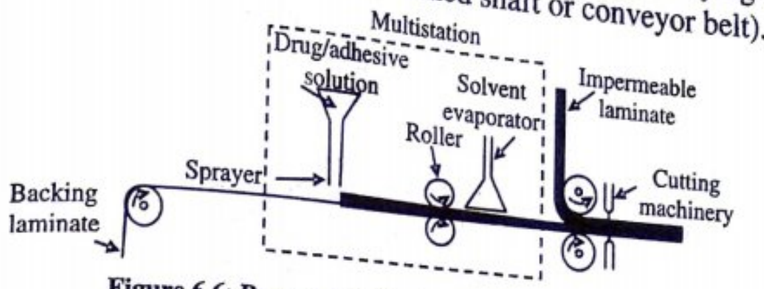


Figure 6.6: Process and Equipment Involved in the Manufacture of an Adhesive Dispersion System

   iii) **Building the Multilayer Laminate:** Lamination is done to form the multilayer matrix system. Two matrix layers, each adhering to one side of the web, are laminated. A carrier material of this two layer laminate is removed and a third layer is pressed, with the laminated side on the laminated side of the two layer laminate. This process is repeated till the final laminate is complete.

   iv) **Separating Unit of the Multilayer Laminate:** The bulk product is longitudinally cut and the individual unit is punched out from the narrow rolls. Precision of the operations is important as it may affect the release rate of the active ingredient. Lastly, the liner is applied to the system with the necessary release aids.

   v) **Packaging:** Primary packaging is done by sealing the four corners, while secondary packaging is done in cardboard boxes.

3) **Matrix Diffusion Controlled System:** In this TDDS, the drug is dispersed in an insoluble matrix of rigid non-swellable hydrophobic material. The rigid matrix is made up of insoluble plastics, **e.g.,** PVC and fatty acid materials, like stearic and beeswax. The drug is kneaded with the PVC solution in an organic solvent and granulated waxy matrix is prepared by dispersing the drug in molten fat followed by congealing. The obtained granules are lastly compressed into tablets. Swellable matrix system is useful for sustaining the release of highly water-soluble drugs.

   Hydrophilic gums, materials of natural origin (guar gum and tragacanth), semi-synthetic materials (HPMC and CMC), or synthetic materials (poly ceramides) are generally suitable for such matrices. The drug and gum are granulated together with a solvent (alcohol) and compressed into tablets. Drug release from such dehydrated hydrogels involves simultaneous absorption of water and desorption of drug via swelling-controlled diffusion mechanism, in which the gum swells and the drug diffuse out of it.

4) **Microsealed Dissolution-Controlled System or Encapsulation:** In this TDDS, the drug particles are coated or encapsulated by any microencapsulation technique using slowly dissolving materials (**e.g.,** cellulose, PEGs, polymethacrylates, waxes). The obtained pellets are filled in the hard gelatin capsules. The dissolution rate of coating depends on its solubility and thickness (ranging from 1-200 microns).

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6.1.9. Evaluation

The evaluation of TDDS involves the following approaches:

1) **Interaction Studies:** Excipients form the integral part of most of the pharmaceutical dosage forms. Stability of a formulation depends on drug-excipients compatibility. A stable product can be produced only if the drug and excipients are compatible; therefore, any potential physical or chemical interaction that may affect the bioavailability and stability of the drug should be detected. If new excipients that have not been used in formulations containing the active substance are used, the compatibility studies hold an important role in formulation development. Interaction studies are carried out in thermal analysis, FTIR, UV spectroscopy, and chromatographic techniques by comparing their physicochemical characters, such as assay, melting endotherms, characteristic wave numbers, absorption maxima, etc.

2) **Patch Thickness:** The thickness of prepared drug-loaded patches is measured at different points by using a digital micrometer. This also determines the average thickness and standard deviation to ensure that the thickness of the prepared patch is within the standard limits.

3) **Weight Uniformity:** Before beginning the test, the prepared patches are dried at 60°C for 4 hours. A specified area of patch is cut from different parts of the patch and weighed in a digital balance. The average weight and standard deviation values are calculated from the individual weights.

4) **Folding Endurance:** A strip of specific area is cut from the prepared patches and repeatedly folded at the same place till it breaks. The number of times the film has been folded at the same place without breaking denotes the folding endurance value.

5) **Percentage Moisture Content:** The prepared patches are individually weighed and kept in a desiccator (containing fused calcium chloride) for 24 hours at room temperature. After 24 hours, the patches are reweighed to determine the percentage moisture content using the formula:

$$\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

6) **Percentage Moisture Uptake:** The prepared patches are individually weighed and kept in a desiccator (containing a saturated solution of potassium chloride) for 24 hours at room temperature to maintain 84% RH. After 24 hours, the patches are reweighed to determine the percentage moisture uptake using the formula:

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

7) **Water Vapour Permeability (WVP):** This can be determined with the foam dressing method, in which the air-forced oven is replaced with a natural air circulation oven. WVP of the prepared patches (expressed in gm/m^2 per 24 hours) can be determined using the formula:

$$WVP = W/A$$

Where, W = Amount of vapour permeated through the patch (gm per 24 hours);
A = Surface area of the exposure samples (m^2).

8) **Drug Content:** A specified area of the prepared patch is dissolved in a suitable solvent taken in a specific volume. The obtained solution is filtered through a filter medium and the drug content is analysed with UV spectroscopy or HPLC technique. Each value represents the average value of three different samples.

9) **Uniformity of the Dosage Unit Test:** An accurately weighed portion of the prepared patch is cut into small pieces and transferred to a volumetric flask containing a specific volume of suitable solvent. The patch is dissolved in the solvent, sonicated for complete extraction of the drug from the patch, and made up to the mark with the same. The resulting solution is left undisturbed for an hour and the supernatant is diluted with a suitable solvent to obtain the desired concentration. The solution is filtered through a 0.2µm membrane, analysed by UV spectroscopy or HPLC technique, and the drug content per piece is determined.

10) **Polariscope Examination:** This test examines the drug crystals from the prepared patch by a polariscope. A piece of specific surface area is cut from the patch, kept on the object slide, and observed for the drug crystals to determine whether the drug in the patch is in crystalline form or in amorphous form.

11) **Shear Adhesion Test:** This test is performed for measuring the cohesive strength of an adhesive polymer, which can be influenced by the molecular weight, degree of cross-linking, polymer composition, and the type and amount of tackifier added. An adhesive-coated tape is applied on a stainless steel plate, a specified weight is hung from the tape to affect it, and pulled in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time taken to pull the tape off the plate. Longer the time taken for removal, greater is the shear strength.

12) **Peel Adhesion Test:** The force required to remove an adhesive coating from a test substrate is the peel adhesion. Peel adhesion properties can be determined by molecular weight of the adhesive polymer and the type and amount of additives added. In this test, a single tape is applied to a stainless steel plate or a backing membrane of choice. Then the tape is pulled from the substrate at 180° angle, and the force required for removing the tape is measured.

13) **Thumb Tack Test:** This qualitative test determines the tack property of the adhesive. In this test, the thumb is pressed on the adhesive and the relative tack property is detected.

14) **Flatness Test:** In this test, three longitudinal strips are cut from each film at different portions (one from the centre, one from the left side, and another from the right side). Length of each strip is measured and variation in length due to non-uniformity in flatness is also measured by determining the percent constriction (with 0% constriction equivalent to 100% flatness).

15) **Percentage Elongation Break Test:** The percentage elongation break is determined by recording the length just before the break point. Percentage elongation value can be determined using the formula:

$$\text{Elongation percentage} = \frac{L1 - L2}{L2} \times 100$$

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Where, L1 = Final length of each strip.
L2 = Initial length of each strip.

16) **Rolling Ball Tack Test:** This test measures the softness of a polymer that relates to tack. In this test, a stainless steel ball (7/16 inches in diameter) is released on an inclined track so that it rolls down and comes in contact with the horizontal, upward facing adhesive. Distance travelled by the ball along the adhesive is the measurement of tack (expressed in inches).

17) **Quick Stick (Peel-Tack) Test:** In this test, the tape is pulled away from the substrate at 90° angle at a speed of 12 inches/min. The peel force required to break the bond between the adhesive and the substrate is the tack value (expressed in ounces or gm/inch width).

18) **Probe Tack Test:** In this test, the tip of a clean probe having a defined surface roughness is brought into contact with the adhesive. When a bond is formed between the probe and the adhesive, the subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at a fixed rate is the tack value (expressed in grams).

19) ***In vitro* Drug Release Studies:** USP apparatus V (paddle over disc) is used for determining drug release from the prepared patches. Dry films of known thickness are cut in a definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate is placed in 500ml of dissolution medium or phosphate buffer (pH 7.4) and the apparatus is equilibrated to 32±0.5°C.

The paddle is set at a distance of 2.5cm from the glass plate and operated at a speed of 50rpm. Samples of 5ml aliquots are withdrawn at appropriate time intervals for up to 24 hours and analysed by UV spectroscopy or HPLC technique. This experiment is performed in triplicate to calculate the mean value.

20) ***In vitro* Skin Permeation Studies:** This test is carried out by using diffusion cells. Male Wistar rats (weighing 200-250gm) are selected and hair from the abdominal region is removed using an electric clipper. The dermal side of the skin is cleaned properly with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer (pH 7.4), and then placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant.

The cell temperature is maintained at 32±0.5°C using a thermostatically controlled heater. The isolated rat skin piece is placed between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Definite volume of sample is removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is added simultaneously. Samples are filtered through the filtering medium, and analysed by UV spectroscopy or HPLC technique. Flux can be determined directly from the slope of the curve between the steady state values of the amount of drug permeated (mg/cm^2) and time (hours), and permeability coefficients can be determined by dividing the flux by the initial drug load (mg/cm^2).

6.2. SUMMARY

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

1) A **transdermal** or **skin patch** is a medicated adhesive patch that is applied on the skin to deliver a specific dose of drug into the systemic circulation through the skin.
2) TDDS are preferred over injectables and oral routes as they increase patient compliance and avoid first-pass metabolism.
3) Transdermal route has competed with oral route as the most successful innovative research area in drug delivery because treatment through oral route aims to attain and maintain drug concentration in the body within a therapeutically effective range.
4) The TDDS aims to achieve systemic levels of medication through topical application on intact skin.
5) Skin receives about $1/3^{rd}$ of all blood circulating through the body. **Epidermis**, having 150µm thickness, arises from an active epithelial basal cell population.
6) Epidermis comprises of five layers, namely **stratum germinativum** (basal layer), **stratum spinosum** (spinous layer), **stratum granulosum** (granular layer), **stratum lucidium**, and **Stratum Corneum** (SC), from inside to outside.
7) **Dermis** or corium is a firm connective tissue (of mesoderm origin) on which the epidermis is present. It comprises of a dense network of connective tissue, having bundles of collagen fibres mingled with elastic tissue in the superficial levels.
8) **Transdermal permeability coefficient** is linearly dependent on partition coefficient.
9) Transdermal permeability across mammalian skin is a passive diffusion process that depends on the concentration of penetrant molecule on the skin surface.
10) Transdermal permeability can be increased by hydration of SC layer.
11) Increase in skin temperature enhances the skin permeation rate.
12) Polymers form the backbone of TDDS, and control drug release from the device. A polymer matrix can be prepared by dispersing drug in a liquid or solid state synthetic polymer base.
13) The **polar pathway** can be altered by causing protein conformational change or by solvent swelling.
14) The **non-polar pathway** can be altered by altering the rigidity of lipid structure and by fluidising the crystalline pathway, which in turn increases diffusion.
15) The **fatty acid enhancers** increase the fluidity of lipid portion of the SC layer. Some enhancers or binary vehicles act on both polar and non-polar pathways by altering the multi-laminate pathway for penetrants.
16) **Ultrasonic energy** is used in this process to enhance the transdermal delivery of solutes through pre-treatment.
17) **Sonophoresis** involves exposure of intercellular lipids to ultrasound waves, which disrupt the stratum corneum, form gaseous cavities, and consequently increase the skin permeability.
18) **Iontophoresis** involves the oppositely charged ions are driven or repelled through the dermal layers into the area to be treated (either into the surrounding tissues for localised treatment or into the systemic circulation for systemic treatment).

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19) **PSAs** are materials that adhere to a substrate (skin in TDDS) with the application of light force and leave behind no residue on removal.
20) In **membrane patches**, a delivery rate-controlling membrane is present between the drug reservoir and skin. **Microporous membranes** (control drug flux by the size and tortuosity of pores in the membrane) or dense polymeric membranes (through which the drug permeates by dissolution and diffusion) can also be used.
21) **Drug in microreservoir** TDDS is a combination of reservoir and matrix-dispersion systems.
22) An **example** of **structure-based system** belonging to this class of TDDS is microneedles, developed by Alza and called **Macroflux**.
23) In **matrix diffusion controlled TDDS**, the drug is dispersed in an insoluble matrix of rigid non-swellable hydrophobic material. The rigid matrix is made up of insoluble plastics, **e.g.,** PVC and fatty acid materials, like stearic and beeswax.
24) In **microsealed dissolution-controlled system or encapsulation TDDS**, the drug particles are coated or encapsulated by any microencapsulation technique using slowly dissolving materials (**e.g.,** cellulose, PEGs, polymethacrylates, waxes).
25) **Water Vapour Permeability (WVP)** can be determined with the foam dressing method, in which the air-forced oven is replaced with a natural air circulation oven.
26) **Shear adhesion test** is performed for measuring the cohesive strength of an adhesive polymer, which can be influenced by the molecular weight, degree of cross-linking, polymer composition, and the type and amount of tackifier added.
27) USP apparatus V (paddle over disc) is used for determining drug release from the prepared patches.

6.3. EXERCISE

6.3.1. Very Short Answer Type Questions

1) Define transdermal patch and percentage elongation break test.
2) Write the advantages of transdermal drug delivery system.
3) Name the layers of epidermis.
4) Name the designs of developed patch-type TDDS.
5) What are the limitations of drug in adhesive matrix?
6) Write the names of the systems in formulation of TDDS.
7) Mention the formula for percentage moisture content and percentage moisture uptake.

6.3.2. Short Answer Type Questions

1) Write a note on transdermal permeation.
2) Mention the factors affecting permeation.
3) Briefly discuss about rate programmed transdermal DSS.
4) Discuss on physical stimuli-activated transdermal DSS

6.3.3. Long Answer Type Questions

1) Explain in detail about the components of TDDS.
2) Write a brief note on formulation and evaluation of TDDS.

CHAPTER 7

Gastroretentive Drug Delivery System

7.1. GASTRORETENTIVE DRUG DELIVERY SYSTEM (GRDDS)

7.1.1. Introduction

Gastroretentive drug delivery is a newly discovered drug delivery system. Main approach of this delivery is to prolong the drug's gastric residence time, thus targeting site-specific drug release in the upper GIT for local or systemic effects. Dosage forms formulated as gastroretentive drug delivery system remain in the gastric region for prolonged periods, and thus the Gastric Retention Time (GRT) of such drugs increases significantly. Many gastroretentive drug delivery approaches have been developed over the last few decades. **For example,**

1) **High Density (Sinking) System:** In this system, the drug is retained in the bottom of the stomach.
2) **Low Density (Floating) System:** This system causes buoyancy in gastric fluid.
3) **Mucoadhesive System:** This system causes bioadhesion of the drugs to stomach mucosa.
4) **Unfoldable, Extendible, or Swellable System:** This system limits emptying of the dosage forms through the pyloric sphincter of stomach.
5) **Superporous Hydrogel System and Magnetic System:** These are some other examples of GRDDS.

Various gastroretentive approaches have been discussed here that have recently became popular in the field of site-specific orally administered controlled release drug delivery systems.

Tables 7.1 and **7.2** enlist the drug candidates that are considered suitable and unsuitable for GRDDS:

Table 7.1: Potential Drug Candidates For GRDDS

Suitable Drug Candidates	Examples
Drugs acting locally in the stomach	Antacids, Anti-ulcer drugs, Anti-*H. pylori*, Misoprostol, Clarithromycin, and Amoxicillin.
Drugs with narrow absorption window in GIT	Cyclosporine, Methotrexate, Levodopa, Repaglinide, Riboflavin, Furosemide, *para*-Aminobenzoic Acid, Atenolol, and Theophylline.
Drugs having unstable properties in the intestinal or colonic environment	Captopril, Ranitidine HCl, Metronidazole, and Metformin HCl.
Drugs causing imbalance of normal colonic microbes	Antibiotics against *H. pylori* and Amoxicillin Trihydrate.
Drugs having low solubility at high pH values	Diazepam, Chlordiazepoxide, Furosemide, and Verapamil HCl.

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Table 7.2: Unsuitable Drug Candidates For GRDDS

Unsuitable Drug Candidates	Examples
Drugs having very limited acid solubility	Phenytoin
Drugs exhibiting instability in the gastric environment	Erythromycin
Drugs used for selective release in the colon	5-Amino salicylic acid & Corticosteroids

7.1.2. Advantages

Following are the advantages of GRDDS:

1) It increases the bioavailability and curative efficiency of drugs.
2) It increases the economic usage of dosage.
3) It reduces the risk of antibiotic resistance by stabilising therapeutic levels over prolonged periods by removing fluctuations.
4) It increases the efficiency of drug release in case of short half-life drugs.
5) It causes flip-flop of pharmacokinetics.
6) It ensures patient compliance with reduced dosage frequency.
7) It removes the drawbacks of Gastric Retention Time (GRT) and Gastric Emptying Time (GET) as the system remains buoyant on gastric fluid due to its lower bulk density than gastric fluids.
8) It is used to treat problems related to stomach and small intestine as the system sustains the drug release, thus increases the gastric residence time and provides local therapy on these organs.
9) Being a systemic and controlled drug delivery system, it reduces the chances of drug over-exposure at the diseased site.
10) It provides a narrow curative index.
11) It reduces any fluctuations in drug concentration and their effects.
12) It is a highly efficient system due to reduced counter activity by the body.
13) It provides controlled rates of fluctuation, thus a wider array is provided for selectivity in receptor activation.

7.1.3. Disadvantages

Following are the disadvantages of GRDDS:

1) It increases the level of fluids required in the stomach.
2) It is not suitable for drugs having low solubility in gastric fluid, causing gastrointestinal irritation, ineffective in acidic environment, and meant for selective release in the colon.
3) In such a system, adherence of drugs with the mucus cannot be predicted due to the continuous renewal of mucus wall of stomach.
4) GRDDS is fed into the system after the meal; the drug's residence time in stomach depends on digestive state of the subject.
5) The drug's residence time in stomach depends on the subject being positioned upright.
6) Drugs which are formulated as hydrogel-based swelling system takes longer time to swell.

7) In case of multiple administrations, concentration of drug increases in the body, and this may be life-threatening due to the possible hazard of permanent retention in stomach.
8) Super-porous systems have a drawback of problematical storage of hydrolysable and biodegradable polymers.

7.1.4. Factors Affecting Gastric Retention Time of the Dosage Form

Following factors affect the gastric retention time of the dosage form:

1) **Density:** Dosage form should have a less density than that of the gastric contents (1.004gm/ml).
2) **Size:** Dosage form with a diameter of more than 7.5mm show more gastric residence time as compared to the dosage form having 9.9mm diameter.
3) **Shape of the Dosage Form:** The tetrahedron-shaped dosage form remains for a longer period in the stomach than other devices of similar size. More predictable release profile is observed for single or multiple unit formulation, along with insignificantly impaired performance due to failure of the units.

   As compared to single unit dosage form, multiple unit formulations allow co-administration of units with different release profile or showing incompatibility with gastric substances and have a large safety margin against dosage form failure.
4) **Fed or Unfed State:** During fasting the gastrointestinal motility shows periods of strong motor activity at intervals of 1.5-2 hours. The Migrating Motor Complex (MMC) allows passing of undigested food material from the stomach; and if the timing of the formulation coincides with that of MMC, the GRT of the unit can be very short; but, MMC is delayed and GRT is longer during fasting.
5) **Nature of Meal:** The motility pattern of the stomach changes to a fed state due to intake of indigestible polymers or fatty acids. This reduces the gastric emptying rate and prolongs the drug release.
6) **Caloric Content:** Due to intake of high caloric food (such as protein and fat), GRT can be increased by 4-10 times.
7) **Frequency of Feed:** If successive meals are given, the GRT can be increased over 400 minutes in comparison to the single meal due to low frequency of MMC.
8) **Gender:** Mean ambulatory GRT in males (3.4 hours) is lesser than that of females (4.6 hours) of the same age and race, irrespective of height, weight, and body surface.
9) **Age:** Significantly longer GRT is observed in people of more than 70 years of age.
10) **Concomitant Drug Administration:** Anticholinergic drugs (**e.g.,** atropine and propantheline) and opiates (**e.g.,** codeine) can extend the GRT.

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7.1.5. Applications

Following are the applications of the GRDDS:

1) **Enhanced Bioavailability:** Riboflavin Gastroretentive Dosage From (GRDF) shows enhanced bioavailability as compared to the non-GRDF polymeric formulations. Many other processes, related to drug absorption and transit in the GIT, act concurrently to influence the drug absorption rate.
2) **Sustained Drug Delivery/Reduced Frequency of Dosing:** Drugs having short biological half-life, and sustained and slow input from GRDF enhance the pharmacokinetic factors and decrease the dosing frequency. This property increases patient compliance, and thus improves therapy.
3) **Targeted Therapy for Local Ailments in the Upper GIT:** Local therapy can be exerted on stomach and small intestine with prolonged and sustained administration of the drug from GRDF to the stomach. Such targeted therapy helps to achieve the therapeutic drug concentrations locally; while, minimal systemic concentrations are achieved after drug absorption and distribution.
4) **Reduced Fluctuations of Drug Concentration:** By continuous intake of the drug following GRDF administration, blood-drug concentrations can be maintained within a narrower range as compared to the immediate release dosage forms. This minimises the fluctuations in drug effects and prevents the adverse effects caused due to higher concentration.
5) **Site Specific Drug Delivery:** Drugs having limited absorption sites in upper small intestine can be formulated as a floating dosage form. Controlled and slow delivery of drug to the stomach provides local therapeutic levels and also limits the systemic exposure to the drug. This approach also decreases side effects caused by the drug in blood circulation. Along with this, dosing frequency is also reduced by the prolonged gastric availability from a site directed delivery system.

7.2. APPROACHES FOR GRDDS

7.2.1. Introduction

The following three strategies delay drug transit through GIT:

1) **Pharmacological Approach:** In this approach, a drug is co-administered or incorporated into the dosage form to delay gastrointestinal emptying; **for example,** antimuscarinic agents (**e.g.,** propantheline) are formulated by this approach.
2) **Physiological Approach:** Natural materials or fat derivatives (**e.g.,** triethanolamine myristate) are formulated by this approach to stimulate the duodenal or jejunal receptors for slowing gastric emptying.
3) **Pharmaceutical Approach:** Due to the related toxicity issues, the above two approaches are not used. The various pharmaceutical approaches are:
   i) **Low Density or Floating Drug Delivery System:** The bulk density of this system is less than that of gastric fluids; therefore, they remain buoyant in the stomach. Such systems are also called as Hydrodynamically Balanced Systems (HBS).

Floating can be achieved by using:

a) Effervescent System:
   - Gas-generating system, and
   - Volatile liquid-containing system.
b) Non-Effervescent System:
   - Expandable or swellable system, and
   - Inherently low density system.

ii) **High Density (Sinking) or Non-Floating Drug Delivery System:** In this system, the drug is retained in the bottom of the stomach.
iii) **Modified Shape or Unfolding System:** In this system, the drug unfolds to a large size to limit passage through pyloric sphincter.
iv) **Bioadhesive or Mucoadhesive or Gastroadhesive Drug Delivery System:** In this system, the drug adheres to the gastric mucosa.
v) Super porous hydrogel system, and
vi) Magnetic system.

7.2.2. Low Density or Floating Drug Delivery System

A careful gastric retention can achieve optimum level of drug bioavailability, and floating drug delivery system is a novel approach used for the same purpose. Drugs that undergo absorption in the stomach or upper small intestine are formulated in this system. This method has no effect on the rate of gastric emptying over a prolonged time. Since the density of floating drug delivery system is lower than that of gastric fluid, the drugs remain buoyant in the stomach and are released slowly. In stomach, the emptying of residual system is followed by the drug release. This increases the gastric retention time and controls the fluctuations in plasma drug concentration. Following are the pre-requisites for floating drug delivery system:

1) It requires a reservoir for slow content release.
2) It should be maintained at a specific gravity lower than that of gastric contents (1.004-1.01gm/cm^3)
3) It should form a cohesive gel barrier.

7.2.2.1. Mechanism of Floating Drug Delivery System

Slow release of drug is accompanied with the required rate during the system flow on the gastric contents. Release of drug is followed by removal of the residual system from the stomach. However, minimum levels of gastric contents and an appropriate level of floating force (F) are required to achieve buoyancy retention principle and to keep the dosage form buoyant over meal surface.

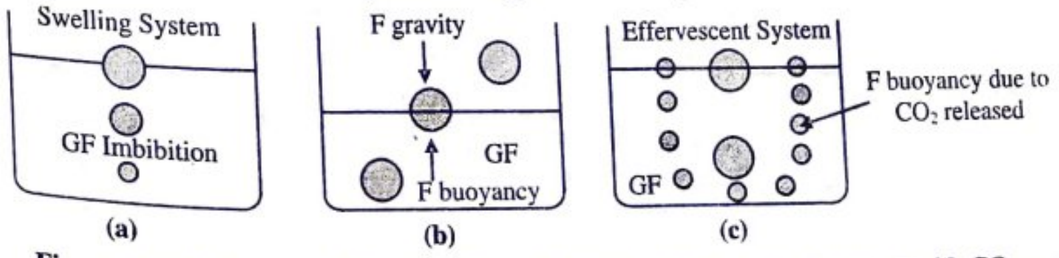


Figure 7.1: Mechanism of Floating Drug Delivery Systems, GF– Gastric Fluid, CO_2– Carbon Dioxide

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The kinetics of floating force can be measured using an apparatus that measures a force equivalent to F (with respect to time) by keeping the object submerged. If the force (F) is higher on the positive side, the flow of object is better (**figure 7.1**). By this apparatus, FDDS can be optimised and its drawbacks of unexpected intragastric buoyancy capability variations, related to stability and durability, can be prevented.

$$F = F_{buoyancy} - F_{gravity}$$

$$= (D_f - D_s)\, gv$$

Where, F = Total vertical force.
D_f = Fluid density.
D_s = Object density.
v = Volume.
g = Acceleration due to gravity.

7.2.2.2. Classification of Floating Drug Delivery System

Floating drug delivery system is classified as shown in **figure 7.2**, based on the buoyancy mechanism:

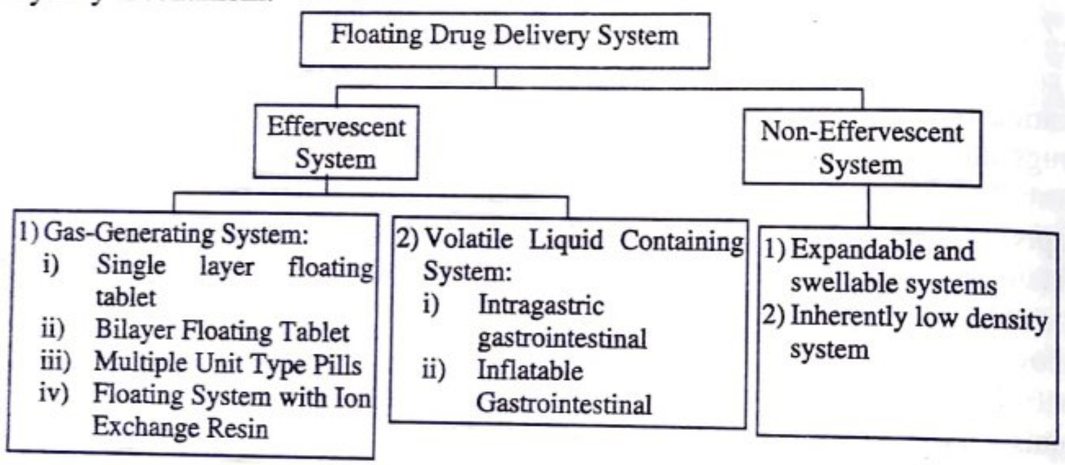


Figure 7.2: Classification of Floating System

7.2.2.3. Effervescent System

In effervescent systems, gas-generating agents, carbonates (**e.g.,** sodium bicarbonate), and other organic acids (**e.g.,** citric acid and tartaric acid) are used to produce carbon dioxide (CO_2) gas. This decreases the density of system and allows it to float on the gastric fluid. An alternative of this system involves incorporating matrix-containing portion of liquid, which produces a gas that evaporates at body temperature.

Effervescent systems are further categorised into the following **two types**:

1) **Effervescent/Gas-Generating System:** This system generates gas bubbles to achieve floatability or buoyancy. Such a buoyant system uses matrices made up of swellable polymers, such as **polysaccharides** (**e.g.,** chitosan), and effervescent components (**e.g.,** sodium bicarbonate, citric acid, or tartaric acid). The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation should be 0.76:1. In gas-generating system, carbon dioxide is released and the formulation starts floating in the stomach (**figures 7.3 and 7.4**).

Other approaches and materials include sodium alginate and sodium bicarbonate mixture, multiple unit floating dosage forms that generate carbon dioxide gas on ingestion, floating mini capsules with a core of sodium bicarbonate, lactose and PVP coated with HPMC, a floating system based on ion exchange resin technology, etc. Bilayer or multilayer system can also be formulated, in which drugs and excipients are formulated independently and the gas-generating material is incorporated in any of the layers. Further modifications include coating the matrix with a polymer that is permeable to water, but impermeable to carbon dioxide.

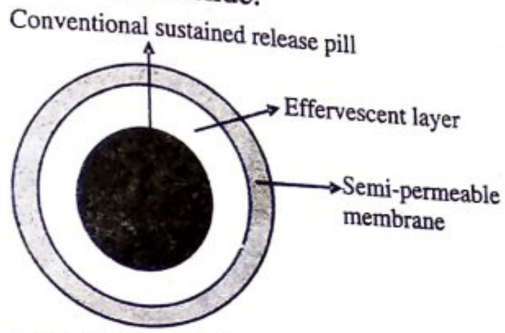


Figure 7.3: Effervescent (Gas-Generating) System

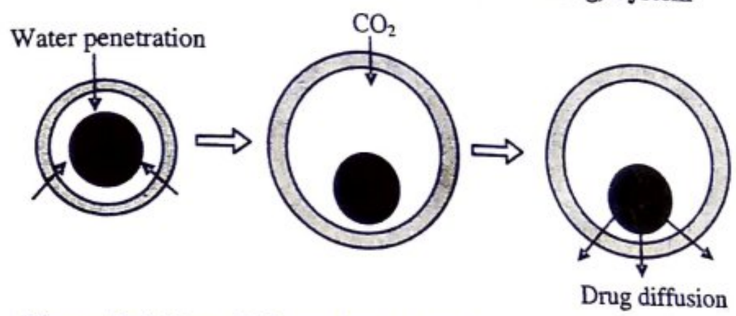


Figure 7.4: Drug Release from Effervescent (Gas-Generating) System

The main **drawback** of gas-generating system is to find a difference among elasticity, plasticity and permeability of the polymers. The gas-generating system is further categorised as follows:

i) **Single Layer Floating Tablet or Hydrodynamically Balanced System (HBS):** This system (**figure 7.5**) is formulated by mixing the drug with CO_2-generating agents within the matrix tablet. The bulk density of this system is lower than that of the gastric fluids; thus, they float in the stomach for a prolonged period, irrespective of the gastric emptying rate. The drug from this floating system is released slowly at a desired rate. Once the drug is completely released, the residual system is expelled from the stomach. This increases the GRT and controls the fluctuations in plasma drug concentration.

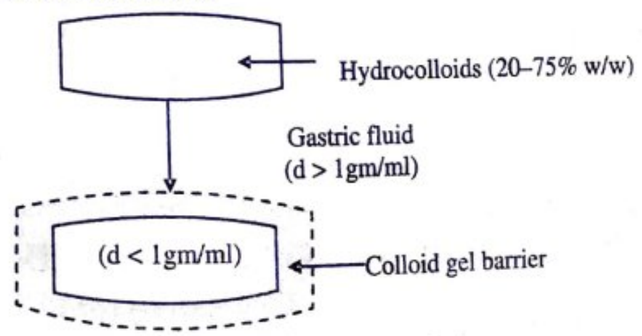


Figure 7.5: Single Layer Floating Tablet

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ii) **Bilayer Floating Tablet:** This is a two-layered compressed tablet (**figure 7.6**), which comprise of immediate release layer and sustained release layer.

iii) **Multiple Unit Type Floating Pill:** This system (**figure 7.7**) comprises of sustained release pills surrounded by double layers. The inner layer contains effervescent agents and the outer layer is of swellable membrane. On immersing the system in dissolution medium at body temperature, it immediately sinks and forms swollen pills, which float due to their low density. This lower density is obtained due to the generation and entrapment of CO_2 within the system.

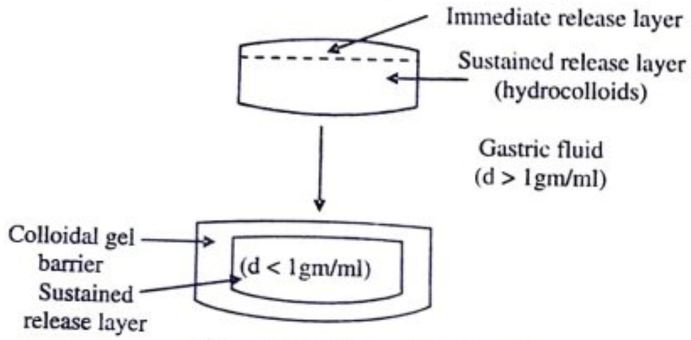


Figure 7.6: Bilayer Floating Tablet

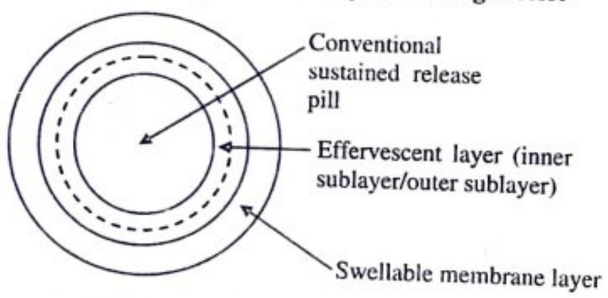


Figure 7.7: Multiple Unit Floating Tablet

iv) **Ion Exchange Resin:** It is a multiple-unit type of oral floating dosage system that prolongs the gastric emptying time of dosage form. The ion exchange resin system includes beads of drug-resin complex that are loaded with bicarbonate ions and coated with a hydrophobic polymer. When the beads reach the stomach, the chloride ions get exchanged with the bicarbonate and drug ions. The generated CO_2 gas is entrapped in the polymeric coated resins, and thus the beads float.

2) **Volatile Liquid-Containing System:** In order to sustain the GRT of a drug delivery system, it is incorporated with an inflatable chamber, containing a liquid (**e.g.,** ether, cyclopentane) that gasifies at body temperature to cause the chamber to inflate in the stomach. This system may also include a bioerodible plug (of polyvinyl alcohol, polyethylene, etc.) that gets dissolved slowly to release gas from the inflatable chamber. Thus, the chamber collapses after a pre-determined time to allow spontaneous ejection of the inflatable systems from the stomach.

i) **Intragastric Floating Gastrointestinal Drug Delivery System:** In this system (**figure 7.8**), floatation chamber is used to make the system float in the stomach. The floatation chamber is either vacuum or filled with air or a harmless gas. The drug is encapsulated within a microporous compartment.

ii) **Inflatable Gastrointestinal Delivery System:** This system is incorporated with an inflatable chamber, containing liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach (**figure 7.9**). Inflatable gastrointestinal delivery system is fabricated by loading the inflatable chamber with a drug reservoir (which can be a drug, impregnated polymeric matrix), and then encapsulating in a gelatin capsule. Once administered orally, the capsule dissolves and releases the drug reservoir, along with the inflatable chamber, which automatically inflates and retains the drug reservoir in the gastric fluid.

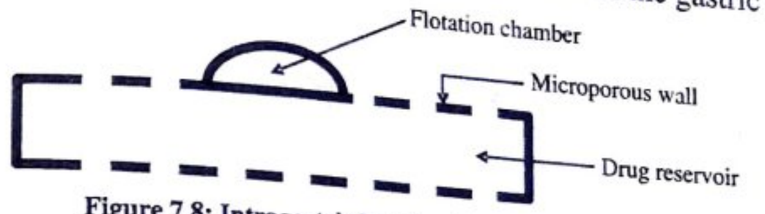


Figure 7.8: Intragastric Floating Gastrointestinal Drug Delivery System

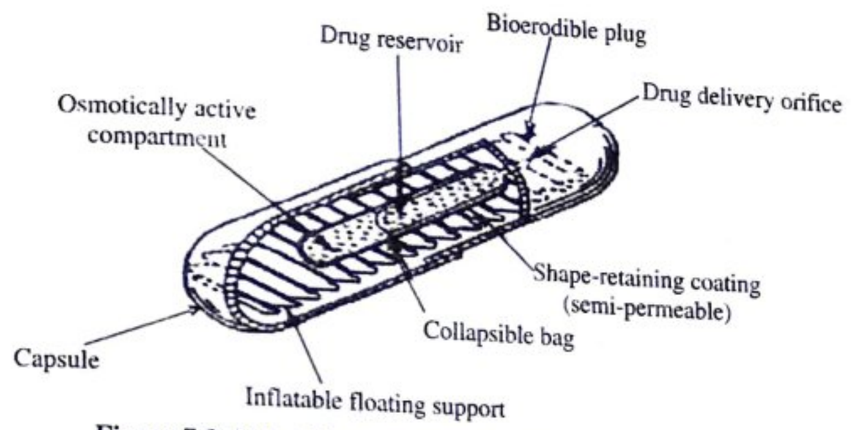


Figure 7.9: Inflatable Gastrointestinal Delivery System

7.2.2.4. Non-Effervescent System

The non-effervescent floating drug delivery system works on the mechanism of swelling of polymer or bioadhesion to mucosal layer in GIT. This system utilises gel-forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides, and matrix-forming materials (**e.g.,** polycarbonate, polyacrylate, polymethacrylate, polystyrene), and bioadhesive polymers (**e.g.,** chitosan) as the most common excipients.

The non-effervescent system is of the following **types**:

1) **Expandable or Swellable System:** If the dosage form is bigger than the pyloric sphincter, it will withstand gastric transit in the stomach. But the dosage form should be small enough to be swallowed, and should not cause gastric obstruction, either alone or by accumulation. Therefore, expandable or swellable system (**figure 7.10**) is formulated such to prolong the gastric retention time:
   i) A small configuration for oral intake,
   ii) An expanded gastroretentive form, and
   iii) A final small form that enables evacuation after drug release from the device.

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Gastroretentivity can be improved by combining substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Recently, various swellable systems have been investigated to develop an effective GRDDS. Swellable systems, owing to their mechanical properties, are also retained in the GIT. Swelling occurs by osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid (**figure 7.10**).

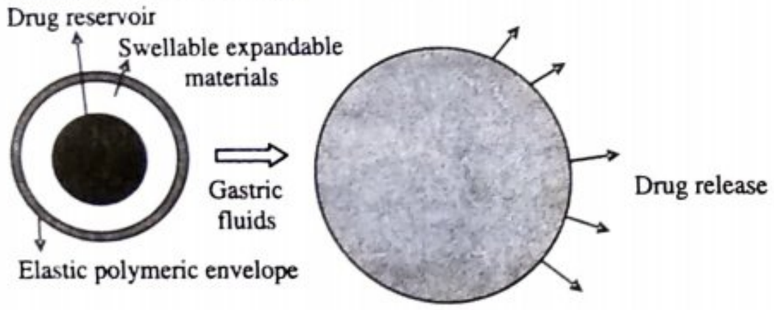
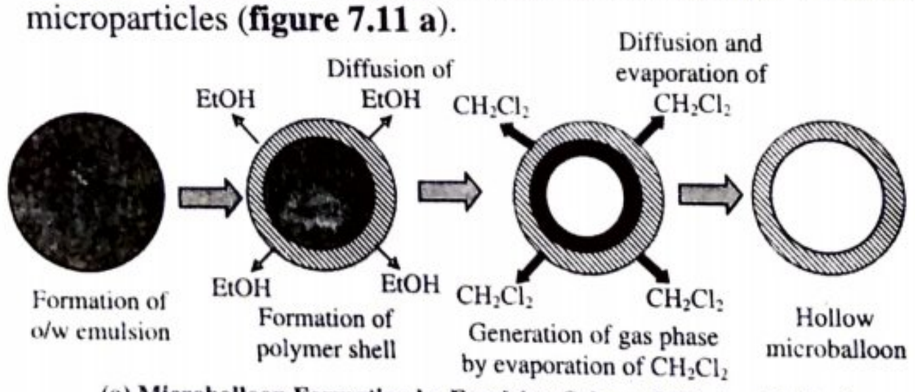
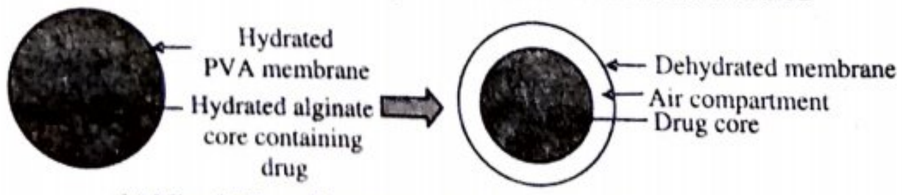


Figure 7.10: Drug Release from Swellable System

2) **Inherently Low Density System:** This system is a solution to the previous system that settles down initially before floating, and thus poses a risk of premature gastric emptying. Inherently low density system can be provided by one of the two ways:
   i) **Entrapment of Air (Hollow Mircrospheres/Microballoons):** These can be prepared by the following methods:
      a) **Emulsion-Solvent Diffusion Method:** In this method, solution of polymer and drug (in ethanol/methylene chloride) is mixed with an agitated aqueous solution of polyvinyl alcohol. Ethanol rapidly divides into the external aqueous phase, and the polymer precipitates around methylene chloride droplets. The entrapped methylene chloride undergoes evaporation and forms internal cavities in the microparticles (**figure 7.11 a**).



(a) Microballoon Formation by Emulsion-Solvent Diffusion Method



(b) Microballoon Formation by Dehydration of Swollen Hydrogel

Figure 7.11: Microballoons for GRDD

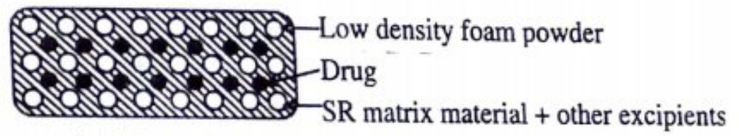
   b) **Modified Solvent Evaporation Method:** In this method, the drug powder is dispersed in a 1:1 solution of cellulose acetate butyrate and Eudragit RL 100 in acetone. The resultant dispersion is pressurised

under carbon dioxide gas, which dissolves and form bubbles to release the pressure. Once the bubbles are formed, the system is immediately emulsified into an external oil phase. Some of the generated carbon dioxide bubbles are entrapped in the dispersed drug-polymer droplets and form internal cavities in the hardened microspheres.

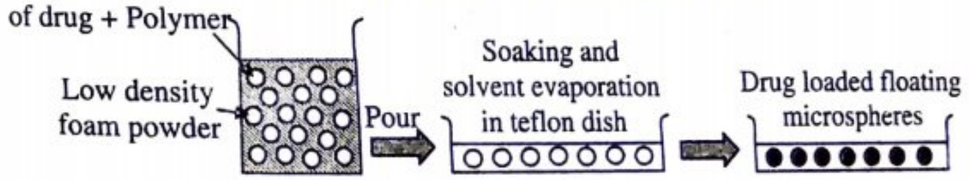
   c) **Dehydration of Swollen Hydrogel:** In this method, each single unit of this multiple-unit system is made up of a hydrated drug-loaded calcium alginate core, coated with a polyvinyl alcohol membrane. An air compartment is formed when the hydrogel dries and results in the shrinkage of hydrated core (**figure 7.11 b**).

   d) **Hollow Chamber System:** This system is prepared by coating the drug on hollow cores (such as pop rice, empty gelatin capsules, or polystyrene beads), and then coating the drug with rate-controlling membrane.

ii) **Incorporation of Low Density Materials:** In this method, inherently low density materials (fats or low density polymers) are used for the preparation of floating drug matrices. **For example,** a floating system made up of polypropylene foam powder, matrix-forming polymer(s), drug, and a filler (**figure 7.12a**). The highly porous foam powder is used to provide a low density, so that excellent *in vitro* floating behaviour of the system can be obtained. Microporous foam particles are soaked in an organic solution of the drug and polymer (**e.g.,** Eudragit RS 100) and then dried to form polypropylene foam powder based floating drug microparticles (**figure 7.12 b**).



(a) Matrix Tablet Based on Foam Powder



(b) Foam Powder Based Drug Microsphere Preparation

Figure 7.12: GRDDS Based on Foam Powder

7.2.3. High Density (Sinking) or Non-Floating Drug Delivery System

In high density or non-floating drug delivery system, dosage forms having density more than that of the normal stomach content (~1.004gm/cm^3) are formulated. Such formulations are prepared by coating the drug on a heavy core or by mixing the drug with inert materials (like iron powder, barium sulphate, zinc oxide, titanium oxide, etc.). These materials increase the density by up to 1.5-2.4gm/cm^3. A density of about 2.5gm/cm^3 is essential for significant prolongation of gastric residence time. But, this system is not effective in humans, and thus such dosage form are not marketed.

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7.2.4. Modified Shape or Unfolding System

Modified shape or unfolding system unfolds to a large size to limit passage through pyloric sphincter. In this system, drugs are incorporated in several geometric shapes (like tetrahedron, ring, cloverleaf, disc, string, spiral, and pellet/sphere), so that they can be tightly packed into a gelatin capsule and unfold in the stomach after the dissolution of capsule shell.

Modified shape or unfolding system comprises of at least one erodible polymer, one non-erodible polymer, and a drug dispersed in the polymer matrix. The main drawback of this system is that the expanded material remain for a long time in the stomach.

7.2.5. Bioadhesive or Mucoadhesive or Gastroadhesive Drug Delivery System

In gastroadhesive drug delivery system, a mucoadhesive polymer is used that adheres to the gastric mucosal surface and prolong its gastric retention time in the GIT. The property of mucoadhesive polymers to adhere to the mucus layer makes them very useful excipients in GRRDS. Mucoadhesive polymers can be of natural origin (**e.g.,** sodium alginate, gelatin, guar gum, etc.) or of semi-synthetic (**e.g.,** HPMC, carbopol, sodium carboxymethyl cellulose). Mucoadhesive polymers can be cationic, anionic, or neutral.



Figure 7.13: Mucoadhesive Drug Delivery System

Adhesion of these polymers to mucus membrane is facilitated by hydration, bonding, or receptor-mediated adhesion. In **hydration-mediated adhesion**, hydration of hydrophilic polymer makes it sticky and mucoadhesive. In **bonding-mediated adhesion**, a mechanical or chemical bonding is involved. Chemical bonding involves ionic or covalent bonds or Van der Waal forces between the polymer molecule and the mucus membrane.

In **receptor-mediated adhesion**, certain polymers adhere on specific receptors expressed on gastric cells.

1) **Hydration-Mediated Adhesion:** Some hydrophilic polymers acquire bioadhesive properties by imbibing a large amount of water and becoming sticky. By controlling the dissolution rate of the polymers, the prolonged gastroretention of the bio/muco-adhesive delivery system can be controlled.
2) **Bonding-Mediated Adhesion:** In this type of adhesion, polymers adhere to mucus/epithelial cell surface through various bonding mechanisms. Deposition and inclusion of the adhesive material in the crevices of mucosa may form physical or mechanical bonds. Secondary chemical bonds, that provide bioadhesive properties, comprises of dispersive interactions (i.e., Van der Waals forces) and stronger specific interaction, which include on the cell surface. In receptor-mediated hydrogen bonds, the hydroxyl (OH) and the carboxylic groups (COOH) are the hydrophilic functional groups that form hydrogen bonds.

3) **Receptor-Mediated Adhesion:** Some polymers bind to specific receptor sites following the mechanism of bio/muco-adhesion, and thus enhance the gastric retention of dosage forms. Some plant lectins (tomato lectins) undergo specific interaction with the sugar groups present in mucus or on the glycocalyx.

7.2.6. Super-Porous Hydrogel System

The super-porous hydrogel system is different from the conventional type system to warrant separate classification. This system involves improvement of the gastric retention time of super porous hydrogels of average pore size >100µm. The super-porous hydrogels swell to equilibrium size within 60 seconds due to rapid water uptake by capillary wetting through numerous interconnected open pores. The super-porous hydrogels swell to a large size (swelling ratio: 100 or more) and gain sufficient mechanical strength to withstand pressure by gastric contraction. The super-porous hydrogel system is used to formulate hydrophilic particulate materials.

7.2.7. Magnetic System

The magnetic system is used to increase the gastric retention time. It is based on the principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of stomach. Although it has been observed that magnetic system works, the external magnet should be placed with a degree of precision that might compromise patient compliance.

7.3. SUMMARY

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

1) Main approach of gastroretentive delivery is to prolong the drug's gastric residence time, thus targeting site-specific drug release in the upper GIT for local or systemic effects.
2) In **high density (sinking) system**, the drug is retained in the bottom of the stomach.
3) **Low density (floating) system** causes buoyancy in gastric fluid.
4) **Mucoadhesive system** causes bioadhesion of the drugs to stomach mucosa.
5) **Unfoldable, extendible, or swellable system** limits emptying of the dosage forms through the pyloric sphincter of stomach.
6) Dosage form should have a less density than that of the gastric contents (1.004gm/ml).
7) The tetrahedron-shaped dosage form remains for a longer period in the stomach than other devices of similar size.

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CHAPTER 8

Nasopulmonary Drug Delivery System

8.1. NASAL ROUTES OF DRUG DELIVERY

8.1.1. Introduction

Nasal mucosa is considered a potential administration route to achieve faster and higher level of drug absorption. This is because nasal mucosa in comparison to gastrointestinal mucosa is permeable to more compounds due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus, and less dilution by gastrointestinal contents.

Nasal drug delivery is in practice since thousands of years. Drugs that are potent (active in low doses) and show no minimal oral bioavailability (proteins and peptides) are successfully delivered by the nasal route. Peptides and proteins show low degree of absorption via nasal route as they rapidly move away from the absorption site in the nasal cavity due to mucociliary clearance mechanism.

The **ideal properties** for a nasal drug candidate are:

1) It should exhibit appropriate aqueous solubility to provide the desired dose in a 25-150ml volume of formulation administration per nostril.
2) It should exhibit appropriate nasal absorption properties.
3) It should not produce nasal irritation.
4) It should exhibit appropriate clinical rationale for nasal dosage forms, **e.g.,** rapid onset of action.
5) It should be potent, i.e., should be effective below 25mg per dose.
6) It should not produce toxic nasal metabolites.
7) It should not exhibit offensive odour/smell.
8) It should exhibit appropriate stability characteristics.

8.1.2. Advantages

Nasal drug delivery has the following advantages:

1) Drug absorption through this route is rapid due to highly vascularised mucosa.
2) A large nasal mucosal surface area is available for drug absorption.
3) Its onset of action is rapid.
4) It is a non-invasive technique and the drugs can be easily administered.
5) It bypasses the blood-brain barrier.
6) It does not undergo degradation in GIT.
7) It does not undergo hepatic first pass metabolism.
8) It shows improved bioavailability.
9) Small drug molecules exhibit good nasal bioavailability.
10) Bioavailability of large drug molecules can be increased by adding absorption enhancers in the formulation.

11) Drug candidates that cannot be given via oral route can be successfully administered through nasal route.
12) It can be used as an alternative to parenteral route for proteins and peptides.
13) It is a convenient route for the patients on long-term therapy.
14) Since it delivers low doses of drugs, it produces minimum side effects.
15) It improves patient convenience and compliance.
16) It eases self-administration.
17) It directly delivers the drug into systemic circulation and CNS.
18) It offers lower risk of overdose.
19) It does require any complex formulation.

8.1.3. Disadvantages

Nasal drug delivery has the following disadvantages:

1) The drug delivery volume in nasal cavity is restricted to 25-200µl.
2) Drugs with high molecular weight (mass cut off ~1 kDa) cannot be delivered through this route.
3) This route is adversely affected by pathological conditions.
4) Large interspecies variability is observed in this route.
5) Drug permeability is affected by normal defence mechanisms, like mucociliary clearance and ciliary beating.
6) Some drugs, like Budesonide and Azilactine, irritate the nasal mucosa.
7) Systemic toxicity occurs due to the absorption enhancers added in the formulation.
8) The absorption surface is smaller than that of the GIT.
9) There is a chance of nasal irritation, hence it is inconvenient as compared to the oral route.
10) It faces the enzymatic barrier to permeability of drug.

8.1.4. Mechanism of Drug Absorption from Nose

When a drug absorbs from the nasal cavity, it first passes through the mucus. This passage is difficult for large or charged particles; however, the small or uncharged particles can easily cross the mucus layer. Absorption through nasal mucosa involves mechanisms of paracellular transport (i.e., movement between the cell) and transcellular or simple diffusion (i.e., across the membrane):

1) The **first mechanism** involves slow and passive aqueous route of transport or the paracellular route. Drugs with molecular weight >1000 Daltons show poor bioavailability via this route as molecular weight and absorption are inversely related.
2) The **second mechanism** involves transcellular process, i.e., transport through a lipoidal route. Lipophilic drugs that show a rate dependency on their lipophilicity are transported by this process. Drugs also cross the cell membranes via active transport route through carrier-mediated transport through the opening of tight junctions. **For example**, the natural biopolymer, chitosan, opens tight junctions between epithelial cells to facilitate drug transport.

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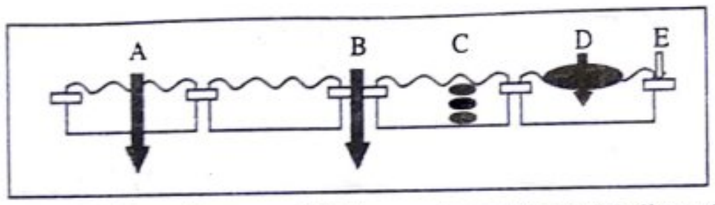


Figure 8.1: Drug Transport Pathways Across the Epithelium. (A) Paracellular Transport, (B) Transcytosis, (C) Carrier-Mediated Transport, and (D) Intercellular Tight Junction

8.1.5. Factors Influencing Nasal Drug Absorption

The systemic bioavailability of drugs administered through nasal route is affected by several factors. These factors significantly help the drugs to reach the therapeutic blood levels on nasal administration. These factors include physiochemical properties of the drugs, anatomical and physiological properties of the nasal cavity, and the type and characteristics of selected nasal drug delivery system:

1) **Physiochemical Properties of Drug:** These include:
   i) **Molecular Size:** Drug absorption through nasal route is influenced by the drug's molecular size. The molecular weight and permeation rate of lipophilic drugs are directly related while those of water-soluble drugs are inversely related. The permeation rate is highly sensitive to drugs with molecular weight ≥300 Daltons.
   ii) **Lipophilic-Hydrophilic Balance:** Drug absorption is also affected by the hydrophilic and lipophilic nature of the drug. Increase in lipophilicity of a drug increases its permeation through nasal mucosa. Although nasal mucosa was found to be of hydrophilic nature, these mucosae are primarily lipophilic in nature and the lipid domain plays an important role in their barrier function.
   iii) **Enzymatic Degradation in Nasal Cavity:** Since peptides and proteins have low bioavailability across the nasal cavity, they may undergo enzymatic degradation in the lumen of the nasal cavity or while crossing the epithelial barrier.

2) **Nasal Effect Factors:** These include:
   i) **Nasal Membrane Permeability:** This factor plays a significant role in the absorption of drug through nasal route. The water-soluble drugs and large molecular weight drugs (**e.g.,** peptides and proteins) have low membrane permeability, and thus get absorbed in low amounts via endocytotic transport mechanism.
   ii) **Environmental pH:** This factor also plays an important role in the efficiency of drug absorption through nasal route. It was observed that in rats, the nasal absorption of small water-soluble drugs (**e.g.,** benzoic acid, salicylic acid, and alkaloid acid) occurred to the greatest extent at the pH values where these compounds are in non-ionised form.
   iii) **Mucociliary Clearance:** This process is a function of the upper respiratory tract to prevent the entry of noxious substances (i.e., allergens, bacteria, viruses, toxins, etc.) in lungs. When these materials adhere to or dissolve in the mucus lining of the nasal cavity, they get transported towards the nasopharynx to be discharged into the GIT.

   iv) **Cold, Rhinitis:** Drug bioavailability is commonly affected by rhinitis. It is mainly classified into allergic rhinitis, and the common symptoms are hypersecretion, itching and sneezing caused by the viruses, bacteria, or irritants.

3) **Delivery Effect Factors:** Delivery of drug across the nasal mucosa is affected by the surfactants, dose pH, osmolarity, viscosity, particle size, nasal clearance, and drug structure, and these factors improve drug absorption:
   i) **Formulation (pH, Concentration, and Osmolarity):** Drug permeation can be affected by the pH of formulation and nasal surface. The pH of nasal formulation should be between 4.5 and 6.5 to avoid nasal irritation as lysozyme found in nasal secretions destroys certain bacteria under acidic conditions.

   On the other hand, the lysozyme is inactivated and the tissue becomes vulnerable to microbial infection under alkaline conditions. Apart from avoiding irritation, it also obtains efficient drug permeation and prevents bacterial growth.

   Concentration gradient plays a significant role in absorption or permeation of drug through nasal membrane due to nasal mucosal damage. **For examples**, nasal absorption of L-tyrosine increases with drug concentration in nasal perfusion experiments; nasal absorption of salicylic acid decreases with drug concentration due to nasal mucosa damage by the permanent.

   Osmolarity of the dosage form affects the nasal absorption of drug. Sodium chloride concentration of the formulation affects the nasal absorption. Maximum absorption was achieved by 0.462M sodium chloride concentration; higher concentration increases the bioavailability and also causes toxicity of the nasal epithelium.

   ii) **Drugs Distribution and Deposition:** The efficiency of nasal absorption is influenced by drug distribution in the nasal cavity. Distribution of drug in nasal cavity is also affected by the mode of drug administration, which eventually determines the absorption efficiency of a drug. The absorption and bioavailability of nasal dosage forms depends on the disposition site.

   Anterior chamber of nasal cavity provides a prolonged nasal residential time for disposition of formulation, and thus improves the drug absorption. Posterior chamber of nasal cavity will use for the deposition of dosage form; it is eliminated by mucociliary clearance process and hence lowers the bioavailability.

   iii) **Viscosity:** A formulation with high viscosity increases contact time between the drug and the nasal mucosa, and thus increases the permeation time. Also, formulations with high viscosity hamper the normal functions, like ciliary beating or mucociliary clearance, and alter the drug permeability.

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8.1.6. Barriers to Nasal Absorption

Nasal drug delivery system is a profitable route for the formulation scientists due to its easy and simple formulation strategies. Therapeutic efficacy and toxicity of the drugs administered intranasally are influenced by the barriers to the absorption of drugs through nasal cavity:

1) **Low Bioavailability:** Absorption of lipophilic drugs from the nasal cavity is much more than that of polar drugs. Pharmacokinetic profiles of lipophilic drugs are similar to those obtained after an intravenous injection and bioavailability approaching 100%. **For example**, both intravenous and nasal administration of Fentanyl reaches its t_{max} very rapidly (7 minutes or less) and its bioavailability for anterior chamber of nasal cavity can decrease clear administration was near 80%. **Table 8.1** enlists the strategies for improving nasal bioavailability of drugs:

Table 8.1: Strategies to Improve Nasal Bioavailability

i)	Nasal enzyme inhibitors, **e.g.,** bestatin, amastatin, boroleucine, fusidic acids, and bile salts.
ii)	Nasal permeation enhancers, **e.g.,** cyclodextrins, surfactants, saponins, fusidic acids, and phospholipids.
iii)	Prodrug approach, **e.g.,** cyclic prodrug, esters, and derivatisation of C and N termini.
iv)	Nasal mucoadhesives in nasal drug delivery, **e.g.,** carbopol, polycarbophil, cellulose derivatives, lecithin, and chitosan.
v)	Particulate drug delivery, **e.g.,** microspheres, nanoparticles, and liposomes.

2) **Low Membrane Transport:** This significant factor involves rapid clearance of the administered formulations (drugs not easily absorbed across the nasal membrane) from the nasal cavity due to mucociliary clearance mechanism. It has been shown that the half-life of clearance for non-mucoadhesive liquid and powder formulations is 15-20 minutes.

3) **Enzymatic Degradation:** This factor is contributing but less important to the transport of peptides and proteins across the nasal membrane due to the possibility of enzymatic degradation of the molecule either within the nasal cavity lumen or while passing through the epithelial barrier. These sites contain exopeptidases (such as mono- and diaminopeptidases) that can cleave peptides at their N- and C-termini and endopeptidases (such as serine and cysteine) that can attack internal peptide bonds.

8.1.7. Strategies to Improve Nasal Absorption

The strategies that improve bioavailability of drugs in the nasal mucosa include:

1) Improving the nasal residence time,
2) Enhancing nasal absorption, and
3) Modifying drug structure to change physicochemical properties.

Either one or combination of the above approaches is used for enhancing the absorption and bioavailability of nasal formulations. The following methods have been adopted to facilitate nasal absorption of drugs:

1) **Nasal Enzyme Inhibitors:** These are used to inhibit nasal metabolism of drugs. Development enzyme inhibitors, like peptidases and proteases, are used for

protein and peptide formulations. Absorption enhancers, like salts and fusidic acid derivatives, show enzyme inhibition activity to increase the absorption and bioavailability of drugs. Trypsin, aprotinin, borovaline, amastatin, bestatin, and boroleucin are the **examples** of other commonly used enzyme inhibitors.

2) **Permeation Enhancers:** These are used for enhancing the absorption of the active drug. Absorption enhancers act via one of the following mechanisms:
   i) Inhibition of enzyme activity,
   ii) Reduction of mucus viscosity or elasticity,
   iii) Reduction of mucociliary clearance,
   iv) Opening of tight junctions, and
   v) Solubilisation or stabilisation of the drug.

The action mechanism of absorption enhancers is increasing the rate at which drug passes through the nasal mucosa. Many enhancers alter the structure of epithelial cells in such a way that neither any damage is caused nor the nasal mucosa is permanently changed.

An **ideal permeation enhancer** should have the following characteristics:
i) It should effectively increase the drug absorption.
ii) It should not cause any damage or permanent change to the tissues.
iii) It should be non-irritant and non-toxic.
iv) It should be effective in small quantity.
v) It should produce the enhancing effect when absorption is required.
vi) It should produce temporary and reversible effect.
vii) It should be compatible with other excipients.

Examples of various types of permeation enhancers that have been evaluated for organic drugs include surfactants, bile salts, chelators, fatty acid salts, phospholipids, glycyrrhetinic acid derivatives, cyclodextrins, and glycols.

3) **Prodrug Approach:** This is meant for optimising favorable physicochemical properties (such as solubility, taste, odour, stability, etc.). Prodrug is a promoiety used to mask the undesired functional groups with other functional groups. This approach improves the nasal bioavailability of proteins and peptides to enhance their membrane permeability along with increased enzymatic stability. The prodrug, while crossing the enzymatic and membrane barrier, undergoes enzymatic transformation and releases the active medicament. Absorption of peptides, like angiotensin II, bradykinin, cauline, carnosine, enkephalin, vasopressin, and calcitonin, are improved by preparing them into enamine derivatives, which enhance absorption with prodrug approach.

4) **Structural Modification:** Nasal absorption can be improved by modifying the drug structure without changing its pharmacological activity. Chemical modification of drug molecule modifies the physicochemical properties of a drug, such as molecular size, molecular weight, pka, and solubility; and this in turn improves the nasal absorption of drug. **For example**, chemical modification of salmon calcitonin to elcatonin (C-N bond replaces the S-S bond) shows improved bioavailability than salmon calcitonin.

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5) **Particulate Drug Delivery:** Particle design plays a significant role in enhancement of absorption. Microspheres, nanoparticles, and liposomes can be used as carriers for encapsulating an active drug. The properties of these systems can be altered to maximise the therapeutic efficacy of the encapsulated drug. This increases the absorption efficacy and stability, and reduces the toxicity of the active ingredient. Mucoadhesive systems are designed to increase the retention time and facilitate sustained release.

   Microspheres increase the drug absorption and bioavailability by adhering to the nasal mucosa, and also increase the drug nasal residence time. Microspheres prepared with polymers (like dextran, chitosan, biodegradable starch) improve the bioavailability of various drugs. Liposomes are amphiphilic and facilitate drug permeation through the biological membranes, so the water-soluble drugs have been delivered to nasal drugs. The permeation capacity of cationic liposomes is better than that of the negatively charged anionic liposomes.

6) **Bioadhesive Polymer:** The nasal residence time and absorption of the drugs can be improved by using bioadhesive polymers. These polymers improve the drug retention time in the nasal cavity by making an adhesive force between the formulation and nasal mucosa, which minimises the mucociliary clearance of the formulation.

8.1.8. Applications

Nasopulmonary drug delivery system has the following applications:

1) **Delivery of Non-Peptide Pharmaceuticals:** Low molecular weight (<1000 Daltons), small, non-peptide lipophilic drugs are well-absorbed through the nasal mucosa even if permeation enhancers are not added in the formulation. Since the epithelial nasal membrane is highly vascularised and is of a large surface area, it is readily accessible for drug absorption due to the presence of nasal turbinates.

   Drugs susceptible to pre-systemic metabolism, **e.g.,** progesterone, estradiol, propranolol, nitroglycerine, sodium cromoglycate, etc., can be rapidly absorbed through the nasal mucosa with a systemic bioavailability of around 100%. These drugs reach the systemic circulation in a few minutes after administration as the venous blood passes directly from the nose into the systemic circulation. Many intranasally administered drugs are often absorbed faster and more efficiently than those from oral administration translating into a quick uptake.

   Given below are some non-peptide drugs being studied for nasal delivery and have shown good bioavailability:

   i) Adrenal corticosteroids.
   ii) **Sex Hormones:** 17G-estradiol, progesterone, norethindrone, and testosterone.
   iii) **Vitamins:** Vitamin B.
   iv) **Cardiovascular Drugs:** Hydralazine, angiotensin-II antagonist, nitroglycerine, isosorbide dinitrate, propranolol, and clofilium tosylate.

   v) Autonomic Nervous System:
      a) **Sympathomimetics:** Ephedrine, epinephrine, phenylephrine, xylometazoline, dopamine, and dobutamine.
      b) **Parasympathomimetics:** Nicotine and methacholine.
      c) **Parasympatholytics:** Scopolamine, atropine, and ipratropium.
      d) Prostaglandins
   vi) **Central Nervous System Stimulants:** Cocaine and lidocaine.
   vii) **Narcotics and Antagonists:** Buprenorphine and naloxone.
   viii) **Histamine and Antihistamines:** Disodium cromoglycate and meclizine.
   ix) **Antimigraine Drugs:** Dierogotamine and ergotamine tartrate.
   x) **Antibiotics:** Penicillin, cephalosporins, and gentamycin.
   xi) **Antivirals:** Phenyl-*p*-guanidine benzoate and enviroxime.
   xii) **Inorganic Compounds:** Inorganic salts, colloidal gold, colloidal carbon, and colloidal silver.

2) **Delivery of Peptide-Based Pharmaceuticals:** Peptides and proteins have low oral bioavailability due to their physicochemical instability and susceptibility to hepato-gastrointestinal first-pass elimination. Insulin, calcitonin, pituitary hormones, etc. are hydrophilic polar molecules of high molecular weight, are poorly absorbed across biological membranes, and achieve 1-2% bioavailability when administered as simple solutions. This bioavailability can be increased by using absorption enhancers, **e.g.,** surfactants, glycosides, cyclodextrin, and glycols.

3) **Delivery of Drugs to Brain through Nasal Cavity:** Nasal delivery system proves to be helpful in Parkinson's disease, Alzheimer's disease, or pain as these conditions require rapid and/or specific targeting of drugs to the brain. Nasal delivery system increases the fraction of drug that reaches the CNS after nasal delivery. The olfactory region in the upper remote parts of the nasal passages allows some compounds to pass through the blood-brain barrier and enter the brain. Recent studies have shown that neurotrophic factors (NGF, IGF-I, FGF and ADNF) on intranasal administration increases the drug bioavailability in the CNS. Studies in humans have shown that proteins (AVP, CCK analog, MSH/ACTH, and insulin) are directly delivered to the brain from the nasal cavity.

4) **Delivery of Vaccines through Nasal Route:** Mucosal sites offer first line of defence against the microorganisms that enter the body. Pathogens from the inspired air are filtered by the nasal mucosa via compaction and mucociliary clearance. Nose with Nose-Associated Lymphoid Tissue (NALT) is an effective site of immune system, and is called Waldeyer's Ring in human beings and nasal secretions mainly contains immunoglobulins (IgA, IgG, IgM, IgE), protective proteins as well as neutrophils and lymphocytes in the mucosa. **Nasal route** is considered to be **suitable for vaccine delivery** because:

   i) Nasal mucosa is the first site of contacts with inhaled pathogens,
   ii) Nasal passages are rich in lymphoid tissue,
   iii) Creation of both mucosal and systemic immune responses, and
   iv) Low cost, patient friendly, non-injectable, and safe.

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Recent studies have shown that conditions of anthrax and influenza can be treated by using nasal vaccines, prepared by using the recombinant Bacillus anthracis Protective Antigen (rPA) and chitosan, respectively. Pathogens causing measles, pertussis, meningitis, and influenza enter the body through nasal mucosal surfaces, and thus these conditions can be treated with nasal vaccines. Nasally administered vaccines, based on attenuated live cells or adjuvanted by an immunostimulator or a delivery system, can induce mucosal as well as systemic (i.e., humoral and cell-mediated) immune responses.

5) **Delivery of Diagnostic Drugs:** Nasal drug delivery system also plays an important role in the delivery of diagnostic agents for diagnosing various diseases. The intranasal route offers better systemic release of medicament, thus it causes less toxicity. **For example**, phenolsulphonaphthalein is a diagnostic agent used for diagnosing kidney function; pancreatic disorders in diabetic patients are diagnosed using secretin; and secretory function of gastric acid is determined by pentagastrin.

8.2. PULMONARY ROUTES OF DRUG DELIVERY

8.2.1. Introduction

Respiratory tract is one of the oldest routes for drug administration. Over the past decades, inhalation therapy has established itself as a valuable tool in the local therapy of pulmonary diseases, like asthma or COPD (Chronic Obstructive Pulmonary Disease). Pulmonary drug application in the therapy of these diseases is a type of targeted drug delivery. The latest promising applications of pulmonary drug administration are:

1) This route achieves systemic absorption of the administered drug substances.
2) This route is suitable for drugs that show poor bioavailability on administration via oral route, **e.g.,** peptides or proteins.
3) The lungs are susceptible to various disorders caused by genetic factors, infection, and air pollutants. The most common problems of the respiratory system are asthma, bronchiolitis, Chronic Obstructive Pulmonary Disease (COPD), common cold, cough, Cystic Fibrosis (CF), lung cancer, pneumonia, pulmonary hypertension, and respiratory diseases of newborns.

8.2.2. Advantages

The pulmonary drug delivery route has the following advantages:

1) This route provides local action in the respiratory tract.
2) This route provides rapid drug action.
3) This route provides reduced dose.
4) This route reduces the systemic side effects.
5) This route is used as an alternative route to drug interaction when two or more medications are concurrently used.
6) This route reduces extracellular enzyme levels compared to GIT due to the large alveolar surface area.
7) This route reduces evasion of first pass hepatic metabolism by absorbed drug.
8) This route provides the potential for pulmonary administration of systemically active materials.

8.2.3. Disadvantages

The pulmonary drug delivery route has the following disadvantages:

1) Duration of activity is short due to the rapid removal of drugs from the lungs or due to drug metabolism.
2) This route necessitates frequent dosing.

8.2.4. Principal Mechanisms of Respiratory Deposition

Deposition of inhaled particles in different regions of the respiratory system is a complex process, which is influenced by the following factors:

1) Breathing rate,
2) Mouth or nose breathing,
3) Lung volume,
4) Respiration volume,
5) Health of the individual, and
6) Bifurcations in the airways that constantly changes the hydrodynamic flow field.

Particle deposition occurs via one of the following principal mechanisms, depending on the particle size, airflow, and location in the respiratory system:

1) **Impaction:** Each time when the airflow changes through the bifurcated airways, the suspended particles under the influence of inertia travel along their original path and impact on an airway surface. This mechanism depends on aerodynamic diameter, since very small particles have a low stopping distance. Impaction occurs in larger particles that are very close to airway walls, near the first airway bifurcations. Therefore, deposition by impaction mainly occurs in the bronchial region. Impaction accounts for the majority of particle deposition on a mass basis.

2) **Sedimentation:** This mechanism involves settling of the particles in the smaller airways of bronchioles and alveoli having low air flow and small airway dimensions. The sedimentation rate depends on the terminal settling velocity of the particles, thus sedimentation is important in the deposition of particles exhibiting larger aerodynamic diameters. The size of hygroscopic particles increases while passing through the warm, humid air passages; this increases the possibility of deposition by sedimentation.

3) **Interception:** This occurs when a particle contacts an airway surface due to its physical size or shape. Particles deposited by interception do not deviate from their air streamlines. Interception mainly occurs in small airways or when the air streamline is close to an airway wall. Interception is most significant for fibers that easily contact airway surfaces due to their length. Fibers also have small aerodynamic diameters relative to their size, thus can reach the smallest airways.

4) **Diffusion:** This is the primary mechanism of deposition for particles having <0.5μ diameter. Diffusion is directed by geometric size (and not aerodynamic size). Diffusion involves transport of particles from a region of high concentration to a region of lower concentration due to Brownian motion (random wiggling motion of a particle due to constant bombardment of air molecules). Deposition by diffusion occurs just when the particles enter the nasopharynx. It also occurs in the smaller airways of the pulmonary (alveolar) region having a low air flow.

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5) **Absorption:** Pulmonary membrane is naturally permeable to small drug molecules and to therapeutic peptides and proteins. Epithelium of the lung is a significant barrier to absorption of inhaled drugs. It has a thickness of 50-60µm in the trachea, but its thickness reduces to 0.2µm in the alveoli. A very dramatic change occurs in cell types and morphology of trachea, bronchi, bronchioles, and alveoli. Lungs are more permeable to macromolecules than any other portal of entry into the body. Peptides and proteins can be inhaled instead of injected, thereby improving compliance. Peptides that have been chemically altered to inhibit peptidase enzymes have a very high bioavailability when inhaled via pulmonary route. If small molecules are highly soluble or cationic, they exhibit prolonged absorption.

8.3. FORMULATION OF NASAL PRODUCTS

8.3.1. Introduction

The excipients that are commonly and frequently added in nasal formulations are the following:

1) **Bioadhesive Polymers:** These compounds can interact with biological material via interfacial forces and can be retained on such material for prolonged time periods. Bioadhesive polymers are also called **mucoadhesive** if the biological material is mucus membrane. On molecular level, mucoadhesion process relies on attractive molecular interactions involving Van der Waal forces, electrostatic interactions, hydrogen bonding, and hydrophobic interactions. Bioadhesive force of a polymer depends on the polymer nature, pH of the surrounding medium, swelling index, and physiological factors (like mucin turnover and disease state).

Table 8.2: Bioadhesive Polymers Used in Nasal Drug Delivery

Polymers	Characteristics
Cellulose Derivatives: 1) **Soluble:** Hydroxypropyl Methylcellulose (HPMC), Hydroxypropyl Cellulose (HPC), Methyl Cellulose (MC), Carboxymethyl Cellulose (CMC). 2) **Insoluble:** Ethylcellulose, Microcrystalline Cellulose (MCC).	1) Prolong the residence time of drug in nasal cavity. 2) Sustain the release of drug due to high viscosity. 3) Act as absorption enhancers. 4) Increase intranasal bioavailability.
Polyacrylates: 1) Carbomers 2) Polycarbophils	1) Excellent mucoadhesive and gel-forming capability. 2) Attach to mucosal surfaces, hence ensure intimate contact between the formulation and membrane surface.
Starch: 1) Maize starch 2) Degradable Starch Microspheres (DSM)	1) Improve absorption of small hydrophobic and hydrophilic macromolecular drugs. 2) Used in mucoadhesive microparticulate nasal delivery system.
Chitosan	1) Insoluble at neutral & alkaline pH. 2) Form water-soluble salts with inorganic and organic acids. 3) Low cost, biodegradable and biocompatible.

2) **Gelling Agents:** A study revealed that on increasing viscosity of a solution, the therapeutic effect of nasal preparations can be enhanced. In another study it was revealed that a drug carrier (hydroxypropyl cellulose) can be effectively used for improving the absorption of low molecular weight drugs (and not of high molecular weight peptides).

3) **Penetration Enhancers:** These compounds are widely used in the nasal formulations. Penetration enhancers are chemically classified into solvents, alkyl methyl sulphoxides, pyrrolidones, 1-dodecyl azacycloheptan-2-one, and surfactants.

4) **Buffers:** Nasal formulations are administered in small volumes that range from 25-200µl (100µl is the most common dose volume); thus, the pH of administrated dose gets altered by the nasal secretions and this affects the concentration of un-ionised drug available for absorption. Therefore, an adequate formulation buffer capacity is required to maintain the *in-situ* pH.

5) **Solubilisers:** Aqueous solubility of drug is a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents [**e.g.,** glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides, and Labrasol (saturated polyglycolyzed C8- C10 glyceride)] can be used for enhancing drug solubility. Other compounds, like surfactants or cyclodextrins (HP-β-cyclodextrin), serve as a biocompatible solubiliser and stabiliser in combination with lipophilic absorption enhancers.

6) **Preservatives:** Nasal formulations are mostly aqueous-based, and thus should be added with preservatives to prevent microbial growth. Parabens, phenyl ethyl alcohol, benzalkonium chloride, EDTA, and benzoyl alcohol are the **examples** of some commonly used preservatives in nasal formulations.

7) **Antioxidants:** These are required in small quantity to prevent drug oxidation. Sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite, and tocopherol are the **examples** of commonly used antioxidants. They do not affect drug absorption or cause nasal irritation. Their chemical or physical interaction with drugs, excipients, manufacturing equipment, and packaging components is a part of the formulation development program.

8) **Humectants:** Due to allergic and chronic diseases, crust formation and drying of mucous membrane may occur. Some of the preservatives or antioxidants, added in higher quantities, may also cause nasal irritation. Intranasal moisture should be sufficient enough for preventing dehydration. Humectants are mainly added in gel-based nasal products. They avoid nasal irritation and do not affect drug absorption. Glycerin, sorbitol, and mannitol are the **examples** of commonly used humectants.

9) **Surfactants:** These compounds are added in nasal formulations as they facilitate

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8.3.2. Inhalers

The medicament added in an inhaler directly enters the airways, thus require much smaller dose than tablets or liquid formulations to be taken orally. Inhalation is an attractive, rapid and user-friendly route for the delivery of systemically acting **drugs**, and for the drugs that act locally on the lungs. The concept of inhalation **is** especially exciting now that the concept of an inhaled systemic macromolecule, one of the key factors for success in this area, is the ability to control the combined powder and device properties. This is essential for the development of Dry-Powder Inhaler (DPI) products; but, still it remains a major technical hurdle to those who wish to succeed with this route and exploit the product opportunities arising from the numerous market drivers:

1) Rapid onset of action,
2) Improving patient acceptance and compliance for a non-invasive systemic route,
3) Reduction of side effects,
4) Differentiation of new product and competitive brand opportunities, and
5) Expedition of regulatory approval through improved consistency of delivery and product stability and life cycle enhancement.

New forms of inhaled therapeutics require high doses and/or greater efficiency and accuracy. Attractive devices are formed with convenient and easy operation and delivery.

8.3.3. Nebulisers

Since many years, nebulisers are in use for the treatment of asthma and other respiratory diseases. Jet and ultrasonic nebulisers are the two basic types. The functioning of **jet nebulisers** relies on the Bernoulli principle as per which compressed gas (air or oxygen) passes through a narrow orifice and create an area of low pressure at the outlet of the adjacent liquid feed tube. Under the influence of this pressure, the drug solution is drawn up from the fluid reservoir and shattered into droplets in the gas stream. The **ultrasonic nebulisers** use a piezoelectric crystal that vibrates at a high frequency (usually 1-3 MHz) to generate a fountain of liquid in the nebuliser chamber; higher the frequency, the smaller droplets are produced.

These disposable nebulisers are inexpensive, but the air- or oxygen-supplying compressors are expensive. Most of the prescribed drug never reaches the lung with nebulisation. Majority of the drug is either retained in the nebuliser (and this volume of drug is called the dead volume) or released into the environment during expiration. Only 10% of the dose within the nebuliser gets deposited in the lungs.

8.3.4. Squeezed Bottle

Squeezed nasal bottles are used for delivering decongestants. They comprise of a smooth plastic bottle having a simple jet outlet. When this plastic bottle is pressed, the air inside the container is pressed out of the small nozzle, thereby atomising a certain volume of medicament. When the pressure is released, the air is drawn inside the bottle. This procedure, however, results in contamination of the liquid by microorganisms and nasal secretion sucked inside.

8.3.5. Metered Dose Pump Sprays

The pharmaceutical nasal preparations in the market mainly contain solutions, emulsions, or suspensions and are delivered by metered-dose pump sprays. They comprise of a container, a pump with a valve, and an actuator. Nasal sprays or mists are used for nasal delivery of drugs, either locally to alleviate cold or allergy symptoms (like nasal congestion) or systemically.

Although delivery methods vary, the nasal sprays mainly act by instilling a fine mist into the nostril via hand-operated pump mechanism. The three main types available for local effect are antihistamines, corticosteroids, and topical decongestants.

8.3.6. Dry Powders

Dry powders are less frequently used for nasal drug delivery. They have the **advantages** of the lack of preservatives and improved formulation stability. Administration of dry powders, in comparison to solutions, results in a prolonged contact with the nasal mucosa.

Dry powders are of the following **types**:

1) **Insufflators:** These devices deliver the drug substances for inhalation. They comprise of a straw or tube containing the drug substance and also a syringe. The particles of insufflators undergo insufficient deaggregation and thus their particle size is increased compared to the size of the powder particles. This results in a high coefficient of variation for initial deposition areas. Many insufflators work with pre-dosed powder doses in capsules.
2) **Dry Powder Inhalers (DPIs):** These devices deliver a dry powder formulation of an active drug for local or systemic effect via pulmonary route. DPIs are bolus drug delivery devices that contain a solid drug that is suspended or dissolved in a non-polar volatile propellant or in a dry powder inhaler that is fluidised when the patient inhales. DPIs are used in the treatment of respiratory diseases (like asthma, bronchitis, emphysema, and COPD) and also in diabetes mellitus.

   In DPIs, the medication is held either in a capsule for manual loading or as a proprietary form from inside the inhaler. Once loaded or actuated, the users put the inhaler mouthpiece in their mouth, inhale deeply, and hold their breath for 5-10 seconds. The dose that can be delivered is typically less than a few tens of milligrams in a single breath since larger powder doses may provoke cough.

8.3.7. Pressurised MDIs

MDIs are devices that deliver to the lungs a specific amount of medication in the form of a **short burst** of aerosolised medicine. This delivery system is commonly used in the **treatment** of asthma, COPD, and other respiratory diseases. MDIs are used for delivering bronchodilators, corticosteroids, or a combination of both for the treatment of asthma and COPD. Mast cell stabilisers (like cromoglicate or nedocromil) can also be administered via MDIs, but are used less commonly.

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The **advantages** of MDIs are their portability and small size, availability over a wide dosage range per actuation, dose consistency, dose accuracy, protection of the contents, and ready for use.

Propellants in MDIs make up more than 99% of the delivered dose. Actuation of the device releases a single metered dose of the formulation, containing the medication which is dissolved or suspended in the propellant. The volatile propellant breakdown into droplets, rapidly evaporates, and results in the generation of an aerosol consisting of micrometer-sized medication particles that are inhaled.

8.3.8. Nasal Sprays

Nasal sprays contain therapeutically active drug substances that are dissolved or suspended in solutions or mixtures of excipients (**e.g.,** preservatives, viscosity modifiers, emulsifiers, and buffering agents) in non-pressurised dispensers that deliver a spray containing a metered dose of the active ingredient (dose can be metered by the spray pump).

A nasal spray unit is designed for unit dosing or for discharging up to several hundred metered sprays of the drug formulation. Nasal sprays deliver drugs to the nasal cavity for local and/or systemic effects. Many features of nasal sprays are similar to other drug products; however, it is unique in some aspects, like formulation, container-closure system, manufacturing, stability, and drug product. Metering and spray-producing (**e.g.,** orifice, nozzle, jet) pump mechanisms and components are used for reproducible delivery of drug formulation, and these can be constructed in different design controlled in terms of dimensions and composition.

Nasal sprays require energy for dispersing the formulation as a spray, and this energy is gained by forcing the formulation through the nasal actuator and its orifice. The formulation and the container-closure system (involving the container, closure, pump, and any protective packaging) together constitute the drug product. The dosing performance of the drug product depends on the design of container-closure system. Nasal sprays can be incorporated with solution as well as suspension formulations.

8.3.9. Nasal Gels

Nasal gels are high-viscosity thickened solutions or suspensions. Their **advantages** include reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients, and target delivery to mucosa for better absorption.

The administration mode of nasal gels influences their deposition in nasal cavity, because gels have poor spreadability due to their viscosity. If special application techniques are not used, gels only occupy a narrow distribution area in the nasal cavity, i.e., the area where they are applied.

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

1) The **first mechanism** involves slow and passive aqueous route of transport or the paracellular route. Drugs with molecular weight >1000 Daltons show poor bioavailability via this route as molecular weight and absorption are inversely related.
2) The **second mechanism** involves transcellular process, i.e., transport through a lipoidal route. Lipophilic drugs that show a rate dependency on their lipophilicity are transported by this process.
3) Drug absorption through nasal route is influenced by the drug's molecular size.
4) The molecular weight and permeation rate of lipophilic drugs are directly related while those of water-soluble drugs are inversely related.
5) The permeation rate is highly sensitive to drugs with molecular weight ≥300 Daltons.
6) Increase in lipophilicity of a drug increases its permeation through nasal mucosa.
7) **Mucociliary clearance** is a function of the upper respiratory tract to prevent the entry of noxious substances (i.e., allergens, bacteria, viruses, toxins, etc.) in lungs.
8) Delivery of drug across the nasal mucosa is affected by the surfactants, dose pH, osmolarity, viscosity, particle size, nasal clearance, and drug structure, and these factors improve drug absorption.
9) The pH of nasal formulation should be between 4.5 and 6.5 to avoid nasal irritation as lysozyme found in nasal secretions destroys certain bacteria under acidic conditions.
10) The absorption and bioavailability of nasal dosage forms depends on the disposition site.
11) **Prodrug approach** is meant for optimising favorable physicochemical properties (such as solubility, taste, odour, stability, etc.). Prodrug is a promoiety used to mask the undesired functional groups with other functional groups.
12) **Permeability approach** improves the nasal bioavailability of proteins and peptides to enhance their membrane permeability along with increased enzymatic stability.
13) Microspheres, nanoparticles, and liposomes can be used as carriers for encapsulating an active drug.
14) **Mucoadhesive systems** are designed to increase the retention time and facilitate sustained release.
15) The nasal residence time and absorption of the drugs can be improved by using bioadhesive polymers.
16) Peptides and proteins have low oral bioavailability due to their physicochemical instability and susceptibility to hepato-gastrointestinal first-pass elimination.
17) **Nasal delivery system** proves to be helpful in Parkinson's disease, Alzheimer's disease, or pain as these conditions require rapid and/or specific targeting of drugs to the brain.
18) Nose with **Nose-Associated Lymphoid Tissue (NALT)** is an effective site of immune system, and is called **Waldeyer's Ring** in human beings and nasal secretions mainly contains immunoglobulins (IgA, IgG, IgM, IgE), protective proteins as well as neutrophils and lymphocytes in the mucosa.

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19) **Phenolsulphonaphthalein** is a diagnostic agent used for diagnosing kidney function; pancreatic disorders in diabetic patients are diagnosed using secretin; and secretory function of gastric acid is determined by pentagastrin.
20) **Sedimentation** mechanism involves settling of the particles in the smaller airways of bronchioles and alveoli having low air flow and small airway dimensions.
21) **Interception** occurs when a particle contacts an airway surface due to its physical size or shape.
22) **Diffusion** is the primary mechanism of deposition for particles having <0.5μ diameter.
23) **Bioadhesive polymers** can interact with biological material via interfacial forces and can be retained on such material for prolonged time periods.
24) Bioadhesive polymers are also called **mucoadhesive**.
25) The functioning of **jet nebulisers** relies on the Bernoulli principle as per which compressed gas (air or oxygen) passes through a narrow orifice and create an area of low pressure at the outlet of the adjacent liquid feed tube.
26) The **ultrasonic nebulisers** use a piezoelectric crystal that vibrates at a high frequency (usually 1-3 MHz) to generate a fountain of liquid in the nebuliser chamber; higher the frequency, the smaller droplets are produced.
27) **Insufflators** deliver the drug substances for inhalation. They comprise of a straw or tube containing the drug substance and also a syringe.
28) **Dry Powder Inhalers (DPIs)** deliver a dry powder formulation of an active drug for local or systemic effect via pulmonary route.
29) **MDIs** are devices that deliver to the lungs a specific amount of medication in the form of a short burst of aerosolised medicine. This delivery system is commonly used in the treatment of asthma, COPD, and other respiratory diseases.

8.5. EXERCISE

8.5.1. Very Short Answer Type Questions

1) Write the ideal properties for a nasal drug candidate.
2) What are the barriers to nasal absorption?
3) Give the strategies to improve bioavailability of drugs in the nasal mucosa.
4) What are the mechanisms of absorption enhancers?
5) Write four examples of some non-peptide drug for nasal delivery.
6) Give the full form of NALT and define Waldeyer's ring.
7) Give two examples of bioadhesive polymers used in nasal drug delivery system.

8.5.2. Short Answer Type Questions

1) Give a note on mechanism advantages and disadvantages of nasal drug delivery system.
2) Mention the factors influencing nasal drug absorption.
3) Write a short note on strategies to improve nasal absorption.
4) Enlist the application of nasopulmonary drug delivery system.

8.5.3. Long Answer Type Questions

1) Briefly explain the different formulation of nasal products.
2) Write an illustrative note on pulmonary route of drug delivery.

CHAPTER 9

Targeted Drug Delivery System

9.1. TARGETED DRUG DELIVERY SYSTEM

9.1.1. Introduction

In targeted drug delivery system, the pharmacologically active medicament is selectively targeted or delivered to its action or absorption site (and not to the non-target organs, tissues, or cells). This drug delivery system involves selective and effective localisation of pharmacologically active moiety at pre-identified (or pre-selected) target in therapeutic concentration, and restriction to its access into non-target normal cellular linings, thereby reducing toxic effects and enhancing therapeutic index.

Targeting drugs to special cells and tissues of the body without their involvement in systemic circulation is a highly remarkable and novel idea. A drug should be administered in such a form that it reaches the receptor sites in sufficient concentration and it does not disturb the extraneous tissue cells.

Properties of Targeted Drug Delivery

1) It should be non-toxic, biodegradable, biocompatible, and physicochemically stable *in vivo* and *in vitro*.
2) Drug delivery should be confined to target cells or tissues or organs.
3) It should have uniform capillary distribution.
4) It should have a predictable and controllable rate of drug release.
5) Drug release should not influence the drug delivery.
6) It should release a therapeutic amount of drug.
7) Minimal drug leakage should occur during transit.
8) Biodegradable carrier should be used that gets readily eliminated from the body without causing any problem and should not modulate the diseased state.

9.1.2. Concept

Paul Ehrlich (a microbiologist) gave the concept of designing targeted delivery system and proposed the idea of delivering drug in the form of magic bullet. Targeted drug delivery means accumulation of pharmacologically active moiety at the desired target in therapeutic concentration and at the same time restricting its entry into normal cellular lining, thereby improving therapeutic index. Different scientific strategies, that have been proved to be highly efficient, are used for targeting the drug to intracellular sites, virus cells, bacterial cells, and parasites. Minimum distribution of the parent drug to the non-target cells in higher and effective concentration at the targeted site enhance the benefits of targeted drug delivery.

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The drug through targeted delivery system can be delivered:

1) To the capillary bed of the active sites,
2) To the specific type of cell or to an intracellular region, **e.g.,** tumour cells, and
3) To a specific organ or tissues by forming complex with the carrier that recognises the target.

Reasons for Drug Targeting

1) It can be used in the treatment or prevention of diseases.
2) Pharmaceutical drug instability in conventional dosage form solubility, biopharmaceutical low absorption, high-membrane bounding, biological instability, short half-life, large volume of distribution, low specificity, and low therapeutic index.

9.1.3. Approaches of Drug Targeting

Targeting a drug to the desired site within the body increases therapeutic effectiveness and also reduces toxicity that may arise otherwise. Strategies used for targeting drug to the desired organs or tissues are as follows:

1) **Passive Targeting:** This approach (**figure 9.1**) involves accumulation of the drug at areas around the desired site, **e.g.,** in case of tumour tissues; this effect is called **Enhanced Permeability Retention** (EPR). This type of targeting occurs with most of the drug delivery carriers.

   Passive targeting is a misnomer as it cannot be described as a form of selective targeting. Although the EPR effect is applied for nanoparticle administered, majority (>95%) of these nanoparticles accumulate in other organs (other than the desired ones), like liver, lungs and spleen. Thus, it is the distribution of drug by blood circulation. **Examples** are targeting anti-malarial drugs for the treatment of microbial infections, such as leishmaniasis, candidiasis, and brucellosis.

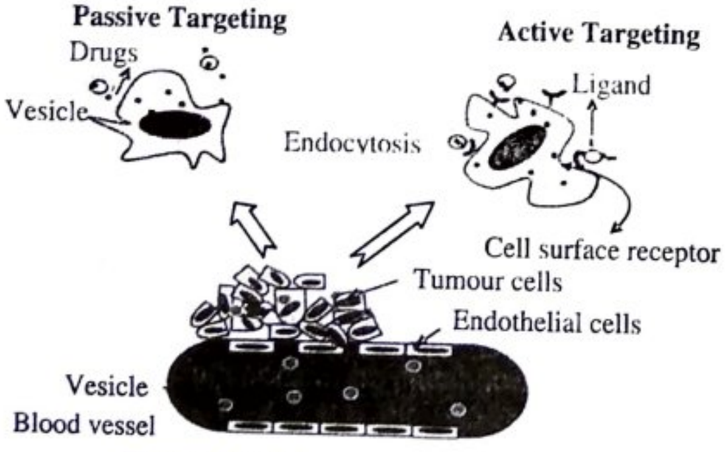


Figure 9.1: Active *versus* Passive Targeting

2) **Active Targeting:** This approach (**figure 9.1**) utilises ligand-receptor interactions, and describes drug targeting interactions. However, a ligand and a receptor interact only when the two are in close proximity (i.e., <0.5mm). The drug delivery systems that are currently available reach the desired target by means of blood circulation and extravasation. Therefore, active receptor targeting can be considered a ligand-receptor interaction that takes place after

blood circulation and extravasation. Active targeting is sub-divided into the following **three different targeting levels**:

i) **First Order Targeting:** This involves distribution of drug to capillary beds of target organs or tissues, **e.g.,** lymphatic tissue, peritoneal cavity, pleural cavity, cerebral ventricles, eyes, joints, etc.

ii) **Second Order Targeting:** This involves targeting of drugs to specific sites, **e.g.,** tumour cells, kupffer cells in liver, etc.

iii) **Third Order Targeting:** This involves intracellular localisation of the drugs at the target site via endocytosis or receptor-based ligand mediated entry.

3) **Inverse Targeting:** This approach avoids passive uptake of colloidal carrier by RES, and hence named so. Inverse targeting can be achieved by suppressing the normal function of RES by pre-injecting blank colloidal carriers or macromolecules (like dextran sulphate) in large amounts. This approach saturates the RES and suppresses the defense mechanism. Inverse targeting is effectively used to target drug(s) to non-RES organs.

4) **Dual Targeting:** This approach utilises carrier molecules exhibiting their own therapeutic activity, and thus increases the therapeutic effect of drug. **For example**, a carrier molecule with its own antiviral activity can be loaded with antiviral drug and the net synergistic effect of drug conjugate is observed.

5) **Double Targeting:** This approach involves combining of temporal and spatial methodologies to target a carrier system. Spatial placement refers to targeting drugs to specific organs, tissues, cells or even sub-cellular compartment; whereas, temporal delivery refers to controlling the rate of drug delivery to target sites.

9.1.4. Components of Drug Targeting

Targeted drug delivery system comprises of a target and the drug carriers or markers:

1) **Target:** It is an organ, a tissue, or a cell to which the drug is to be targeted.
2) **Drug Carrier or Marker:** A carrier system is required for drug delivery. Carriers are molecules or any other systems used for successfully transporting a drug to the desired site. They are especially designed vectors to be used for holding a drug within by means of encapsulation. An **ideal drug carrier** has the following **features**:
   i) It should be able to cross the anatomical barriers, and the tumour vasculature in case of tumour chemotherapy.
   ii) It should be specifically and selectively recognised by the target cells and should maintain the specificity of surface ligands.
   iii) The linkage of the drug and the ligand (directing unit) should be stable in plasma, interstitial fluid, and other body fluids
   iv) It should be a non-toxic, non-immunogenic, and biodegradable particulate or macromolecule.
   v) It should release the drug moiety in the target organs, tissues, or cells after recognition and internalisation.
   vi) The biomolecules used as carrier should not be ubiquitous (existing everywhere at the same time).

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Types of Drug Carriers

i) Liposomes,
ii) Monoclonal antibodies and fragments,
iii) Modified (plasma) proteins,
iv) Soluble polymers,
v) Lipoproteins,
vi) Microspheres and nanoparticles,
vii) Polymeric micelles, and
viii) Cellular carriers.

Targeting Moieties

i) Antibodies,
ii) Lectins and other proteins,
iii) Lipoproteins,
iv) Hormones,
v) Charged molecules,
vi) Polysaccharides, and
vii) Low molecular weight ligands.

9.1.5. Advantages

Targeted drug delivery system has the following advantages:

1) Drug administration protocols are simplified.
2) Toxicity and harmful systemic effects are reduced as the drug is delivered to its target site.
3) The desired effect can be produced even by administering the drug in a smaller dose.
4) It incorporates a less dose than other conventional drug delivery systems.
5) Hepatic first pass metabolism of the drug is prevented.
6) Absorption of target molecules (such as peptides and particulates) is enhanced.
7) No peak and valley plasma concentration is observed.
8) It offers selective targeting to infectious cells than the normal cells.

9.1.6. Disadvantages

Targeted drug delivery system has the following disadvantages:

1) The targeted systems undergo rapid clearance.
2) Immune reactions may occur against the intravenously administered carrier systems.
3) Targeted systems undergo insufficient localisation in the tumour cells.
4) Released drugs undergo diffusion and redistribution.
5) Highly sophisticated technology is required for the formulation.
6) Skill personnel are required for the manufacturing, storage, and administration of TDDS.
7) Drug deposition at the target site may give rise to symptoms of toxicity.
8) Stability maintenance of the dosage form is difficult; **for example,** re-sealed erythrocytes need to be stored at 4°C.
9) Drug loading is low, **e.g.,** in micelles; thus, it is difficult to predict/fix the dosage regimen.

9.2. LIPOSOMES

9.2.1. Introduction

Liposomes are synthetic vesicles of small size and spherical shape. They can be prepared from cholesterol and natural non-toxic phospholipids. Being of hydrophobic and hydrophilic nature, small size, and biocompatible, liposomes are promising drug delivery systems. Their properties differ with lipid composition, surface charge, size, and the preparation method. Liposomes are widely used as carriers for various molecules in cosmetic and pharmaceutical industries. In food and farming industries also, liposome encapsulation is used for growing delivery systems to entrap unstable compounds (**e.g.,** antimicrobials, antioxidants, flavours, and bioactive elements) and shield their functionality. Liposomes can trap hydrophobic as well as hydrophilic compounds, avoid decomposition of the entrapped combinations, and release the entrapped compounds at target sites.

9.2.2. Structure

Liposomes are made up of naturally-derived phospholipids with mixed lipid chains (like egg phosphatidylethanolamine) or other surfactants. They should not be confused with micelles and reverse micelles composed of monolayers. The major structural components of liposomes are:

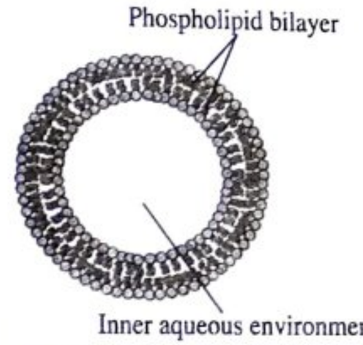


Figure 9.2: Structure of Liposome

1) **Phospholipid:** It is the major component of the biological membrane. The most common natural phospholipid is Phosphatidylcholine (PC) or lecithin, which is an amphipathic molecule and is obtained from animal (hen egg) and vegetable (soyabean).
2) **Cholesterol:** Adding cholesterol in the liposome bilayer causes big changes in their preparation. High concentration of cholesterol (up to 1:1 or 2:1 molar ratios of cholesterol to phosphatidylcholine) is incorporated into phospholipids membrane. Since cholesterol is an amphipathic molecule, it inserts into the membrane with its hydroxyl group oriented towards the aqueous surface and aliphatic chain aligned parallel to the acyl chains in the centre of the bilayers. It also increases the separation between choline head groups and eliminates the normal electrostatic and hydrogen bonding interaction.

9.2.3. Types

Liposomes, on the basis of their **size and number of bilayers**, are of the following three basic types:

1) **Multilamellar Vesicles (MLVs):** These liposomes have more than one lamella, and their size varies between 100-1000nm.
2) **Small Unilamellar Vesicles (SUVs):** These liposomes have a single lamella, and are smaller than 0.1μm in size. Composition of the membrane and the aqueous medium influence the minimum size that can be attained. The size variation of SUVs is small when the liposomes approach the minimum size.

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3) **Large Unilamellar Vesicles (LUVs):** These liposomes have a single lamella, and their size ranges from 0.1μm to 1000nm (close to the size of living cells).

Liposomes, on the basis of their **composition and mechanism of intracellular delivery**, are of the following **five types**:

1) Conventional liposomes,
2) pH-sensitive liposomes,
3) Cationic liposomes,
4) Immunoliposomes, and
5) Long circulating liposomes.

9.2.4. Methods of Preparation

Liposomes can be prepared by the following methods (**figure 9.3**):

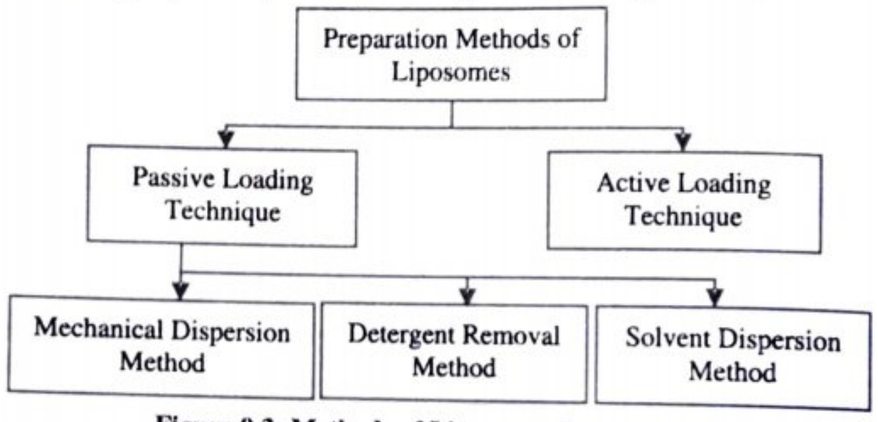


Figure 9.3: Methods of Liposomes Preparations

1) **Mechanical Dispersion Method:** In this method, lipid is solubilised in an organic solvent, the drug to be entrapped is solubilised in an aqueous solvent, the lipid phase is hydrated at high speed stirring, and due to affinity of aqueous phase to polar head it is entrapped in lipid vesicles. **For example,** lipid film hydration, micro-emulsification (micro-fluidiser), sonication, and dried reconstituted vesicle.

2) **Detergent Removal Method:** In this method, phospholipids are brought into contact with an aqueous phase via detergent that associates with phospholipid molecules and screen the hydrophobic portions of the molecules from water. Detergent (Cholate, Alkyglycolate, Triton X-100) removal from mixed micelles occurs by dialysis, column chromatography, and dilution.

3) **Solvent Dispersion Method:** In this method, lipids are dissolved in an organic solvent, and then brought into contact with an aqueous phase, that contains the material to be entrapped, under rapid dilution and rapid evaporation of organic solvent. **For example**, ethanol injection, ether injection, and de-emulsification.

9.2.5. Evaluation

The characterisation parameters for the evaluation of liposomes are classified into the following three categories:

1) **Physical Characterisation Parameter:** This parameter evaluates size, shape, surface features, lamellarity, phase behaviour, and drug release profile.

2) **Chemical Characterisation Parameter:** This parameter evaluates the purity and potency of various liposomal constituents.

3) **Biological Characterisation Parameter:** This parameter establishes the safety and suitability of the formulations for *in vivo* use or therapeutic application.

Physical and chemical characterisations play a significant role in making meaningful comparison of different liposome preparations for different batches. Biological characterisation helps in ensuring safety of liposome use in humans.

Table 9.1: Parameters to be Evaluated for Liposomes and the related Techniques

Parameters	Evaluation Techniques
1) Vesicle shape	Electron microscopy
2) Lamellarity	Freeze fracture electron microscopy and nuclear magnetic resonance spectroscopy
3) Vesicle size and distribution	Light microscopy, fluorescent microscopy, electron microscopy, laser scattering photon correlation spectroscopy, and gel permeation technique
4) Surface morphology and size of vesicles	Cryo-transmission electron microscopy
5) Encapsulation efficiency	Mini column centrifugation method and protamine aggregation method
6) Phase response and transitional behaviour	Freeze fracture electron microscopy and differential scanning calorimetry
7) Drug release	*In vitro* diffusion cell

9.2.6. Applications

Liposomes have the following applications:

1) They are used as drug/protein delivery vehicles to:
   i) Provide controlled and sustain release *in situ*,
   ii) Enhance drug solubilisation,
   iii) Used in enzyme replacement therapy and lysosomal storage disorders, and
   iv) Alter pharmacokinetic profile and biodistribution.
2) They are used in antimicrobial, antifungal and antiviral therapy.
3) They are used in tumour therapy as:
   i) Carrier of small cytotoxic molecules, and
   ii) Vehicle for macromolecules, like cytokines and genes.
4) They are used in gene delivery in:
   i) Genes and antisense therapy, and
   ii) Genetic (DNA) vaccination.
5) They are used in immunology.
6) They are used as radiopharmaceutical and radio-diagnostic carrier.
7) They are used in cosmetic and dermatology.
8) They are used in enzyme immobilisation and bioreactor technology.

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9.2.7. Advantages

Liposomes have the following advantages:

1) They are biocompatible, biodegradable, non-toxic, flexible, and non-immunogenic for systemic and non-systemic administrations.
2) They provide a lipophilic environment and aqueous "milieu interne" in one system, and thus are suitably used for delivering hydrophobic, amphipathic, and hydrophilic drugs.
3) They provide protection to the encapsulated drug from external environment.
4) They act as sustained release depots.
5) They can be formulated as suspensions, aerosols, gels, creams, lotions, and dry vesicular powders for reconstitution.
6) They can be administered via ocular, pulmonary, nasal, oral, intramuscular, subcutaneous, topical, and intravenous routes.
7) They can encapsulate small molecules, and also macromolecules, like superoxide dismutase, haemoglobin, erythropoietin, interleukin-2, and interferon-G.
8) They reduce toxicity and increase the stability of entrapped drug via encapsulation.
9) They increase the efficacy and therapeutic index of drugs.
10) They reduce the exposure of sensitive tissues to toxic drugs.
11) They alter the pharmacokinetic and pharmacodynamic property of drugs by reducing elimination and increasing circulation life time.
12) They provide flexibility to couple with site-specific ligands to achieve active drug targeting.

9.2.8. Disadvantages

Liposomes have the following disadvantages:

1) Their production cost is high.
2) Leakage and fusion of encapsulated drug/molecules may occur.
3) Sometimes phospholipid undergoes oxidation- and hydrolysis-like reaction.
4) They have a short half-life.
5) They have a low solubility.
6) They have a low stability.

9.3. NIOSOMES

9.3.1. Introduction

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle of a bilayer of non-ionic surfactants. Most of the surfactants yield micellar structures on immersing in water; while, some of them yield bilayer vesicles, i.e., niosomes. Niosomes are either unilamellar or multilamellar, depending on their preparation method. They are classified based on the number of bilayer (**e.g.,** MLVs and SUVs), on their size (**e.g.,** LUVs and SUVs), and on their preparation method (**e.g.,** REVs and DRVs). Niosomes are structurally similar to liposomes and hence represent alternative vesicular systems with respect to liposomes, due to their ability to encapsulate different drugs in their multi-environmental structure.

9.3.2. Structure

Niosomes are microscopic lamellar structures that are formed by the admixture of the non-ionic surfactant of alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. Since niosomes are also made up of a bilayer, they are structurally related to liposomes, with the only difference that the bilayer in niosomes is made up of non-ionic surfactants, while that of liposomes is made up of phospholipids.

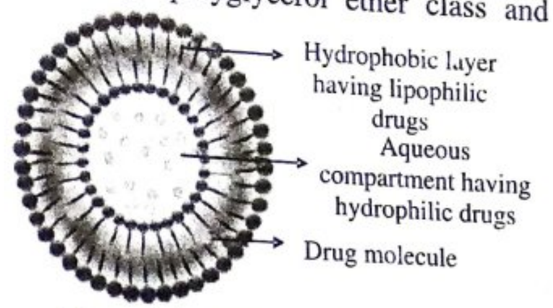


Figure 9.4: Structure of Niosome

Most of the surfactants yield micellar structures on immersing in water; while, some of them yield bilayer vesicles, i.e., niosomes. Niosomes are either unilamellar or multilamellar, depending on their preparation method. They are made up of a surfactant bilayer with hydrophilic ends oriented towards the outside and inside of the vesicle, and the hydrophobic chains facing each other within the bilayer. Hence, the space within the vesicle encapsulates hydrophilic drugs, while the bilayer has embedded hydrophobic drugs. Niosome vesicles consist of a vesicle-forming amphiphile (a non-ionic surfactant, **e.g.,** Span-60), which is stabilised by adding cholesterol and a small amount of anionic surfactant (**e.g.,** diacetyl phosphate) that also stabilises the vesicle.

9.3.3. Types

Niosomes are of the following three types:

1) **Small Unilamellar Vesicles (SUVs):** These are produced by sonication and French Press procedures. They can be prepared by ultrasonic electrocapillary emulsification or solvent dilution techniques. The approximate size of these vesicles is **0.025-0.05µm**.
2) **Multi-Lamellar Vesicles (MLVs):** These are made up of a few bilayers surrounding the aqueous lipid compartment separately. They exhibit increased-trapped volume and equilibrium solute distribution. Their lipid compositions vary. They are prepared by hand-shaking method. The approximate size of these vesicles is **0.5-10µm**.
3) **Large Unilamellar Vesicles (LUVs):** These are prepared by injecting lipids (solubilised in an organic solvent) into an aqueous buffer. However, reverse phase evaporation or detergent solubilisation methods are mostly preferred for their preparation. The approximate size of these vesicles is **>0.10µm**.

9.3.4. Methods of Preparation

The preparation methods for niosomes are selected depending on their use as they influence the number of bilayers, size, size distribution, entrapment efficiency, and membrane permeability of vesicles. The preparative methods for niosomes are as follows:

1) **Ether Injection Method:** In this method, the surfactant/cholesterol mixture is dissolved in diethyl ether and slowly injected into the aqueous phase

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through a needle at 60°C temperature. Evaporation of ether results in the formation of LUVs. This method has a **disadvantage** that a small amount of ether remains in the vesicle suspension and its removal is very difficult.

2) **Hand Shaking (Film) Method:** In this method, a surfactant/lipid film is formed by evaporating an organic solution of surfactants/lipids. Then the film is hydrated with a drug solution.

3) **Sonication:** In this method, an aqueous phase is added to the surfactant/cholesterol mixture in a glass vial. Then the mixture is probe-sonicated for a certain time period to yield SUVs.

4) **Extrusion Method:** In this method, a mixture of cholesterol and diacetyl phosphate is prepared. The solvent is evaporated in a rotary vacuum evaporator to leave behind a thin film, which is then hydrated with aqueous drug solution. The obtained suspension is extruded through the polycarbonate membrane (of 0.1mm mean pore size) and placed in series up to eight passages to yield niosomes of uniform sizes.

5) **Microfluidisation Method:** In this method, two fluidised streams (one containing the drug and the other containing the surfactant) are made to interact at ultra-high velocity in accurately defined microchannels within the interaction chamber. The interaction is such that the energy supplied to the system remains in the area of niosomes formed. This is called **submerged jet principle**, and it improves uniformity, and yields niosomes of smaller size and better reproducibility.

6) **Reverse Phase Evaporation:** In this method, an o/w emulsion is formed from an aqueous solution of the drug. The organic solvent is evaporated to leave niosomes dispersed in the aqueous phase. In some cases, the resulting gel is further hydrated to yield niosomes.

The size and number of bilayers of vesicles, containing polyoxyethylene alkyl ethers and cholesterol, can be changed by increasing the temperature to more than 60°C. As a result, the SUVs get converted into unilamellar vesicles. This conversion from unilamellar to MLVs at higher temperatures is due to the polyoxyethylene alkyl ether (ester) surfactants, as PEG and water mix at a higher temperature due to the breakdown of hydrogen bonds between the water and PEG moieties.

9.3.5. Evaluation

Niosomes are evaluated as follows:

1) **Size, Shape, and Morphology:** Freeze fracture electron microscopy is used to determine the structure of surfactant-based vesicles, while photon correlation spectroscopy is used to determine the mean diameter of the vesicles. Electron microscopy is used in morphological studies. Laser light scattering techniques are used to determine the size distribution of niosomes.

2) **Entrapment Efficiency:** Hydration of surfactant/lipid mixtures result in the encapsulation of entire drug. Entrapment efficiency can be determined by separating the untrapped drug. Dialysis, gel filtration, and ultracentrifugation

methods are used for removing the untrapped materials. Entrapment efficiency can also be determined by using Carboxyfluorescein (CF) marker. CF in 200mM concentration is used for hydration within the vesicles, because CF is self-quenched and does not produce fluorescence at this concentration. Vesicles are disrupted using hydrophilic surfactants (**e.g.,** Triton s X-100 or 50% propranolol) that increase the fluorescence by releasing the entrapped CF. Entrapment efficiency can be established by determining the ratios of CF before and after the disruption of vesicles. Entrapment efficiency is expressed as a millilitre of CF per mole of surfactant.

3) **Osmotic Activity:** The osmotic activity of niosomes can be determined by dispersing them in a hypertonic or hypotonic medium and observing the change in their size. In some systems, it is not possible to determine osmotic activity, as the vesicles undergo initial aggregation when the ions in the dispersed phase shield the electrostatic charge on the vesicle surface. This aggregation is prevented and study of osmotic activity of niosomes is made possible by adding steric stabilisers (**e.g.,** polyoxyethylene compounds) in the vesicle membrane.

4) **Vesicle Surface Charge:** Vesicular dispersions should carry surface charge as aggregation of vesicles in isotonic saline solution occurs when the vesicles are prepared with charged molecules in the bilayer. Surface charge is characterised in terms of voltage at the particle surface and zeta or surface potential (occurs at a distance from the surface and is measured by the Doppler shift of light scattered by moving particles in an electric field).

9.3.6. Applications

Niosomes are potentially used to deliver many pharmacological agents for their action against various diseases. Some of their therapeutic applications are:

1) **Targeting of Bioactive Agents**
   i) **To Reticulo-Endothelial System (RES):** The cells of RES take up the niosomal vesicles by circulating serum factors, known as opsonins, which mark them for clearance. Such localised drug accumulation has been used for treating animal tumours that metastasize to the liver and spleen, and for treating parasitic infestation of liver.
   ii) **To Organs other than RES:** Carrier system can be directed to specific body sites by using antibodies. Immunoglobulins readily bind to the lipid surface, and thus are conveniently used for targeting drug carrier. Many cells have the intrinsic ability to recognise and bind carbohydrate determinants to direct carrier systems to particular cells.

2) **Neoplasia:** Doxorubicin is an anthracycline antibiotic with broad spectrum anti-tumour activity. It shows a dose-dependent irreversible cardiotoxic effect. By delivering this drug via niosomes into mice bearing S-180 tumour, their life span increased and the proliferation rate of sarcoma decreased. Niosomal entrapment of this drug also increased its half-life, prolonged its circulation, and altered its metabolism. Intravenous administration of methotrexate entrapped in niosomes to S-180-tumour bearing mice resulted

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in total regression of tumour and also higher plasma level and slower elimination. Niosomes containing anti-cancer drugs, if suitably designed, will be expected to accumulate within tumours in a similar manner to liposomes.

3) **Leishmaniasis:** Niosomal drug targeting is used for treating diseases in which the infecting organism resides in the organ of RES. Leishmaniasis is a disease in which the parasite invades the cells of liver and spleen. Antimonials (related to arsenic) are the commonly prescribed drugs; however, they can damage the heart, liver and kidneys at high concentration. **Hunter *et al.*** studied antimony distribution in mice, and showed high liver level after intravenous administration of the carrier forms of the drug.

4) **Delivery of Peptide Drugs: Yoshida *et al.*** studied oral delivery of 9-desglycinamide and 8-arginine vasopressin entrapped in niosomes in an *in-vitro* intestinal loop model, and showed a significant increase in peptide stability.

5) **Immunological Application of Niosomes:** Niosomes have been used for studying the nature of immune responses provoked by antigens. **Brewer** and **Alexander** showed that niosomes are potent adjuvant in terms of immunological selectivity, low toxicity, and greater stability.

6) **Niosomes as Carriers for Haemoglobin:** Niosomes can be used as a haemoglobin carrier. Niosomal suspension shows a visible spectrum superimposable onto that of free haemoglobin. Vesicles are permeable to oxygen and haemoglobin dissociation curve can be modified similarly to non-encapsulated haemoglobin.

7) **Transdermal Delivery of Drugs by Niosomes:** Transdermal delivery has a disadvantage of slow drug penetration through skin. Transdermal delivery of drug incorporated in niosomes increases the drug penetration rate. **Jayraman *et al.*** studied the topical delivery of erythromycin via niosomes in hairless mouse, and showed that non-ionic vesicles can be formulated to target pilosebaceous glands.

8) **Other Applications**
   i) **Sustained Release:** Niosomes offer a sustained release action, and this property can be used for drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via niosomal encapsulation.

   ii) **Localised Drug Action:** Drug delivery through niosomes helps in achieving localised drug action, as their size and low penetrability through epithelium and connective tissue keeps the drug localised at the administration site. Localised drug action enhances the efficacy of drug potency and also reduces its systemic toxic effects.

   For example, antimonials encapsulated in niosomes are taken up by mononuclear cells, and result in localisation of drug, increased potency, reduced dose requirement, and decreased toxicity.

9.3.7. Advantages

Niosomes have the following advantages:

1) The vesicle suspension is water-based vehicle, and this offers high patient compliance than the oily dosage forms.
2) They are structurally composed of hydrophilic, amphiphilic and lipophilic moieties, and thus can accommodate drug molecules with varied ranges of solubility.
3) Their formulation characteristics are variable and controllable, thus vesicle characteristics can be controlled by altering vesicle composition, size, lamellarity, trapped volume, surface charge, and concentration.
4) The vesicles act as a depot and release the drug in a controlled manner.
5) They are osmotically active and stable, and also increase the stability of entrapped drug,
6) The surfactants are biodegradable, biocompatible, and non-immunogenic.
7) Handling and storage of surfactants require no special conditions.
8) They improve oral bioavailability of poorly absorbed drugs and enhance their skin penetration.
9) They can reach the site of action when administered by oral, parenteral and topical routes.
10) They improve the therapeutic performance of the drug by delaying clearance from the circulation, protecting the drug from biological environment, and restricting the effects to target cells.

9.3.8. Disadvantages

Niosomes have the following disadvantages:

1) They have a low solubility.
2) They have a short half-life.
3) Their production cost is high.
4) They may undergo aggregation and fusion.
5) Leakage of the entrapped drug may occur.
6) They show physical instability.

9.4. NANOPARTICLES

9.4.1. Introduction

Nanoparticles are 10-1000nm (1µm) sized, solid colloidal particles that comprise of macromolecular materials in which the active ingredient (drug or biologically active material) is dissolved, entrapped, encapsulated, adsorbed, and/or attached. On the basis of their preparation, nanoparticles are of the following **two types**:

1) Nanospheres, and
2) Nanocapsules.

9.4.2. Structure

Nanospheres have a matrix-type structure in which the drug is dispersed; while, **nanocapsules** have a membrane-wall structure in which the drug is contained within an oily core (**figure 9.5**).

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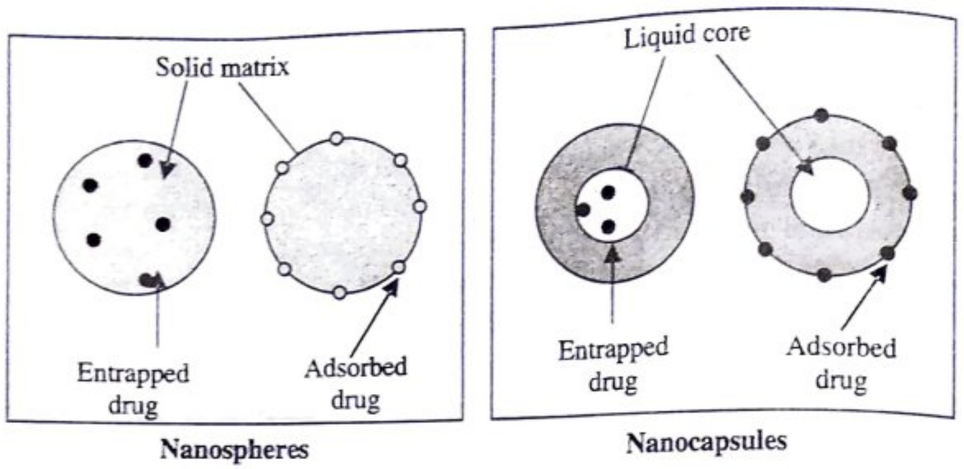


Figure 9.5: Structure of Nanospheres and Nanocapsules

Surface area of nanoparticles is very high, and can adsorb drug particles. They are made up of either artificial or natural polymers, and use of such polymers depends on their bioacceptability, which in turn depends on the properties of the carrier material, i.e., polymer and auxiliary substances. These systems can also be used for intravenous injection, if their particle size is reduced. As the smallest blood capillaries have the diameter of 4µm, the solid particles should have a smaller diameter to pass through the capillaries. Smaller particles are also required for intramuscular and subcutaneous administration. Irritant reactions occurring at the injection site can also be minimised if particles are small in size.

The final choice of appropriate polymer, particle size, and manufacturing method depends on the following three characters:

1) Bioacceptability of the polymer,
2) Physicochemical properties of the drug, and
3) Therapeutic goal to be achieved.

9.4.3. Methods of Preparation

Various methods are available for the preparation of nanoparticles, and these methods allow extensive modulation of structure, composition, and physicochemical properties of nanoparticles. The preparation method is selected on the basis of the raw materials to be used and the solubility characteristics of the drug to be associated with the particles.

The traditional methods used for manufacturing nanoparticles were derived from the field of latex engineering, developed by polymer chemists. These methods were selected on the basis of *in situ* polymerisation of a monomer in different media.

These polymerisation-based methods have the following **drawbacks** and **limitations**, despite of the technological advancements in this field:

1) Nanoparticles prepared by polymerisation method are insufficiently biodegradable, therefore are not used for regular therapeutic administration.
2) Sometimes, it is very difficult to predict the molecular weight of the final polymerised material because of the multicomponent nature of polymerisation media.

3) Drug activity can be inhibited as drug particles may interact with activated monomers or with the numerous H^+ ions present in the anionic polymerisation process.
4) The toxic residues (**e.g.,** unreacted monomer, initiator, and surfactant molecules) that may be present undergo a time-consuming elimination.

In order to avoid these limitations and to achieve biodegradable polymers, well-characterised and non-toxic nanoparticles, new methods based on the dispersion of well-characterised, pre-formed polymers (natural macromolecules such as biopolymers and synthetic polymers) have been developed in the recent years. Such efforts have enlarged the possibilities for biodegradable nanoparticulate formulation. These new manufacturing techniques are used for the production of both nanospherical and nanocapsular systems.

Nanoparticle Preparation from Synthetic Pre-formed Polymers

Various synthetic polymers are available for the preparation of nanoparticles, and the most common synthetic polymers belong to the family of polyesters [**e.g.,** Poly D,L-lactide-co-glycolide (PLGA) and Poly D,L-lactide (PLA)]. These polymers are most preferred because they have adequate biodegradability, biocompatibility and bioresorbability properties.

Given below are the preparation methods for nanoparticles, using the synthetic pre-formed polymers:

1) **Solvent Emulsification Evaporation:** In this method, the pre-formed polymer and the drug are dissolved in a water-immiscible organic solvent. This mixture is emulsified in an aqueous solution having a stabiliser. In order to reduce the globule size, the resultant crude emulsion is exposed to a high-energy source (an ultrasonic sonicator) or passed through homogenisers, colloid mills, or microfluidisers. Thereafter, the organic solvent is removed by exposing the solution to heat and vacuum, thus a fine aqueous dispersion of nanoparticles is formed.

2) **Salting Out:** A new procedure for preparation of pseudolatexes was developed by **Bindsdhaedler *et al.*** in 1988. This method was adapted and optimised by **Allemann** and **Leroux** for drug-loaded nanoparticles. In this method, a water-miscible solvent is separated from aqueous solutions through a salting-out effect.

   Due to its solubility properties and ability to separate from aqueous solutions by salting out the electrolytes, acetone is preferred as the water-miscible solvent. The pre-formed polymer and the drug are dissolved in acetone. The obtained mixture is emulsified under vigorous magnetic stirring in an aqueous gel having the salting-out agent (electrolytes, **e.g.,** magnesium acetate or magnesium chloride) and a colloidal stabiliser. The resultant emulsion is diluted with a sufficient volume of water to increase the diffusion of acetone into the aqueous phase. This increases the formation of nanoparticles. Thereafter, the solvent and the salting-out agent are eliminated by cross-flow filtration.

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3) **Emulsification Diffusion:** This method is the modified form of the salting-out method, but it avoids the use of salts and intensive purification steps. A partially water-soluble solvent, which has been previously saturated in water to ensure the initial thermodynamic equilibrium of both liquids, is used in this method. The pre-formed polymer is dissolved in the water-saturated solvent and this organic phase is emulsified under vigorous agitation in an aqueous solution having a stabiliser.

   Thereafter, water is added to this system, due to which solvent diffuses into the external phase and forms nanoparticles. The solvent can also be eliminated by distillation or cross-flow filtration depending on the boiling point of the solvent.

4) **Spontaneous Emulsification Solvent Diffusion:** This method was developed by **Niwa *et al.*** In this method, nanoparticles are formed by pouring the polymeric organic solution into an aqueous phase with continuous moderate magnetic stirring. One technical feature of this method is that in this a binary mixture of a water-miscible organic solvent is used and a water-immiscible solvent is used for the polymeric solution. Thus, the particles are formed by emulsification and subsequent solvent evaporation.

5) **Solvent Displacement:** This technique was first developed and patented by **Fessi *et al.*** In this method, the polymer, drug and a lipophilic stabiliser (phospholipids) are dissolved in a semi-polar water-miscible solvent (**e.g.,** acetone or ethanol).

   The resultant solution is poured or injected into an aqueous solution having a stabiliser (**e.g.,** poloxamer-188) under magnetic stirring. Thus, nanoparticles are formed instantaneously by rapid solvent diffusion, which is then eliminated from the suspension by heating under reduced pressure.

9.4.4. Evaluation

Nanoparticles are evaluated as given below in **table 9.2**:

Table 9.2: Evaluation of Nanoparticles

Parameters	Evaluation Techniques
Particle size and morphology	Transmission electronic microscopy, scanning (electron, force, tunnelling) microscopy, freeze-fracture electron microscopy, and photon correlation spectroscopy.
Drug content *in vitro* drug release	Ultra centrifugation and quantitative analysis of *in vitro* release characteristics under physiologic and sink conditions.
Molecular weight crystallinity	Gel permeation chromatography, X-ray diffraction, and differential scanning calorimetry.
Surface charge and surface hydrophobicity	Zeta potential measurement, hydrophobic interaction chromatography, and contact angle measurement.
Surface chemical analysis	Secondary ion mass spectrometry, X-ray photoelectron spectroscopy, nuclear magnetic resonance, and Fourier transform infrared spectroscopy.
Protein adsorption	Two-dimensional polyacrylamide gel electrophoresis.

9.4.5. Applications

Nanoparticles have the following therapeutic applications:

1) They are used for intracellular targeting of anti-infective drugs, thus the intracellular infections of human body can be treated easily.
2) They are used for targeting cytostatic drugs, thus their toxicity is reduced and therapeutic activity is enhanced.
3) They are used for specific targeting of anti-inflammatory drugs to areas of inflammation, thus the side effects of these drugs are minimised.
4) They are used for ocular delivery systems, and for delivering pilocarpine and other miotic drugs.
5) They are used as carriers for radio nucleotides and for diagnostic purposes in nuclear medicine.
6) They help to improve the solubility and bioavailability of poorly soluble drugs.
7) They help to deliver drugs across the blood-brain barrier.
8) They are also used to formulate sustained release preparations.
9) They are used for controlled release of disinfectants or algaecides into large bodies, such as insect pest feed on colloidal particles.
10) They are used for targeted delivery of proteins and peptides.
11) They are used as adjuvant to obtain antigens that are potent enough to be used as vaccines.
12) Solid Lipid Nanoparticles (SLN) are used to formulate skin and hair care products in which the oily core contains different cosmetic oils and lipophilic agents.

9.4.6. Advantages

Following are the advantages of using nanoparticles as a drug delivery system:

1) Their particle size and surface characteristics can be manipulated easily, thus both passive and active drug targeting can be achieved after parenteral administration.
2) Modification of nanoparticle surface can be performed easily to alter the biodistribution of drugs with subsequent clearance of the drug, thus maximum therapeutic efficacy of the drug can be obtained with minimal side effects.
3) The characteristics of controlled release and particle degradation can be easily modulated by selecting the matrix constituents.
4) In nanoparticles, drug loading is comparatively high and drugs can be incorporated without any chemical reaction; this characteristic is used to preserve the drug activity.
5) By attaching the targeting ligands to surface of nanoparticles or by using magnetic guidance, site-specific targeting can be achieved.
6) Liposomes and polymer-based nanoparticles are biodegradable, therefore are possibly risk free as do not accumulate in the body.
7) Small-sized nanoparticles can enter the smaller capillaries to allow efficient drug accumulation at the target sites.
8) They can be administered through various routes including oral, nasal, parenteral, intra-ocular, etc.

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9.4.7. Disadvantages

In spite of the above mentioned advantages, nanoparticles have the following disadvantages:

1) They may alter physical properties and cause particle-particle aggregation, thus making physical handling of nanoparticles difficult in liquid and dry forms due to smaller size and larger surface area.
2) It has been observed that nanoparticles are very reactive in the cellular environment because their smaller particle size leads to greater surface area.
3) Small particle size is also responsible for limited drug loading and burst release.

These problems related to nanoparticles have to be sorted out before their clinical or commercial use.

9.5. MONOCLONAL ANTIBODIES

9.5.1. Introduction

Monoclonal antibodies were developed by **Köhler** and **Milstein** in **1975** and were used for antibody therapy for disease. Since then, various pre-clinical and clinical studies have been performed with monoclonal antibodies and derivatives. Most of the studies were based on antigen recognition by antibodies and to develop cancer therapy. These strategies are mainly targeted to tumour-associated antigens present on normal cells, but over-expressed by tumour cells.

More recently developed clinical application is the use of these antibodies against other molecules; **for example,** anti-TNFα antibodies are used to treat chronic inflammatory diseases; anti-VEGF (Vascular Endothelial Growth Factor) antibodies are used to inhibit new blood vessel formation or angiogenesis.

9.5.2. Methods of Preparation

Monoclonal antibodies can be developed by the following methods:

1) Immunisation of mice and selection of mouse donors for generation of hybridoma cells,
2) Screening of mice for antibody production,
3) Fusion of myeloma cells with immune spleen cells,
4) Selection of hybridoma cells,
5) Checking for hybridoma cells, and
6) Cloning of hybridoma cell lines.

9.5.3. Applications

Monoclonal antibodies are mostly used as reagents for diagnostic and research purposes. They are used in diagnostic kits, like ELISA and Immunofluorescence to diagnose various diseases. Given below are the uses of monoclonal antibodies:

1) **For Measuring Human Lymphocyte Sub-Populations:** Anti-CD3 identifies all mature T-lymphocytes, anti-CD4 identifies helper T-lymphocyte subset, and anti-CD8 identifies cytotoxic T-lymphocyte subset.

2) **For Immunosuppression:** Anti-CD3 depresses T-cell function and anti-CD4 induces tolerance.
3) **For Passive Immunisation:** High titre antimicrobial human monoclonals are used for passive protection.
4) **For Blood Grouping:** Anti-A monoclonal is used as a more reliable standard reagent than the conventional anti-sera.
5) **For Cancer Diagnosis:** Monoclonal anti-T Acute Lymphocytic Leukaemia (TALL) is used to differentiate non-TALL.
6) **For Imaging Purposes:** Radioactive anti-carcino embryonic antigen is used for localising colonic tumours or secondary metastases by scanning.
7) **For Cancer Treatment:** Monoclonal antibody along with a strongly-radioactive atom (Iodine-131) is used to kill the target cancer cells.
8) **For Antigen Purification:** Antigen is isolated from mixtures by monoclonal affinity chromatography.
9) Chimeric monoclonal antibodies containing human Fc portion are preferred for human use.

9.6. SUMMARY

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

1) In **targeted drug delivery system**, the pharmacologically active medicament is selectively targeted or delivered to its action or absorption site (and not to the non-target organs, tissues, or cells).
2) **Paul Ehrlich** (a microbiologist) gave the concept of designing targeted delivery system and proposed the idea of delivering drug in the form of magic bullet.
3) Targeted drug delivery means accumulation of pharmacologically active moiety at the desired target in therapeutic concentration and at the same time restricting its entry into normal cellular lining, thereby improving therapeutic index.
4) **Passive targeting** involves accumulation of the drug at areas around the desired site, **e.g.,** in case of tumour tissues; this effect is called **Enhanced Permeability Retention** (EPR).
5) **Active targeting** utilises ligand-receptor interactions, and describes drug targeting interactions. However, a ligand and a receptor interact only when the two are in close proximity (i.e., <0.5mm).
6) **Inverse targeting** can be achieved by suppressing the normal function of RES by pre-injecting blank colloidal carriers or macromolecules (like dextran sulphate) in large amounts.
7) **Dual targeting** utilises carrier molecules exhibiting their own therapeutic activity, and thus increases the therapeutic effect of drug.
8) **Double targeting** involves combining of temporal and spatial methodologies to target a carrier system.

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CHAPTER 10

Ocular Drug Delivery System

10.1. OCULAR DRUG DELIVERY SYSTEM

10.1.1. Introduction

Eyes exhibit drug disposition characteristics. In many cases, topical application of drugs is considered the method of choice due to its convenience and safety for ophthalmic chemotherapy. The major challenge to the formulator is to avoid or bypass the protective barriers of the eye without permanently damaging the tissues. Development of innovative, more sensitive diagnostic techniques and novel therapeutic agents offer ocular delivery systems with high therapeutic efficacy. Conventional ophthalmic formulations, like solution, suspension, and ointment have many disadvantages that cause poor bioavailability of drugs in the ocular cavity. The prime objective of designing an ocular therapeutic system is to achieve an optimal drug concentration at the active site for suitable duration.

Ocular disposition and elimination of a therapeutic agent depend on its physicochemical properties and also on the ocular anatomy and physiology. For successfully designing an ocular drug delivery system, the formulator should have an integrated knowledge of the drug molecule and the constraints offered by the ocular administration route.

The various approaches taken to increase the bioavailability and the duration of therapeutic action of ocular drugs can be divided into two categories. The **first** is based on the use of sustained drug delivery systems that provide controlled and continuous delivery of ophthalmic drugs. The **second** is enhancing corneal drug absorption and reducing pre-corneal drug loss. Ideal ophthalmic drug delivery should sustain the drug release and remain in the vicinity of front of the eye for prolonged time period. Therefore, ophthalmic drug delivery should be essentially optimised by adding polymers of various grades, by developing *in situ* gel or colloidal suspension, or by using erodible or non-erodible insert to prolong the pre-corneal drug retention.

An **ideal ophthalmic drug delivery system** should have the following **characteristics**:

1) It should exhibit good corneal penetration.
2) It should enhance ocular drug absorption through prolong contact time with corneal tissue.
3) Its instillation into the eyes of the patient should be easy.
4) It should have a reduced frequency of administration.
5) It should improve patient compliance.
6) It should give rise to less toxic and side effects.

7) It should minimise pre-corneal drug loss.
8) It should be non-irritative and comfortable, i.e., the viscous solution should not cause lachrymal secretion and reflex blinking.
9) It should not cause blurred vision.
10) It should be relatively non-greasy.
11) It should have appropriate rheological properties and concentrations of the viscous system.

10.1.2. Advantages

Ocular drug delivery system has the following advantages:

1) It provides increased accurate dosing to overcome the side effects of pulsed dosing produced by conventional systems.
2) It provides sustained and controlled drug delivery.
3) It improves the ocular bioavailability of drug by increasing the corneal contact time by effective adherence to corneal surface.
4) It provides targeting within the ocular globe to prevent the loss to other ocular tissues.
5) It bypasses the protective barriers of the eyes, like drainage, lacrimation and conjunctival absorption.
6) It enhances therapeutic efficiency of the drug.
7) It provides better housing of delivery system.
8) It can be easily administered by the patient himself.
9) It shows quick absorption and less visual and systemic side effects.
10) It provides comfort and improves patient compliance.

10.1.3. Disadvantages

Ocular drug delivery system has the following disadvantages:

1) The drug solution stays in the eye surface for a very short time.
2) It shows poor bioavailability.
3) It shows instability of the dissolved drug.
4) It requires preservatives.
5) Dosage form cannot be terminated during emergency.
6) It causes interference with vision.
7) Its placement and removal is difficult.
8) It may suffer occasional loss during sleep or while rubbing eyes.

10.1.4. Ocular Drug Delivery Routes

Given below are the various routes of ocular drug delivery:

1) **Intra-Vitreal:** This administration route involves injecting the drug in the vitreous humour of the eyes. Intra-vitreal administration of drugs is preferred for treating various conditions of the eyes.
2) **Intra-Cameral:** This administration route involves injecting the drug in the anterior or posterior chamber of the eye. **For example,** an anaesthetic agent is injected into the anterior chamber of the eye during surgery.
3) **Peril-Ocular:** This administration route involves injecting the drug around the eye. **For example,** through peril ocular steroid injection, steroid is placed around the eye for treating intraocular inflammation or swelling of the eyes.

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4) **Suprachoroidal:** This administration route involves injecting the drug in the suprachoroidal space (between the sclera and the choroid) of the eyes.

5) **Sub-Conjunctiva:** This administration route involves applying the drug to the mucus membrane that lines the exposed part of the eyeball and inner surface of the eyelids.

6) **Topical:** This administration route involves applying the drug in the form of eye drops, ointments, gels, or emulsions for treating anterior segment diseases. This is the most preferred route as it is easy to administer and is also cheap.

7) **Systemic:** The blood aqueous barrier and blood retinal and posterior segment ocular drug delivery, barrier are the major barriers for anterior segment.

10.1.5. Intraocular Barriers

Given below are the intraocular barriers of the eyes:

1) **Drug Loss from the Ocular Surface:** After instillation, the lacrimal fluid removes instilled compounds from the eye surface. The lacrimal turnover rate is only 1µl/min, still excess volume of the instilled fluid flows to the nasolacrimal duct in a few minutes. Another source of non-productive drug removal is its systemic absorption instead of ocular absorption. Systemic absorption may take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity.

2) **Lacrimal Fluid-Eye Barriers:** The epithelium layer of cornea restricts drug absorption from the lacrimal fluid into the eye. The corneal epithelial cells form tight junctions to limit the paracellular drug permeation. Therefore, lipophilic drugs in comparison to hydrophilic drugs have higher permeability in the cornea. Generally, conjunctiva is leakier epithelium than the cornea and its surface area is also 20 times greater than that of the cornea.

3) **Blood-Ocular Barriers:** These barriers provide protection to the eyes from xenobiotics in the bloodstream. These barriers have two parts, namely blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is made up of endothelial cells in the uvaam (middle layer of the eye below the sclera, and consists of iris, ciliary body, and choroid). This barrier prevents the entry of plasma albumin into the aqueous humour, and also restricts the hydrophilic drugs to enter the aqueous humour from plasma.

   The posterior barrier between blood stream and eye is made up of Retinal Pigment Epithelium (RPE) and the tight walls of retinal capillaries. Unlike retinal capillaries, the choroid vasculature has extensive blood flow and leaky walls. Drugs easily enter the choroidal extravascular space, but their distribution into the retina is limited by the RPE and retinal endothelia.

4) **Corneal and Non-Corneal Routes of Absorption:** Lacrimal drainage and systemic absorption from the conjunctiva wash away ophthalmic drops (the most common form of ocular drugs). This allows absorption of only a small concentration of the drug. Small lipophilic molecules of topical drugs absorb through the cornea, while large hydrophilic molecules of topical drugs (such as proteins/gene-based medicines) absorb through the conjunctiva and sclera.

The mechanical and chemical barrier functions of the cornea control the entry of exogenous substances into the eyes, thus protect the intraocular tissues. Human cornea is about 12mm in diameter and 520µm in thickness. It is composed of five layers, namely the epithelium, basement membrane (Bowman's layer), stroma, Descemet's membrane, and endothelium.

Table 10.1: Barriers for Ocular Drug Delivery

	Conjunctiva	Cornea	Sclera
Surface area	17.65 ± 2.12 cm^2	1.04 ± 0.12	16-17
Thickness	–	0.57mm	0.4-0.5mm
Structural composition	Mucous membrane Epithelium Vasculature	5 layers: Epithelium, Bowman's membrane, Stroma, Descemet's membrane, Endothelium	Collagen fibres Water Proteoglycans Monopolysaccharides Elastic fibres Fibroblast

10.1.6. Methods To Overcome- Preliminary Study

The ocular drug delivery systems are a novel initiative and have been formulated with two main objectives, i.e., bioavailability and controlled release. The different approaches to ocular drug delivery are:

1) **Viscous Eye Drops:** The pre-corneal residence time can be increased and the drug loss due to lacrimal drainage can be reduced by adopting several strategies. Eye drops have undergone some modifications, like addition of viscosity enhancers (**e.g.,** hydrophilic polymers, such as celluloses, polyvinyl alcohol, and polyacrylic acid) and bioadhesive agents, and this has proved to be effective.

2) **Gels:** This formulation not only provides effective contact between the formulation and the corneal surface, but also helps to sustain the release rate of drug. The problems associated with gels are difficulty in proper administration due to their high viscosity, and blurred vision and matted eyelids that hamper patient compliance. Still, gels are prescribed for their longer duration of action, reduced frequency of administration, ease of administration, and intermediate cost.

   Polymeric gels are classified into two **pre-formed gels** and ***in situ* forming gels**. Both improve the bioavailability and reduce the side effects produced by the systemic absorption of topically applied ophthalmic drugs.

   ***In situ* gel-forming systems** are viscous liquids that shift to a gel phase on exposure to physiological conditions. The main **advantages** of this formulation are administration of accurate and reproducible quantities in comparison to the already gelled formulations, and promoting pre-corneal retention. Different methods to cause phase transitions in the eye surface involve change in viscosity by changing temperature, pH and electrolyte composition, or eyelids movement.

   Poloxamers are polyols having thermal gelling properties and whose solution viscosity increases when the temperature is increased from a critical temperature (16°C) to physiological temperature (33-34°C, the surface

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temperature of eye). Cellulose acetate phthalate is a polymer having potentially useful properties for sustained drug delivery to the eyes, since latex is a free-running solution at pH 4.4 and it coagulates when the tear fluid increases the pH to 7.4. The gellan gum forms a clear gel in the presence of mono or divalent cations present in the lacrimal fluid.

Bioadhesive polymers have gained much interest recently as it significantly improves the performance of controlled delivery systems, improves drug delivery by prolonging residence time through optimum contact with the absorbing surface, and reduces dosing frequency. These polymers form strong non-covalent bonds with the mucin-coating biological membranes and remain in place till the mucin is present.

Bioadhesives used for drug delivery systems are mostly composed of synthetic mucoadhesives, which include linear chains of water-soluble polymers and swellable networks (joined by cross-linking agents) of water-insoluble polymers. These polymers are of high molecular weight, cannot cross biological membranes, and include cellulosic components, **e.g.,** carboxy methyl cellulose and polyanion bioadhesives, such as polyacrylic acid. Bioadhesive polymers are used in ocular formulations in small quantities as viscosifying or gel-forming agents.

3) **Eye Ointments:** These are formulated with mixtures of semisolid and solid hydrocarbons (paraffin), which are non-irritant to the eyes and have a melting or softening point close to body temperature. Ointments may be simple bases (one continuous phase is formed) or compound bases (a two-phase system, **e.g.,** an emulsion, is employed). The medicament is added to the base either in solution form or as a finely micronised powder. Ointments, after instillation in the eyes, break-up into small droplets and remain as a drug depot in the *cul-de-sac* for prolong time periods. Thus, ointments improve drug bioavailability and are suitable for sustaining drug release. Ointments are safe and well-tolerated by the eyes; however, they have relatively poor patient compliance as they blur the vision and may occasionally irritate the eyes.

4) **Prodrugs:** They enhance corneal drug permeability by changing the hydrophilicity or lipophilicity of the drug. Several ophthalmic drugs have been investigated for prodrug derivatisation using esterase properties found in tears and in anterior chamber. Dipivefin is a prodrug of epinephrine, and exhibits better corneal penetration properties.

5) **Penetration Enhancers:** Chelating agents, preservatives, surfactants, and bile salts are some penetration enhancers that improve the corneal membrane permeability. However, concerns about causing corneal membrane damage on chronic administration of such agents are still to be elucidated. Hydroxypropyl cyclodextrin has shown favourable toxicological properties after ocular administration. Sulfobutyl ether β-cyclodextrin has shown to increase the ocular absorption of drugs. Chitosan has been found to be suitable for ocular drug solutions and gels due to its bioadhesive and permeability enhancing properties.

6) **Viscosity Enhancers:** These agents are added to ophthalmic drug solutions based on the principle that increased vehicle viscosity slow down the elimination from pre-ocular area, and improve the pre-corneal residence time and allow a greater trans-corneal drug penetration in the anterior chamber. Polyvinyl Alcohol (PVA), Polyvinyl Pyrrolidone (PVP), Methylcellulose, Hydroxyethyl Cellulose, Hydroxypropyl Methylcellulose (HPMC), and Hydroxypropyl Cellulose are the **examples** of polymers used as viscosity enhancers.

7) **Microemulsions:** Their main **advantage** is increased solubilisation of drugs (**e.g.,** indomethacin, chloramphenicol, and sodium diclofenac), which in turn enhances the bioavailability. *In vivo* studies in rabbits have shown a delayed effect of the drugs incorporated in microemulsions, and improved bioavailability. This mechanism of delayed action relies on the adsorption of nanodroplets on cornea, which are not eliminated by lacrimal drainage and act as drug reservoirs.

8) **Liposomes:** Their mechanism of enhancing activity is the result of capture of positively charged liposomes on the negatively charged corneal surface. Liposomal formulations are more effective for lipophilic drugs than for hydrophilic drugs as the latter rapidly leak out from the vesicles. Bioadhesive polymers, like carbopol, are added in the vesicular wall to provide bioadhesivity and enhance drug bioavailability.

9) **Niosomes:** These are bilayered structural vesicles of non-ionic surfactant. Niosomes can encapsulate lipophilic as well as hydrophilic compounds. They reduce systemic drainage and improve residence time of the drugs, and thus increase ocular bioavailability of the drugs. Niosomes are non-biodegradable and non-biocompatible.

In a study, cyclopentolate was delivered by encapsulation in niosome, which released the drug independent of pH, and significantly enhanced its ocular bioavailability. Niosomal formulation of coated (chitosan or carbopol) timolol maleate, in comparison to timolol solution, also significantly lowered the intra-ocular pressure in rabbits.

10) **Nanoparticles/Nanospheres:** These are polymeric colloidal particles (10nm-1mm in size), in which the drug is dissolved, entrapped, encapsulated, or adsorbed. Encapsulation of the drug leads to its stabilisation. Nanoparticles or nanospheres are promising drug carriers for ophthalmic application.

11) **Nanosuspensions:** These are sub-micron colloidal system, consisting of poorly water-soluble drug suspended in a dispersion medium stabilised by surfactants. Nanosuspensions consist of inert colloidal carriers, like polymeric resins. They prolong the contact time of drug and improve its ocular bioavailability.

The surface charge of nanoparticles facilitates its adhesion to the cornea. Cloricromene (AD6) was formulated as nanosuspension by using Eduragit RS100 and RL100, and it was found to significantly raise the shelf-life and bioavailability of the drug.

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10.1.7. Ocular Formulations

The conventional dosage forms, like solutions, suspensions, ointments, gels, erodible inserts, ocular films, and non-erodible inserts, fail to meet the requirements of providing a constant rate delivery and prolonged time. The advantages and disadvantages of using conventional drug delivery systems are enlisted in **table 10.2**. Comparison for ophthalmic dosage form, criteria for their selection on the basis of duration of action of drug, bioavailability, its cost effectiveness, safety and patient compliance are summarised in **table 10.3**.

Table 10.2: Advantages and Disadvantages of Conventional Drug Delivery Systems

Dosage Forms	Advantages	Disadvantages
Solutions	Convenience	1) Rapid pre-corneal elimination. 2) Loss of drug by drainage. 3) No sustained action.
Suspensions	1) Patient compliance. 2) Best for drugs with slow dissolution.	1) Drug properties decide performance. 2) Loss of both solution and suspended solid.
Emulsions	1) Prolonged drug release from vehicle. 2) Enhanced pulsed entry.	1) Patient non-compliance. 2) Blurred vision. 3) Possible oil entrapment.
Gels	1) Comfortable 2) Less blurred vision than ointments.	1) No rate control on diffusion. 2) Matted eyelids after use.
Ointments	1) Flexibility in drug choice. 2) Improved drug stability. 3) Increased tissue contact time. 4) Inhibition of dilution by tears. 5) Resistance to nasolachrymal drainage.	1) Sticking of eyelids. 2) Poor patient compliance. 3) Blurred vision. 4) No true sustained effect. 5) Drug choice limited by partition coefficient.
Erodible Inserts	1) Sophisticated and effective delivery system. 2) Flexibility in drug type and dissolution rate. 3) Need only be introduced into eye and not removed.	1) Patient discomfort. 2) Requires patient insertion. 3) Movement of system around eye can cause abrasion.
Non-Erodible Inserts	1) Controlled rate of release. 2) Prolonged delivery. 3) Flexibility for type of drug selected. 4) Sustained release.	1) Patient discomfort. 2) Irritation to eye. 3) Patient placement and removal.

Table 10.3: Criteria for Selection of Ocular Dosage Forms

Gels	Injections	Inserts	Ointments	Orals	Solutions
Drug – Long duration required	Drug – Target site Accessibility Onset of response	Drug – Long duration required	Drug – Long duration required	Drug – Impermeable Topically Few systemic side effects	Drug – Soluble Less potent
Low bioavailability	–	Low bioavailability	Low bioavailability	–	Required high concentration
Intermediate cost	Requires physician	High cost per dose	Low cost	Low to moderate cost	Low cost
Some blurring	–	No blurring	Severe blurring	–	Little blurring
Selection – Simple	Selection – Last alternative	Selection – Good control	Selection – Slight	Selection – Drug	Selection – Convenient

administration; Reduced frequent administration	surgical application	of rate of drug administration younger patient.	threatening	designed not optimised.	accepted
Safety	Safety	Safety – Unnoticed expulsion	Safety	Safety	Safety – Solution clear

The recent formulation trends that are currently being explored are as follows:

1) **Polymeric Solutions:** Polymers, **e.g.,** methylcellulose, polyvinyl alcohol, hydroxypropyl methylcellulose, and polyvinyl pyrrolidone, are added to the eye drop solutions to increases the corneal drug penetration.

2) **Phase Transition Systems:** These are liquid dosage forms, which on instillation in the *cul-de-sac* shift to the gel or solid phase. The commonly used polymers are lutrol c-127 and polxamer-407. Viscosity of these polymers increases when their temperature is increased to 37°C. Cellulose acetate phthalate also coagulates when its pH of 4.5 is increased to pH 7.4 by tear fluid.

3) **Muco-Adhesive Dosage Forms:** A polymer solution or suspension on instillation in the eyes encounters mucin at the cornea and conjunctival surface. Adherence of the polymer to the mucin is termed as muco-adhesion. Mucus on the corneal surface is provided by the goblet-containing conjunctiva that is not tightly bound, so that a corneal adhesive would attach to cornea to be a true bio-adhesion.

4) **Collagen Shields:** They promote wound healing and deliver various medications to the cornea and other ocular tissues. Collagen is a structural protein of bones, tendons, ligaments, and skin. It forms more than 25% of the total body share in mammals. It is the main constituent of food grade gelatin.

5) **Pseudolattices:** These are a new class of polymeric colloidal dispersion and film-forming agents. They are used for application into the animals and humans for sustaining *in-vivo* drug activity. Organic solution of polymer is dispersed in an aqueous phase to form an o/w type emulsion.

6) **Ocular Penetration Enhancers:** These agents increase the bioavailability of topically applied peptides and proteins which are otherwise poorly absorbed due to unfavorable molecular size, charge, hydrophilic nature, and susceptibility to degradation by peptidases in the eyes.

7) **Ocular Drug Delivery Devices:** These are of the following three types:
   i) Matrix type drug delivery systems,
   ii) Capsule type delivery systems, and
   iii) Implantable drug delivery systems.

10.2. OCUSERTS

10.2.1. Introduction

Ocular inserts are thin, multi-layered, drug-impregnated, sterile preparations with solid or semi-solid consistency. Their size and shape are especially designed for ophthalmic application. These devices are instilled into *cul-de-sac* or sac of

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conjunctiva, in lower fornix, in upper fornix (less frequently), or on the cornea. They are made up of polymeric vehicle containing the drug, and are used for topical therapy. Ocular drug delivery is a fascinating and challenging task for the pharmaceutical researchers. A major barrier of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged time period. The anatomy, physiology, and biochemistry of the eyes make them invulnerable to foreign substances.

The challenge to the formulator is to avoid the protective barriers of the eyes without permanently damaging the tissues. The development of newer and more sensitive diagnostic techniques and therapeutics agents urges the development of successful and advanced ocular drug delivery systems.

Given below are the constraints placed by these conventional ocular therapies:
1) Short residence time,
2) Pulsed dosing of drug,
3) Frequent instillation, and
4) Large drainage factors.

For overcoming these constraints, newer ocular drug delivery systems are being explored to develop extended duration and controlled release strategy. Some newer, sensitive, and successful ocular drug delivery systems, like inserts, biodegradable polymeric systems, and collagen shields, are developed to improve ocular bioavailability and impart sustained action of ocular drugs.

10.2.2. Characteristics

Ocular inserts have the following characteristic features:
1) They are biostable and biocompatible with the eye tissues.
2) They are non-toxic and non-carcinogenic.
3) They are retrievable and they release the drug at a constant rate.
4) They are non-immunogenic and non-mutagenic.
5) They exhibit a good mechanical strength.
6) They do not encounter drug leakage.
7) They are easily sterilisable.
8) Their manufacture is easy and inexpensive.
9) They can incorporate various drugs.
10) They do not interfere with vision and oxygen permeability.

10.2.3. Approach

Ocular inserts are preparations with solid or semi-solid consistency, whose size and shapes (i.e., rod or shield) are especially designed for ophthalmic application. They are made up of a polymeric support with or without drug(s). The drug in the polymeric support is incorporated as dispersion or as a solution. The ophthalmic inserts are used for topical therapy. They aim to increase the contact time between the preparation and the conjunctival tissue to offer a sustained drug release that is suitable for topical or systemic treatment.

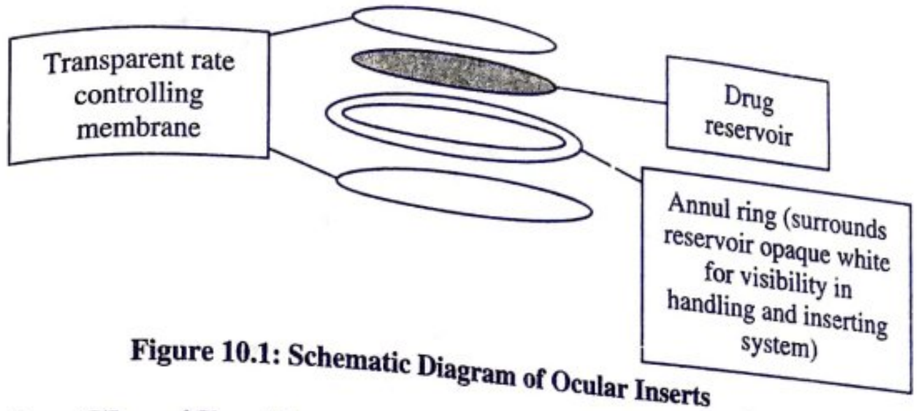


Figure 10.1: Schematic Diagram of Ocular Inserts

10.2.4. Classification

Ocular inserts are classified as shown in **figure 10.2**:

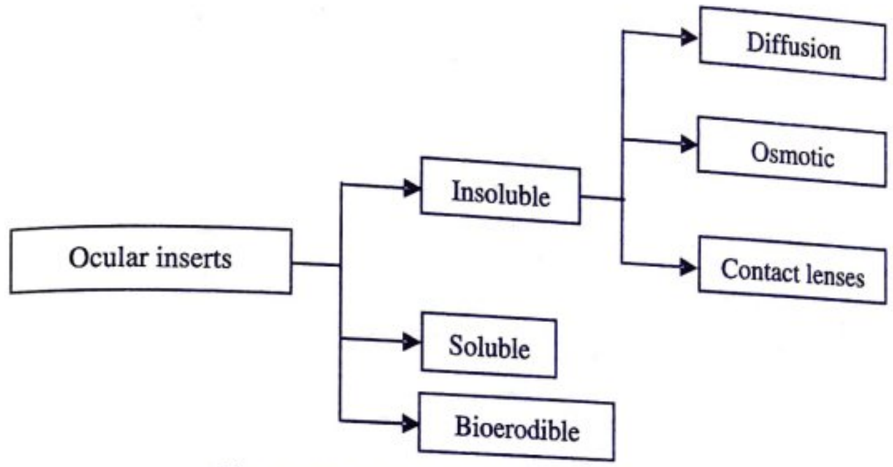


Figure 10.2: Classification of Ocular Inserts

10.2.4.1. Insoluble Ocular Inserts

These inserts are further classified into three classes, namely **diffusion systems**, **osmotic systems**, and **contact lenses**. The first two classes include a reservoir in contact with and supplying drug to the inner surface of the rate controller. The reservoir comprises of a liquid, a gel, a colloid, a semi-solid, a solid matrix, or a carrier, in which the drug is homogeneously or heterogeneously dispersed or dissolved. The third class includes contact lenses. The major **disadvantage** of these inserts is their insolubility, and thus they have to be removed after use.

1) **Diffusion Controlled Ocular Inserts:** The diffusion systems comprise of a central drug reservoir enclosed in a specially designed semi-permeable or micro-porous membrane (**figure 10.3**). This membrane allows the drug to diffuse through the reservoir at a pre-determined rate. The drug release from such a system is controlled by the lachrymal fluid that permeates through the membrane till internal pressure, which is sufficient to drive the drug out of the reservoir, is attained.

   The drug delivery rate is controlled by diffusion through the membrane. This consists of medicated core, prepared of a hydrogel polymer (like alginates) sandwiched between two sheets of transparent, lipophilic, rate controlling polymer (like ethylene/vinyl acetate co-polymer) membrane designed as per the required geometry suitable for insertion in the *cul-de-sac*.

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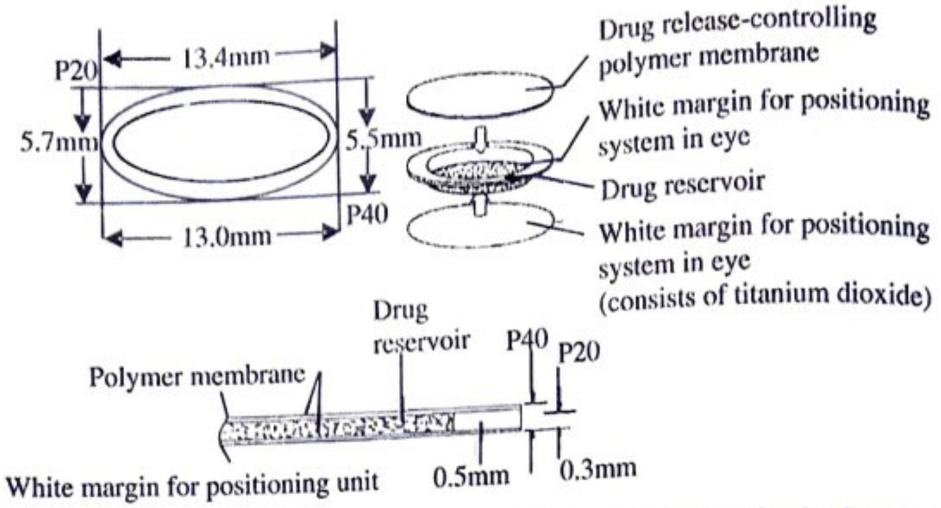


Figure 10.3: Schematic Diagram of a Diffusion Controlled Ocular Insert

When the device is placed in the *cul-de-sac*, the drug molecule penetrates through the rate controlling membrane at zero-order rate process:

$$\frac{Dq}{dt} = \frac{DpKm(Cr - Ct)}{Dm}$$

A typical *in vivo* release rate profile of pilocarpine from the ocusert pilo-20 is shown in **figure 10.4**. In the first hour, pilocarpine is released from the system at a rate three times higher than the programmed rate, i.e., 20 mg/hour.

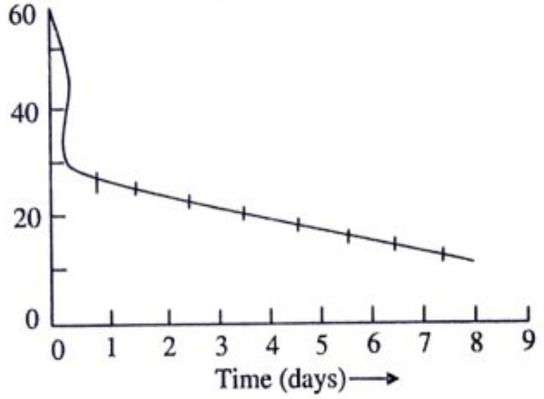


Figure 10.4: *In Vitro* Release Pattern of Pilocarpine from Ocusert Pilo-20 System

Diffusion controlled ocular inserts are used for various other ophthalmic therapeutic agents, like carbonic anhydrase inhibitors, epinephrine, anaesthetics, antibiotics, anti-inflammatory steroids, etc.

2) **Osmotic Ocular Inserts:** These inserts comprise of a central part surrounded by a peripheral part. The central part is composed of a single reservoir or two distinct compartments. It is composed of a drug with or without an osmotic solute dispersed through a polymeric matrix, so that the drug is surrounded by the polymer as discrete small deposits.

The drug and the osmotic solutes are placed in two separate compartments; the drug reservoir is enclosed in an elastic impermeable membrane and the osmotic solute reservoir is enclosed in a semi-permeable membrane. The peripheral part of osmotic inserts is composed of a covering film of an insoluble semi-permeable polymer.

The tear fluid diffuse into peripheral deposits through the semi-permeable polymeric membrane, wets them, and induces their dissolution. The solubilised deposits give rise to a hydrostatic pressure against the polymer matrix, thereby rupturing it in the form of apertures. The drug is released through these apertures from the deposits near the device surface, which is against the eye, under the influence of hydrostatic pressure. This corresponds to the osmotic part characterised by zero-order drug release.

Table 10.4: Components of Osmotic Ocular Inserts

Water-permeable matrix	Ethylene-vinyl esters co-polymers, plasticised Polyvinyl Chloride (PVC), polyethylene, cross-linked Polyvinyl Pyrrolidone (PVP)
Semi-permeable membrane	Cellulose acetate derivatives, Ethyl Vinyl Acetate (EVA), polyesters of acrylic and methacrylic acids (Eudragit).
Osmotic agents	Inorganic – magnesium sulphate, sodium chloride, potassium phosphate dibasic sodium carbonate and sodium sulphate. Organic – calcium lactate, magnesium succinate and tartaric acid.
Central reservoir	Glycerin, ethylene glycol, propylene glycol, water, methyl cellulose mixed with water, sodium alginate, poly (vinyl pyrrolidone), poly ox ethylene stearate
Micropores membrane	Polycarbonates, polyvinyl chloride, polysulfones, cellulose esters, cross-linked poly (ethyl oxide), cross-linked polyvinyl pyrrolidone, and cross-linked polyvinyl alcohol

3) **Contact Lenses:** These are composed of a covalently cross-linked hydrophilic or hydrophobic polymer that forms a three-dimensional network or matrix that can retain water, aqueous solution, or solid components. A hydrophilic contact lens, soaked in a drug solution, absorbs the drug, but does not deliver it as accurately as that delivered by other non-soluble ophthalmic systems. Such a system rapidly releases the drug in the beginning, and then with time the release rate declines exponentially. The release rate can be reduced by adding the drug homogeneously during the manufacture or by adding a hydrophobic component. Contact lenses have good prospects as ophthalmic drug delivery systems.

This type of device prolongs the drug/eye contact time considerably, and thus enhances bioavailability. Some of the polymers that can be used for preparing contact lenses are 2-hydroxyethylmethacrylate, vinyl pyrrolidone acrylic co-polymer, etc. When contact lenses are used as device, they are pre-soaked in the drug solution for a sufficient time for equilibration and are then inserted in the eyes.

10.2.4.2. Soluble Ocular Inserts

These inserts are the oldest class of ophthalmic inserts. They offer a great advantage of being entirely soluble, thus they do not need to be removed from the eyes, and thereby limiting the interventions to insertion only.

Types of Soluble Ocular Inserts

1) Based on natural polymers, **e.g.,** collagen, and
2) Based on synthetic or semi-synthetic polymers.

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The insert is soaked in a solution containing the drug (to absorb the drug), dried, and re-hydrated before applying in the eyes. The amount of drug loaded depends on the amount of binding agent, the concentration of drug solution into which the composite is soaked, and on the duration of soaking.

The drug release from such a system occurs by penetration of tears into the insert, and this induces drug release by diffusion and forms a gel layer around the core of the insert. This external gelification further induces drug release by diffusion. The release rate (J) is derived from Fick's law and yields the following expression:

$$J = \frac{ADKCs}{L}$$

Where, A = Surface area of the membrane.
K = Diffusion coefficient of the drug.
L = Membrane thickness.
Cs = Drug solubility in water.
D = Diffusion coefficient of the ocusert membrane.

Since all the terms on the right side of the above equation are constant, the release rate of the device is also constant.

The soluble ocular insert of cellulose derivatives can be sterilised by exposure to gamma radiation without altering the cellulose components.

Table 10.5: Components of Soluble Inserts Containing Synthetic Polymers

Soluble synthetic polymers	Cellulose derivatives – Hydroxypropyl cellulose methylcellulose, hydroxyethyl cellulose and hydroxypropyl cellulose; Polyvinyl alcohol, ethylene vinyl acetate co-polymer.
Additives	Plasticiser – Polyethylene glycol, glycerin, propylene glycol; Enteric coated polymer – Cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate; Complexing agent – Polyvinyl pyrrolidone; Bioadhesives – Polyacrylic acids.

10.2.4.3. Bioerodible Ocular Inserts

These inserts are fabricated from bioerodible or biodegradable polymers of hydrogel or non-hydrogel type. The drug release mechanism from this system depends on the erosion rate or degradation rate. Some erodible ocuserts are prepared with carboxy methyl cellulose, polyvinyl alcohol, collagen, etc., containing drug (like pilocarpine, gentamicin, etc.) in the form of discs or wafers.

Some of the recently marketed products are:

1) **Lacrisert:** It is a sterile rod-shaped device, made up of hydroxyl propyl cellulose. It does not contain any preservative, and thus is used for treating dry eye syndrome. It is 5mg in weight, 1.27mm in diameter, and 3.5mm in length. Lacrisert is inserted in the inferior fornix, where it imbibes water from conjunctiva and forms a hydrophilic film that stabilises the tear film, and hydrates and lubricates the cornea.

Advantages

By placing a single insert in the eye early in the morning, one can get a day long relief from dry eye syndrome. This once or twice daily regimen replaces 4 times an hour regimen.

2) **Soluble Ocular Drug Insert (SODI):** It is a sterile thin film of oval shape and 15-16mg in weight. When introduced in the inferior *cul-de-sac*, it is wetted by tear film, softens in 10-15 seconds, and takes the curved configuration of globe. In the next 10-15 minutes, the film turns into a viscous polymer mass; and in next 30-60 minutes, the mass becomes a polymer solution.

Advantages

Single SODI application replaces 4-12 drops instillation or 3-6 applications of ointment in cases of glaucoma and trachoma.

3) **Ocular Therapeutic System (OTS or Minidisk):** It consists of countered disc with a convex front and concave back surface that remains in contact with the eyeball. It resembles miniature contact lenses and is 4-5mm in diameter. The silicone-based pre-polymer is the major component of OTS. It can be hydrophilic or hydrophobic to allow extended release of water-soluble as well as water-insoluble drugs.

4) **Corneal Collagen Shield:** It is prepared by moulding collagen mixed with the drug in a contact lens configuration, followed by dehydration and sterilisation by gamma radiation. Many antibiotics and steroids have been delivered through this device.

Biodegradable inserts are composed of homogeneous dispersion of a drug included or not in a hydrophobic coating that is impermeable to the drug. They are made up of biodegradable polymers. The poly (orthoesters) and poly (orthocarbonates) are the biodegradable materials successfully used for ophthalmic dosage form. Contact between the biodegradable inserts and the tear fluid induces a superficial diversion of the matrix, thereby resulting in drug release.

10.2.5. Formulation Methods

Ocular inserts are formulated by the following methods:

1) **Solvent Casting Method:** In this method, different ratios of drug and polymer are used for preparing a number of batches. The polymer is dissolved in distilled water. The resultant solution is added with a plasticiser and an accurately weighed drug, under stirring conditions to obtain a uniform dispersion.

After proper mixing, the casting solution is poured in a clean glass petridish and covered with an inverted funnel to allow slow and uniform evaporation at room temperature for 2 days. The so obtained drug-containing dried films are cut by cork-borer into circular pieces of definite size, each containing equal quantity of the drug. Then the ocular inserts are stored in an airtight container (desiccator) under ambient condition.

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2) **Glass Substrate Technique:** In this method, drug reservoir film (of 1% w/w polymer, like chitosan) is soaked for a day in 1%v/v acetic acid solution to obtain a clear solution of chitosan in acetic acid solution. The undissolved portion of the polymer (chitin) is removed by filtering the solution through a muslin cloth. Required quantity of drug-β-cyclodextrin complex is added to the filtered chitosan solution and vortexed for 15 minutes to dissolve the complex. The obtained solution is added with 1%w/v propylene glycol (plasticiser) under stirring conditions to mix well.

   The resultant viscous solution is left undisturbed for 30 minutes for complete removal of air bubbles. The rate controlling films are casted by pouring the solution in the centre of levelled glass mould and drying at room temperature for 24 hours. The dried films are cut into ocuserts of desired size, each containing equal quantity of the drug. Then the matrix is sandwiched between the rate controlling membranes using non-toxic, non-irritating, water-insoluble gum. They are separately wrapped in aluminium foil and stored in a desiccator.

3) **Melt Extrusion Technique:** In this method, drug (like acyclovir) and the polymer are sieved through 60#, weighed, and blended geometrically. Plasticiser is added and again blended. The obtained blend is then charged to the barrel of melt flow rate apparatus and extruded. The extrudate is cut into appropriate size, packed in polyethylene lined aluminium foil, heat-sealed, and sterilised by gamma radiation.

10.2.6. Evaluation

Ocular inserts are evaluated based on the following parameters:

1) **Thickness of Film:** This parameter is measured with dial calliper at different points and by calculating the mean value. Reading is taken over a circular film of 38.5mm^2 area. The standard deviation in thickness is determined from the mean value.

2) **Drug Content Uniformity:** This parameter measures the drug uniformity in the cast film. This is done by cutting the cast films at different places, and keeping each film in vials containing 5ml of pH 7.4 phosphate buffer. The vials are then shaken to extract the drug from patch. 1ml of the resultant solution is withdrawn and diluted. The obtained solution is analysed spectrophotometrically using pH 7.4 phosphate buffer as a blank. The drug content is calculated using the following formula:

$$\text{Drug content in one patch (mg)} = \frac{As \times Cr}{Ar}$$

   Where, As =Absorbance of sample solution.
   Ar = Absorbance of standard solution.
   Cr = Concentration of drug in standard solution.

   The same procedure is followed for all the batches of cast films in triplicates and mean drug content and standard deviation of variance are computed.

3) **Uniformity of Weight:** This parameter measures the weight variation in the cast film. This is done by cutting three patches from different places of same

formulation and weighing them individually on the digital balance. The mean value of individual weights is calculated, and the standard deviation of weight variation from the mean value is computed.

4) **Percentage Moisture Absorption:** This parameter measures the physical stability or integrity of ocular inserts. This is done by weighing the inserts and placing them in a desiccator containing 100ml of saturated solution of aluminium chloride under 79.5% humid condition. The inserts are taken out after 72 hours and reweighed. The percentage moisture absorption is calculated using the formula:

$$\text{Percentage Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

5) **Percentage Moisture Loss:** This parameter measures the integrity of the film under dry conditions. This is done by weighing the inserts and placing them in a desiccator containing anhydrous calcium chloride. The inserts are taken out after 72 hours and reweighed. The percentage moisture loss is calculated using the formula:

$$\text{Percentage Moisture Loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

6) ***In Vitro* Drug Release:** This parameter simulates the actual physiological conditions prevailing in the eyes. *In vitro* drug release studies are carried out in a bi-chamber donor-receiver compartment model design using commercial semi-permeable membrane of transparent and regenerated cellulose type (sigma dialysis membrane). The membrane is tied at one end of the open cylinder that acts as the donor compartment. The ocular insert is placed in the donor compartment.

   The semi-permeable membrane is used to simulate ocular *in vivo* condition like corneal epithelial barrier to simulate the tear volume. 0.7ml of distilled water is added in the donor compartment and maintained at the same level during the study. The membrane surface is in contact with the reservoir compartment containing 25ml of pH 7.4 phosphate buffer. The contents of this reservoir are stirred continuously with a magnetic stirrer. 1ml samples are withdrawn from the receptor compartment at periodic intervals and replaced with equal volume of distilled water. The drug content is analysed in a UV-visible spectrophotometer at 246nm against reference standard using pH 7.4 phosphate buffer as blank.

7) ***In Vivo* Drug Release Rate Study:** Before beginning the *in vitro* drug release rate studies, the inserts are sterilised with UV radiation. Then the inserts are placed in a Petri dish containing 100mg of pure drug, spread in a thin layer. This dish along with polyethylene bags and forceps are placed in UV sterilisation chamber (hood), and are exposed to UV radiation for an hour. Thereafter, inside the sterilisation chamber the inserts are transferred in the polyethylene bag using forceps. The pure drugs, which were steri ised along with inserts, are diluted with pH 7.4 phosphate buffer and analysed for potency in a UV spectrophotometer.

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The male albino rabbits, weighing 2.5-3.0kg, are used for the experiment. They are housed in individual cages and customised to laboratory conditions for 24 hours. They are given free access to food and water. The previously sterilised drug-containing ocular inserts are placed in the lower conjunctiva's *cul-de-sac*. The inserts are placed in 7 eyes at the same time and one eye of each rabbit is served as control.

Ocular inserts are carefully removed at intervals of 2, 4, 6, 8, 10, 12 and 24 hours and analysed for drug content. The amount of remaining drug is subtracted from the initial drug content of inserts to get the amount of drug released in the rabbit eyes. Any fall out of the inserts during the experiment is also recorded. After 7 days of wash period, the experiment is repeated twice as before.

10.2.7. Advantages

Ocuserts have the following advantages:

1) They increase ocular residence, and thus give rise to prolonged drug activity and higher bioavailability with respect to standard vehicles.
2) They release drugs at a slow and constant rate.
3) They provide accurate dosing contrary to eye drops that are improperly instilled by the patient and are also partially lost after administration; while the ocular inserts contain a precise dose that is retained completely at the administration site.
4) They reduce systemic absorption that occurs freely with eye drops via nasolacrimal duct and nasal mucosa.
5) They improve patient compliance by reducing the frequency of administration and by lowering the occurrence of visual and systemic side effects.
6) They target internal ocular tissues through non-corneal (conjunctival scleral) routes.
7) They exhibit increased shelf-life with respect to aqueous solutions.
8) They do not require preservatives, thus reduce the risk of sensitivity reactions.
9) They may incorporate various novel chemical/technological approaches.

10.2.8. Disadvantages

Ocuserts have the following disadvantages:

1) The major disadvantage is their solidity, i.e., the patients (often oversensitive) feel them as an extraneous body in the eye.
2) Their removal from the eye becomes difficult due to the unwanted movement of the inserts to upper fornix.
3) They may occasionally undergo unintentional loss during sleep or while rubbing the eyes.
4) They cause interference with vision.
5) Their placement and removal (for insoluble types) is difficult.

10.3. SUMMARY

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

1) The prime objective of designing an ocular therapeutic system is to achieve an optimal drug concentration at the active site for suitable duration.
2) The **first** the duration of therapeutic action of ocular drugs is based on the use of sustained drug delivery systems that provide controlled and continuous delivery of ophthalmic drugs.
3) The **second** the duration of therapeutic action of ocular drugs is enhancing corneal drug absorption and reducing pre-corneal drug loss.
4) **Intra-vitreal** route involves injecting the drug in the vitreous humour of the eyes. Intra-vitreal administration of drugs is preferred for treating various conditions of the eyes.
5) **Intra-cameral** route involves injecting the drug in the anterior or posterior chamber of the eye. **For example,** an anaesthetic agent is injected into the anterior chamber of the eye during surgery.
6) **Peril-ocular** route involves injecting the drug around the eye. **For example,** through peril ocular steroid injection, steroid is placed around the eye for treating intraocular inflammation or swelling of the eyes.
7) **Suprachoroidal** route involves injecting the drug in the suprachoroidal space (between the sclera and the choroid) of the eyes.
8) **Sub-conjunctiva** route involves applying the drug to the mucus membrane that lines the exposed part of the eyeball and inner surface of the eyelids.
9) **Topical** route involves applying the drug in the form of eye drops, ointments, gels, or emulsions for treating anterior segment diseases. This is the most preferred route as it is easy to administer and is also cheap.
10) **Gels** not only provide effective contact between the formulation and the corneal surface, but also help to sustain the release rate of drug.
11) **Polymeric gels** are classified into two **pre-formed gels** and ***in situ* forming gels.**
12) ***In situ* gel-forming systems** are viscous liquids that shift to a gel phase on exposure to physiological conditions.
13) The main **advantages** of in-situ formulation are administration of accurate and reproducible quantities in comparison to the already gelled formulations, and promoting pre-corneal retention.
14) **Liposomes** mechanism of enhancing activity is the result of capture of positively charged liposomes on the negatively charged corneal surface.
15) **Niosomes** are bilayered structural vesicles of non-ionic surfactant. Niosomes can encapsulate lipophilic as well as hydrophilic compounds.
16) In a study, cyclopentolate was delivered by encapsulation in noisome, which released the drug independent of pH, and significantly enhanced its ocular bioavailability.
17) **Phase transition systems** are liquid dosage forms, which on instillation in the *cul-de- sac* shift to the gel or solid phase. The commonly used polymers are lutrol c-127 and polxamer- 407.

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CHAPTER 11

Intrauterine Drug Delivery System

11.1. INTRAUTERINE DRUG DELIVERY SYSTEM

11.1.1. Introduction

Intrauterine Device (IUD) is a small object which is placed in the uterus through the cervix route to avoid pregnancy. A small string attached to IUD hangs down into the upper part of the vagina. The IUD can be removed easily by pulling the strings gently using forceps. The effectiveness of IUD as birth control is considered to be 99.2-99.9%. IUD provides zero protection against STDs, including HIV/AIDS.

The mode of action of an IUD is uncertain, and is believed to cause non-specific biochemical and histological endometrial changes and the ionised copper cause spermolytic and gametotoxic effects. These changes decrease the gamete viability, reducing the chances of fertilisation (not implantation). The copper ions impair sperm motility, capacitation, and survival. The hormone-releasing devices elevate the cervical mucus viscosity, thus hindering the entry of sperm in the cervix. The high levels of progesterone and decreased levels of estrogen is an unfavourable condition for implantation. In every three years, the IUD should be changed.

11.1.2. Advantages

Intrauterine drug delivery system has the following advantages:

1) It provides long lasting and reversible contraception.
2) It is a private and discreet method.
3) It is highly effective and safe in use.
4) Its initial cost is high but has no later expenses after its insertion, thus is considered as a cost-effective contraceptive.
5) It is convenient.
6) It is rapidly reversible, hence is preferred for females who opt for long-term birth control and want to retain fertility.
7) It does not cause any effect in breast milk or breast feeding.
8) It does not interfere with sexual life.
9) It does not undergo any drug interaction.
10) Upon its insertion, the user has no botherance to remember about it.
11) The user has nothing to do with it, therefore user related errors are reduced.
12) It does not disturb the hormonal cycle.
13) It is a better option for women avoiding pill.
14) It is a long-term, reversible contraception, equivalent to sterilisation, injectable contraception, and sub-dermal implant.
15) Its failure rate is only 1-2%.
16) A hormone-releasing IUD (Mirena) is suitable for heavy menstrual bleeding.
17) Copper IUD may reduce the risk of endometrial cancer as does the levonorgestrel IUD.
18) Hormonal IUD is preferred over surgical or oral hormonal treatments for heavy menstrual bleeding and for menopausal women ingesting estrogen who can tolerate other progestogen forms.

11.1.3. Disadvantages

Intrauterine drug delivery system has the following disadvantages:

1) A trained medical professional should only insert and remove it.
2) In the first 3-6 months, the user undergoes longer, heavier and sometimes painful menstrual bleeding. Sometimes, spotting and light bleeding occurs in between periods. This condition is, however, normal and reduces over time.
3) Use of levonorgestrel may result in unpredictable bleeding lasting for about 4 months of use. The menstrual flow reduces with increase in duration. In the initial first year, around 20% of women experience amenorrhea (absence of menstrual bleeding).
4) Side effects of levonorgesterel IUD are lower abdominal pain, complexion alteration, back pain, breast tenderness, headache, mood swings, and nausea. These adverse symptoms decline with time and are observed in less than 3% of patients. On using progestin-only methods, benign follicular cysts are reported in 8-12% of users. Most cysts resolve suddenly without medical supervision.
5) Some users undergo hormonal side effects, like mood swings or breast tenderness.
6) Occasionally IUDs can be excluded.
7) IUDs may develop Pelvic Inflammatory Disease (PID), which may cause infertility, in the users within the first three weeks of insertion.
8) In some cases, IUD may perforate the uterus wall due to improper insertion.

11.1.4. Types of Intrauterine Devices

Intrauterine Devices (IUDs) for controlled drug delivery are classified into the following two categories:

1) **Non-Hormonal IUDs/Copper-Medicated IUDs:** These IUDs have polypropylene or polyethylene plastic support of number 7 or letter T, along with a fixed amount of copper wire around them. The T-shaped IUD is used popularly as its shape is somewhat similar to the uterine cavity, and it also avoids displacement and rotation within the cavity and expulsion from the cavity [**figure 11.1 (a)**]. The device bears two flexible arms that favours insertion by folding down and expands back into a T-shape following insertion into the uterus. In its opened state, the device measures 36mm tall and 32mm wide. The device has a vertical stem wound with fine copper wire, and two horizontal arms having a copper cover.

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The surface area of exposed copper is 380mm^2. At the bottom of the vertical stem, a 3mm bulb houses a monofilament polyethylene string for easy removal of the device. Effectiveness duration of the device is up to 12 years. The copper-T IUD elevates uterine fluids containing copper ions, enzymes, prostaglandins, and macrophages. This creates hostile conditions for the sperm and prevents fertilisation of an ovum. This device also disturbs the normal division of oocytes and formation of ova.

Copper-T has the following **advantages**:
i) It is safe being a non-hormonal device.
ii) It works immediately and is highly effective.
iii) It produces a long-term effect (for up to 10 years), thus the user does not have to use a contraceptive regularly or at the time of intercourse.
iv) It is a cost-effective device.
v) It is a reversible device, i.e., fertility returns on its removal.

Copper-T has the following **disadvantages**:
i) It should be inserted and removed only by trained clinicians.
ii) It may get expelled in the first year.
iii) Increased menstrual bleeding and cramping occurs in some users.
iv) It does not provide protection against STDs, including HIV.

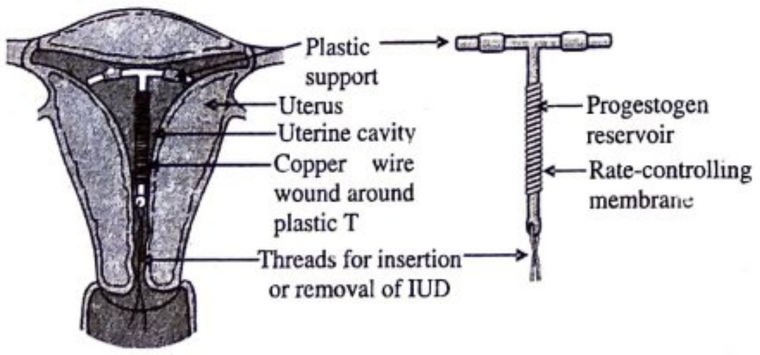


Figure 11.1: Contraceptive IUDs – (a) Non-Hormonal IUD – Copper-T, and (b) Hormonal (Progestogen) IUD

2) **Hormonal IUDs/Progestogen-Containing IUDs:** It is also a T-shaped device, made up of polyethylene frame measuring 32mm in vertical and horizontal directions. This device has a silicon reservoir having levonorgestrel or progesterone dispersed on the vertical stem. This stem is enclosed in an ethylene-vinyl acetate copolymer rate-controlling membrane [**figure 11.1 (b)**]. Pregnancy is avoided by this device for up to 5 years as it continuously releases progestogen directly into the uterus.

The IUD that releases progestogen, prevents pregnancy by:
i) Thickening the mucus of cervical mucosa, thus preventing the entry of sperm in uterus.
ii) Alterating the uterus lining, thus making it unsuitable for pregnancy.

Specific **advantages** of this IUD are:
i) After 5 months of using the device, the users will have light periods.
ii) After 12 months of using the device, 20% of women will get no periods.

iii) It can be used for treating heavy menstrual bleeding.
iv) The pain associated with period is reduced with the use of this device.
v) It is suitable for women approaching menopause as it provides effective contraception and can be used as the progestogen component for hormone replacement therapy.

Apart from the disadvantages of copper-T, some other **drawbacks** of this IUD are:
i) It causes disturbed bleeding pattern in the initial stages.
ii) The users may experience weight gain.

11.1.5. Mechanism of Action

IUDs block fertilisation. Progestogen released by the hormonal IUDs prevents ovulation impartially. Progestogen also thickens the cervical mucus, thus prohibiting the sperm from reaching the fallopian tubes. Copper IUDs have no hormones, but release copper ions in the cervical mucus. These ions are harmful to sperm, uterus, and fallopian tubes. Thus, these devices produce a fluid containing copper ions, WBCs, prostaglandins, and enzymes. The Cu-releasing IUDs are highly effective as emergency contraceptives as they avoid implantation of the blastocyst in uterus. In non-emergency use, inhibition of implantation has no typical mechanism of action.

11.1.6. Development of Intrauterine Devices (IUDS)

The history of IUDs is unclear. Prior to the 20th century, no evidence support insertion of foreign objects in the human uterus for contraception. However, it is reported that centuries ago Middle East traders used to prevent pregnancy in camels by inserting pebbles in their uteri before making long treks across the desert. In 1909, **Dr. Richard Richter** documented the idea of inserting a ring made of silkworm gut into the uterus. He cut off the two ends outside of the cervix to facilitate easy checking and removal.

In the mid-1920's, **Karl Prust** and **Ernest Graefenberg** gave similar theories. **Prust** stated for silkworm insertion in the uterus with a stiff cervical extension of a tightly wound thread and a glass button covering the cervix. **Graefenberg** framed a same model, but removed the extensions of the silkworm ring to avoid infections. Position of the ring in the uterus is detected by X-ray by attaching a silver wire to the ring. This device has a pregnancy rate of around 3%.

Dr. Graefenberg later made a modification by wrapping pure silver around the ring. This, however, resulted in gingival argyrosis (the user's gums turned bluish-black due to absorption of silver). Therefore, he used wire made of German Silver (made up of alloy of a mix of metals like copper). The pregnancy rate was found to drop up to 1.6%. This ring was widely accepted in England and other British Empire countries; however, its sale did not turn out good in continental Europe or the United States.

During World War II, research and development of contraception was minimal. Germany and Japan stopped using any contraception. **Dr. Mary Halton**

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demonstrated the use of silkworm gut in 1949. She wrapped it around her finger and then pushed the ring inside a gelatin capsule. Then she inserted this capsule into the uterus, where the gelatin liquefied and the thread spread out. The pregnancy rate dropped down to the lowest level of 1.1%.

Doctors around the world expressed their success for many years with variations of intrauterine devices. Earlier the concern "tails" on IUDs causing pelvic infection and then most devices had no tails. The presence of the device inside the uterus became difficult to detect and remove. Then a new device made of polyethylene was brought into light by **Dr. Lazar Margulies** in 1960. The concern was then solved making the device end protrude through the cervix. **Dr. Margulies** first patient was his wife. The inserter tube, coil, and a copy of his wife's hysterogram were shown to **Dr. Alan Guttmacher**, **Dr. Aqviles Sobrero**, and **Dr. Christopher Tietze** (the reviewers).

Dr. Jack Lippes developed and inserted the first plastic device, the **Lippes Loop**, in 1962. This simple device was pushed using an inserter tube. This device later became available in different sizes depending on if the woman was pregnant and how many times the woman had been pregnant. A string attached to the device facilitated its detection and removal. The insertion and removal of the loop was ease, and it was also inexpensive; thus, it was widely used and became popular in the world. Later, different kinds of IUDs were introduced, of which some were successful while others had severe complications.

1969 proved a major year for IUDs. Many women reported increased cramps and bleeding. **Dr. Howard Tatum** tried to decrease the size of the IUD to solve this problem. He made plastic T, which was tolerable but had a pregnancy rate of 18%. In the same year, **Dr. Jaime Zipper** discovered that a copper wire in one horn of the uterus of a rabbit protected that horn from pregnancy but not the other horn. By this discovery, the contraceptive effect of intrauterine copper was established and IUD effectiveness was broadened.

In 1970, **Dr. Antonio Scommegna** developed a T-shaped device having progesterone within a semi-permeable capsule in the lower section. FDA approved this device as safe to be used for a year and was marketed till the early 2000's.

A.H. Robins Company brought **Dalkon Shield** named IUD in the market in 1971. It was aggressively and prematurely marketed as a highly effective and low-priced device for preventing pregnancy. After 3 years, it was withdrawn from the market because of an ill-designed removal string. Since the string was not sealed on the other side, it allowed bacteria to enter the uterus, and cause pelvic inflammatory disease, sepsis, and eventually infertility. Around 3,00,000 lawsuits were filed against A.H. Robins, demanding for bankruptcy of the company.

Subsequently in the late 1970's and early 1980's, use of IUD declined and many IUDs were withdrawn from the market. Only progesterone-T sustained in the U.S. market. In 1988, Copper-T 380A (ParaGard) came into existence. FDA initially approved its use for 4 years; and later, approved it for 10 years on

receiving data supporting its effectiveness. In 2001, levonorgestrel-releasing IUD (**Mirena**) was marketed in the U.S.

In January 9, 2013, FDA approved a low-dose hormone IUD (**Skyla by Bayer**) – the first new IUD in 12 years. This device avoids pregnancy for 3 years and was suitable for women who have not had children. It was launched in February, 2013.

Presently, the IUDs are safe, effective, and low-risk form of contraception. As per a study conducted in 2012 by Guttmacher Institute, the proportion of women using long-acting, reversible contraceptive methods (like IUD) increased from 2.0% in 2002 to 7.7% in 2009. These numbers kept increasing as more women became aware about the contraceptive options and increased access to the best birth control for them.

11.1.7. Applications

Intrauterine drug delivery system has the following applications:

1) **Emergency Contraception:** The copper IUD (marketed as Paraguard) can be inserted within 5 days after unprotected intercourse.
2) **Treatment for Heavy Menstrual Bleeding:** The progesterone IUD (marketed as Mirena) is used to reduce heavy menstrual bleeding. It is proved to be better than oral progesterone pills. The IUD should be inserted only when other serious causes of heavy bleeding has been solved by a clinician. It is an alternative therapy to hysterectomy.
3) **Menopausal Hormone Therapy:** Mirena is an alternative method for delivering progesterone of combined menopausal hormone replacement therapy. It is suitable for the women who are intolerant to oral progesterone pills. Women experience similar decreases in hot flashes and night sweats in comparison to the women taking traditional hormone replacement regimens (estrogen and progesterone pills and patches).
4) **Treatment for Pelvic Pain:** Some studies reveal that Mirena IUD reduces pelvic pain associated to endometriosis.

11.2. SUMMARY

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

1) **Intrauterine Device (IUD)** is a small object which is placed in the uterus through the cervix route to avoid pregnancy.
2) The effectiveness of IUD as birth control is considered to be 99.2-99.9%. IUD provides zero protection against STDs, including HIV/AIDS.
3) The **mode of action** of an IUD is uncertain, and is believed to cause non-specific biochemical and histological endometrial changes and the ionised copper cause spermolytic and gametotoxic effects.
4) The copper ions impair sperm motility, capacitation, and survival.
5) The **hormone-releasing devices** elevate the cervical mucus viscosity, thus hindering the entry of sperm in the cervix.

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