Program	B. Pharmacy
Name of Unit	Microencapsulation, mucosal drug delivery system and implantable drug delivery system
Subject /Course name	Novel Drug Delivery System
Subject/Course ID	BP 704T
Class: B.Pharm. Semester	7th Semester
Module	II
Course coordinator	Punam Gaba

Learning Outcome Module 02

LO	Learning Outcome (LO)	Course Outcome Code
LO1	Students will learnt about the concepts of of oral, mucosal and implantable drug delivery system.	BP704.2

Content Table

Topic
• **Microencapsulation:** Definition, advantages and disadvantages, microspheres /microcapsules, microparticles, methods of microencapsulation, applications. • **Mucosal Drug Delivery system :** Introduction, Principles of bioadhesion/ mucoadhesion, concepts, advantages and disadvantages, transmucosal permeability and formulation considerations of buccal delivery systems • **Implantable Drug Delivery System:** Introduction, advantages and disadvantages, concept of implants and osmotic pump.

INTRODUCTION

Microparticles, microspheres, and microcapsules are common constituents of multiparticulate drug delivery systems offering numerous advantages based on their structural and functional abilities, and their application is suitable for convenient and tolerable drug administration via several routes. Depending on the formulation, they can be incorporated into different pharmaceutical dosage forms such as solids (capsules, tablets, sachets), semisolids (gels, creams, pastes), or liquids (solutions, suspensions, and even parenterals). An advantage of microcarriers over nanoparticles is that they do not traverse into the interstitium over the size of 100 nm transported by the lymph, and thus act locally. Possibly toxic substances can be carried encapsulated and liquids can be handled as solids in the form of dried microparticles.

In the case of multiparticulates, the dose is distributed in many small separate particles, which carry and liberate a part of the dose, hence the malfunction of an individual subunit does not cause the failure of the whole dosage.

Multiparticulate drug delivery systems offer outstanding advantages to experts and patients, such as:

- choice of dosage form for the desired drug delivery route (peroral tablets, parenteral injections);
- modified and targeted (even site-specific) drug release and delivery;
- more expectable pharmacokinetics with reduced intra- or inter-subject variability;
- more homogenous distribution in the physiological environment;
- stable fixed-dose combinations of drugs;
- dose titration and less dose-dumping;
- patient centricity through better compliance (e.g., patients with dysphagia) and adherence;
- individual therapy (e.g., for pediatric or geriatric population);
- improving stability of the medicinal preparations;
- isolating the constituents to ensure better compatibility;
- Innovative products with a prolonged life cycle through patent protection.

From the viewpoint of technology, microencapsulation provides several advantages:

- microparticles are formulated in order to protect the core from the environment; masking an unpleasant taste;

- Preserving volatiles or the viability of the cells; separating incompatible substances; protecting the body from the side effects; and optimizing, prolonging, or targeting the effect of a drug.
- The polymer excipient protects the active pharmaceutical ingredient (API) from the environment (oxidation, temperature, pH) or the body from the irritative, or mucosa-damaging effect of the drug substance.
- The lesion (e.g., bisectioning) of the multiparticulate solid dosage form (i.e., micropellets in spansule or compressed) affects only a small number of units, thus does not result in a significant change of the blood level.

However, there are some limitations, such as

Higher product costs due to the more expensive excipients in the formulations or to the more sophisticated equipment and processes, as well as stricter Quality control. In addition, some constituents may not meet the requirements for biocompatibility and biodegradation.

2. Construction and Structure

Microparticles' sizes range from 1 to 1000 µm and the well-known matrix or reservoir structure they exist in have various different structures (Figure 1).

The term "microcapsule" is defined, as a spherical particle with the size varying between 50 nm to 2 mm containing a core substance. Microspheres are in strict sense, spherically empty particles. However, the terms microcapsules and microspheres are often used synonymously. In addition, some related terms are used as well. For example, "microbeads" and "beads" are used alternatively. Sphere and spherical particles are also employed for a large size and rigid morphology. Due to attractive properties and wider applications of microcapsules and microspheres, a survey of the applications in controlled drug release formulations is appropriate

Beyond the excipients used, the structure and the shape determine the function as well. Multiparticulate drug delivery systems (micropellets, microgranules, microspheres, microcapsules, microsponges, liposomal preparations) attract attention because of their wide range of favorable technological properties. Microcapsules are finally dispersed in various dosage forms, such as hard gelatin capsules, which may be enteric coated, soft gelatin capsules, or suspensions in liquids, all of which allow dispersion of individual microcapsules on release.

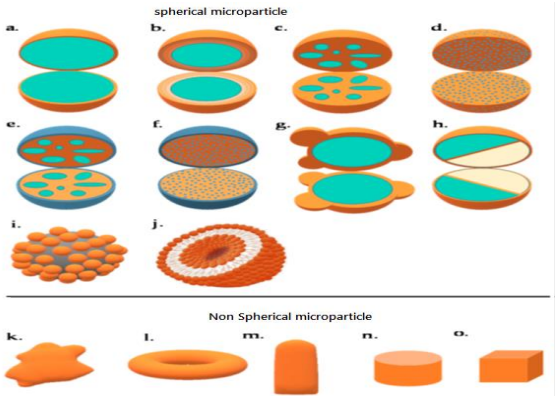

Figure 1. ***Schematic illustration of the different microparticle structures: (a) mononuclear/single core/core-shell, (b) multi-wall, (c) polynuclear/multiple core, (d) matrix, (e) coated polynuclear core,(f) coated matrix particle, (g) patchy microparticle, (h) dual-compartment microcapsule, (i) colloidosome,(j) giant liposome, (k) irregular-shaped microparticle, (l) torus-shaped microparticle, (m) bullet-shaped microparticle, (n) microtablet, and (o) cubic-shaped microparticle.***

Microspheres and Microcapsules

Microspheres can be characterized as matrix systems in which the drug is homogeneously dispersed, either dissolved or homogenously suspended. Microcapsules are heterogenous particles where a membrane shell is surrounding the core forming a reservoir Figure 2

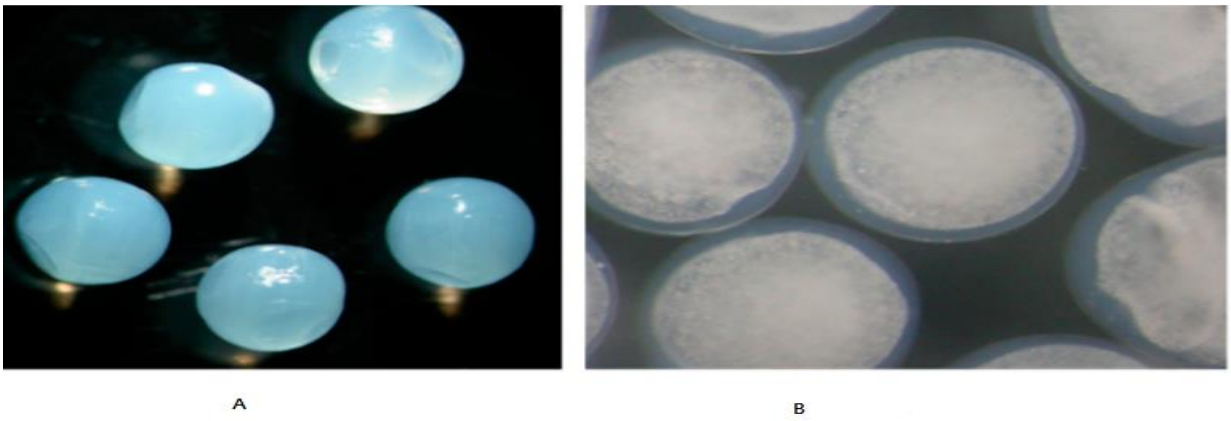

Figure 2. Structures of calcium alginate microparticles: (A) microspheres, (B) microcapsules W/O/W emulsion in core surrounded by calcium alginate shell.

Microparticles:

"Microparticles" refers to the particles having the diameter range of 1-1000 µm, irrespective of the precise exterior and/or interior structures.

Microspheres:

"Microspheres" particularly refers to the spherically shaped microparticles within the broad category of microparticles.

Microcapsules:

"Microcapsules" refers to microparticles having a core surrounded by the coat or wall material(s) distinctly different from that of the core or pay-load or nucleus, which may be solid, liquid, or even gas.

Microcapsules can be classified on three types (**Figure. 3**):

1) Mononuclear: Containing the shell around the core.
2) Polynuclear: Having many cores enclosed with in shell.
3) Matrix type: Distributed homogeneously into the shell material.

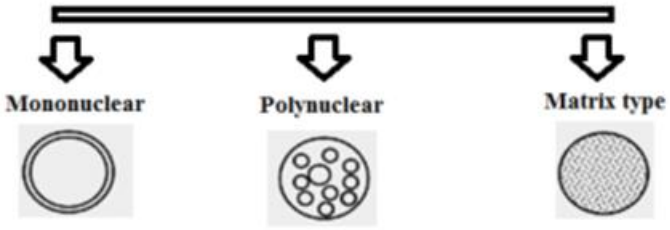

Figure. 3: Classification of microcapsules

Advantages of microencapsulation:

1. Providing environmental protection to the encapsulated active agents or core materials.
2. Liquids and gases can be changed into solid particles in the form of microcapsules.
3. Surface as well as colloidal characteristics of various active agents can be changed.
4. modify and delayed drug release form different pharmaceutical dosage forms
5. Formulation of sustained controlled release dosage forms can be done by modifying or delaying release of encapsulated active agents or core materials.

Disadvantages of microencapsulation:

1. Expensive techniques.
2. This causes reduction in shelf-life of hygroscopic agents.
3. Microencapsulation coating may not be uniform and this can influence the release of encapsulated materials.

Composition of microcapsules

Coating materials

A wide variety of coating materials are available for microencapsulation. Some patent innovative coating polymers have also been developed for some special applications particularly among the bioadhesives and mucoadhesives. However, many traditional coating materials are satisfactory for the use in the gastrointestinal tract. They include inert polymers and pH sensitive ones as carboxylate and amino derivatives, which swell or dissolve according to the degree of cross-linking

The selection of appropriate coating material from a long list of candidate materials needs consideration of the following general criteria by the research pharmacist:

1. What are the specific dosage forms or product requirements, such as stabilization, reduced volatility, release characteristics, and environmental conditions?
2. What coating material will satisfy the product objective and requirements?
3. What microencapsulation method is best suited to accomplish the coated product objectives?

The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules/ microspheres. While selecting a polymer the product requirements i.e. stabilization, reduced volatility, release characteristics, environmen-tal conditions, etc. should be taken into consideration. The polymer should be capable of forming a film that is cohesive with the core material. It should be chemically compatible, non-reactive with the core material and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and stability.

Generally hydrophilic polymers, hydrophobic polymers or a combination of both are used for the microencapsulation process. A number of coating materials have been used successfully; examples of these include gelatin, polyvinyl alcohol, ethyl cellulose, cellulose acetate phthalate and styrene maleic anhydride. The film thickness can be varied considerably depending on the surface area of the material to be coated and other physical characteristics of the system. The micro-capsules may consist of a single particle or clusters of particles. After isolation from the liquid manufacturing vehicle and drying, the material appears as a free flowing powder. The powder is suitable for formulation as compressed tablets, hard gelatin capsules, suspensions, and other dosage forms

Core materials

The core material is the material over which coating has to be applied to serve the specific purpose. Core material may be in form of solids or droplets of liquids and dispersions. The composition of core material can vary and thus furnish definite flexibility and allow effectual design and development of the desired microcapsule properties. A substance may be microencapsulated for a number of reasons. Examples may include protection of reactive material from their environment, safe and convenient handling of the materials which are otherwise toxic or noxious, taste masking, means for controlled or modified release properties means of handling liquids as solids, preparation of free flow powders and in modification of physical properties of the drug

Mechanism and kinetics of drug release

The process of drug release of microparticulates, produced by special manufacturing technologies and/or possibly containing special excipient(s), is the result of various phenomena and mechanisms (dissolution/diffusion, osmotically driven release, erosion) (Figure 4).

Major mechanisms of drug release from microcapsules include diffusion, dissolution, osmosis and erosion.

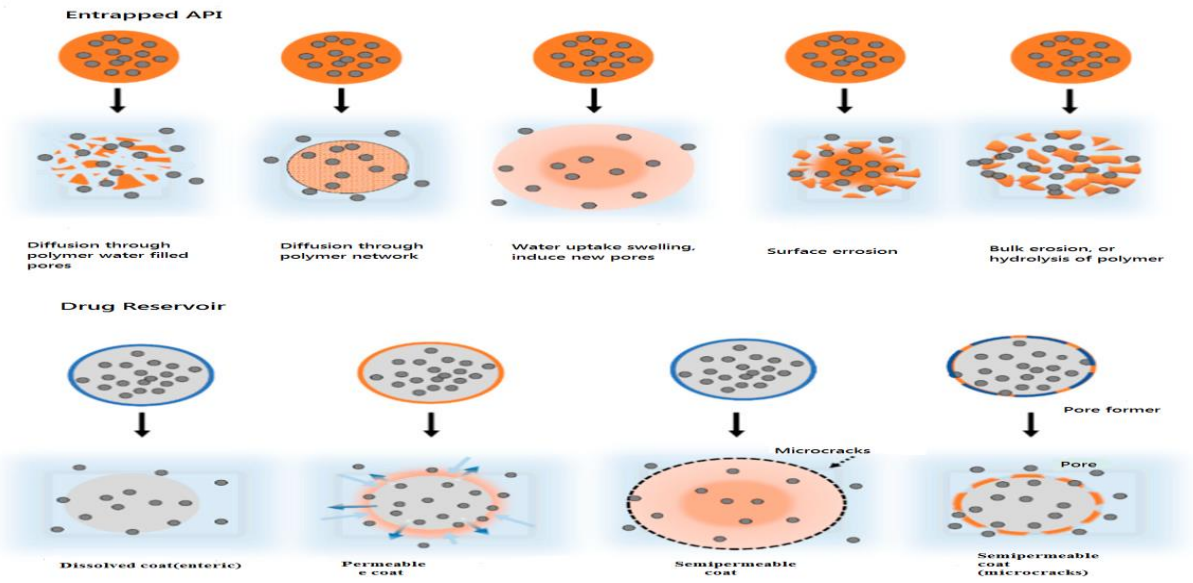

Figure 4. Release mechanisms in microencapsulated products

Diffusion

Diffusion is the most commonly involved mechanism wherein the dissolution fluid penetrates the shell, dissolves the core and leak out through the interstitial channels or pores. Thus, the overall release depends on, (a) the rate at which dissolution fluid penetrates the wall of microcapsules,

(b) the rate at which drug dissolves in the dissolution fluid, and (c) the rate at which the dissolved drug leak out and disperse from the surface. The kinetics of such drug release obeys Higuchi's equation as below:

$$Q = [D/J (2A - \varepsilon C_S) C_S t]^{1/2}$$

Where, Q is the amount of drug released per unit area of exposed surface in time t; D is the diffusion coefficient of the solute in the solution; A is the total amount of drug per unit volume; C_S is the solubility of drug in permeating dissolution fluid; ε is the porosity of the wall of microcapsule; J is the tortuosity of the capillary system in the wall. The above equation can be simplified to Q = vt where, v is the apparent release rate.

Dissolution

Dissolution rate of polymer coat determines the release rate of drug from the microcapsule when the coat is soluble in the dissolution fluid. Thickness of coat and its solubility in the dissolution fluid influence the release rate.

Osmosis

The polymer coat of microcapsule acts as semi permeable membrane and allows the creation of an osmotic pressure difference between the inside and the outside of the microcapsule and drives drug solution out of the microcapsule through small pores in the coat.

Erosion

Erosion of coat due to pH and/or enzymatic hydrolysis causes drug release with certain coat materials like glyceryl monostearate, bee's wax and stearyl alcohol.

Attempts to model drug release from microcapsules have become complicated due to great diversity in physical forms of microcapsules with regard to size, shape and arrangement of the core and coat materials. The physiochemical properties of core materials such as solubility, diffusibility and partition coefficient, and of coating materials such as variable thickness, porosity, and inertness also makes modeling of drug release difficult. However, based on various studies concerning the release characteristics, the following generalizations can be made:

1. Drug release rate from microcapsules conforming to reservoir type is of zero order.
2. Microcapsules of monolithic type and containing dissolved drug have release rates that are $t_{1/2}$ dependant for the first half of the total drug release and thereafter decline exponentially.
3. However, if a monolithic microcapsule containing large excess of dissolved drug, the release rate is essentially $t_{1/2}$ dependant throughout almost the entire drug release.

In monolithic capsules the path traveled by drug is not constant; the drug at the center travels a large distance than the drug at the surface. Therefore, the release rate generally decreases with time.

MICROENCAPSULATION TECHNIQUES:

There are a number of methods of microencapsulation which are are based on Chemical processes in which there are chemical or phase change. Mechanical processes in which there is a physical change in the system by using special equipment.

A. Chemical Processes

(i) Solvent evaporation

(ii) Interfacial polymerization

(iii) In-situ polymerization

B. Physical processes

(i) Physico-chemical processes

(a) Coacervation phase separation

- By temperature change
- By incompatible polymer addition
- By non-solvent addition
- By salt addition
- By polymer-polymer interaction

(b) Encapsulation by poly electrolyte multilayer

(c) Polymer encapsulation by Rapid Expansion of super critical fluids.

(ii) Physico-mechanical processes

a. Spray drying and spray congealing
b. Co-extrusion
c. Fluidized bed technology
d. Spinning disk / Rotating disk atomization
e. Pan coating.

Coacervation

The process of coacervation is the first reported microencapsulation method to be adapted for the industrial production of microparticles. The first significant commercial product that utilizes coacervation was carbonless copy paper. Coacervation involves the partial desolvation of a

homogeneous polymer solution into a polymer-rich phase (coacervate) and a polymer-poor dilute liquid phase (coacervation medium).

Two types of coacervation have been identified, namely

1. simple
2. Complex coacervation.

The mechanisms of microparticle formation for these two processes are similar with the exception of the method in which phase separation is carried out. Simple coacervation requires a change in the temperature of the polymer solution or the addition of a desolvation agent, usually a water-miscible non-solvent such as ethanol, acetone, dioxane, isopropanol or propanol , or an inorganic salt such as sodium sulfate. On the other hand, complex coacervation involves inducing polymer–polymer interaction between two oppositely charged polymers, such that electrostatic interaction between two oppositely charged polymers produces phase separation. In general, for both simple and complex coacervation, formation of immiscible phases is followed by polymer deposition on the core material(s). The deposited polymer can be stabilized by cross-linking, desolvation or temperature change. The successful encapsulation of drugs by coacervation is dependent upon several process parameters. The ability of a coacervating agent to spread and engulf dispersed drugs is highly affected by the types of coacervate used and its viscosity. Complex coacervation involves electrostatic interactions, and thus, the pH of the medium must be carefully controlled to maintain the charges on the polymeric species. For example, in a gelatin–gum arabic system, the pH should be adjusted to below the isoelectric point of gelatin such that the positively charged gelatin is attracted to the negatively charged gum Arabic. In the same study, it was shown that the acidifying rate of the medium affects the microparticle size distribution. Another factor is the concentration of surfactants used in the process. Several studies have demonstrated the effect of various concentrations of surfactant on particle size distribution, coacervation yield and drug-loading.

Polymerization

Polymerization technique forms protective microcapsule coating insitu.It involves the reaction of monomeric units located at the interface existing between a core material substance and a continuous phase in which the core material is dispersed. The continuous or core material supporting phase is usually a gas or liquid and therefore polymerization reactions occurs at liquid-liquid, liquid-gas, solid-liquid, or liquid-solid interface. Polymerization can be classified in to three types:-

1) Interfacial polymerization
2) Matrix polymerization
3) Interfacial cross-linking
4) Insitu polymerization

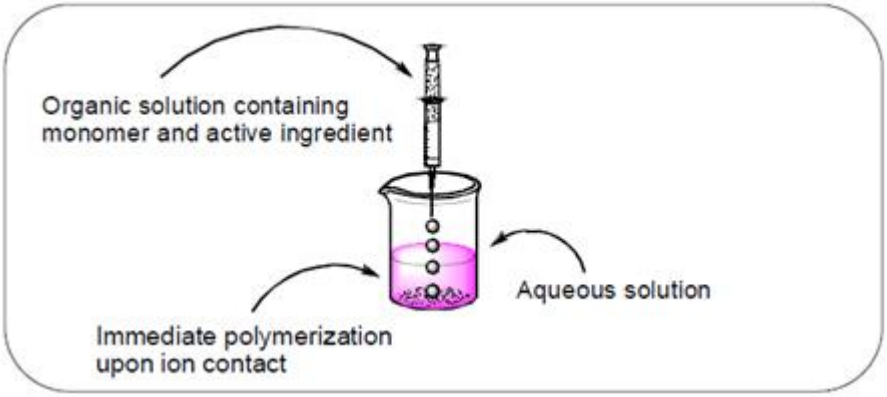

Figure No. 5: Polymerization

Interfacial Polymerization- It involves the condensation of two monomers at the interface of the organic & aqueous phase. In the interfacial polymerization, the two reactants in a polycondensation meet at an interface and react rapidly. The basic of this method is the classical schotten-baumaan reaction between an acid chloride and a compound containing an active hydrogen atom, such as amine or alcohol, polyesters, polyurea, polyurethane. Under the right condition, thin flexible walls form rapidly at the interface. A solution of the pesticide and a diacid chloride are emulsified in the water and an aqueous solution containing an anime and a polyfunctional isocyanate is added. Bases are present to neutralize the acid formed during the reaction. Condensed polymer forms wall instantaneously at the interface of emulsion droplets.

Interfacial cross-linking- A number of hydrophilic polymers from natural origin, such as gelatin, albumin, starch, dextran, hyaluronic acid, and chitosan, can be solidified by a chemical or thermal cross-linking process. Most proteins are cross-linked using glutaraldehyde, but its toxicity remains a problem for pharmaceutical applications.

In-situ polymerization- In this process, the direct polymerization of a single monomer is carried out on the particle surface. In one process, e.g. Cellulose fibers are encapsulated in polyethylene while immersed in dry toluene. Usual deposition rates are about 0.5µm/min. The coating is uniform, even over sharp projection.

Matrix polymerization- a core material is imbedded in a polymeric matrix during formation of the particles. A simple method of this type is spray-drying, in which the particle is formed by

evaporation of the solvent from the matrix material. However, the solidification of the matrix also can be caused by a chemical change.

Ionotropic Gelation

This technique involves cross-linking of poly electrolytes in the presence of multivalent counter ions. For example, spraying a sodium alginate solution into calcium chloride solution produces rigid gel particles. Technique is often followed by polyelectrolyte complexation with oppositely charged poly electrolytes. This complexation forms a membrane of polyelectrolyte complex on the surface of the gel particles, and this membrane increases the mechanical strength of the particles. For calcium alginate gel particles, polylysine is often used for this purpose. Now a days, it has widely been used for both cell and drug encapsulation

Emulsion technique

A common method to prepare microparticles is the emulsion technique. An emulsion is a mixture of two or more immiscible liquids. Pharmaceutically relevant liquids usually include some type of volatile organic solvent as the dispersed phase and water containing appropriate tensioactive substance as the continuous phase.

For example, hydrophobic drugs can be dissolved along with the wall-forming polymer in a common organic solvent, such as methylene chloride or dichloromethane, and the entire mixture emulsified in an aqueous solution containing a polymeric surfactant such as poly(vinyl alcohol). This type of oil-in-water (O/W) emulsion is widely used for encapsulation of lipophilic active moieties like steroidal hormones and neuroleptics. The procedure can be adapted for encapsulation of hydrophilic drugs, where the drug is incorporated into an aqueous dispersed phase and poured into an organic continuous phase containing wall-forming polymer (water-in-oil, W/O). This primary emulsion is then further emulsified in an external aqueous phase, leading to a type of double emulsion known as water-in-oil-in water (W/O/W) emulsion.

Yet another class of emulsions consists of oil-in-oil (O/O) emulsion and multiple emulsions involving O/O procedures (W/O/O and W/O/O/O). W/O/O and W/O/O/O processes are carried out with the primary purpose of protecting highly water-soluble active agents from partitioning into the oil-water interface, causing drug loss and low encapsulation efficiencies. For all types of emulsions, the emulsification procedure is followed by solvent elimination step in complement with solidification step.

Depending on the method of solidification, emulsion can be further classified as solvent evaporation, solvent extraction and cross-linking method.

In the **solvent-evaporation method**, solvent is eliminated in two stages: fi rst the solvent diffuses through the dispersed phase into the continuous phase, and second the solvent is eliminated at the continuous phase–air interface. To facilitate the evaporation of solvent from the continuous phase–air interface, an appropriate amount of heat may be applied to the system. Theoretically, if the solvent can be extracted completely from the microparticle into the continuous phase, then the solvent evaporation step is no longer necessary.

In practice, this is the concept behind the **solvent extraction method**. Using a sufficiently large volume ratio of continuous phase to dispersed phase or by choosing a cosolvent in the dispersed phase that has a great affinity to the continuous phase, the solvent can be extracted from the microparticle to completion. The third type of emulsion method is the **cross-linking method**, which takes advantage of the ability of certain naturally available hydrophilic polymers such as gelatin, albumin, starch, dextran, and chitosan to cross-link and solidify. The crosslinking reactions may take place upon heating or the addition of counter polyions and cross-linking agents. It is crucial to take into consideration of the toxicity of added reagents when formulating pharmaceutically relevant microparticles using this method.

The characteristics of microparticles produced by emulsion may be affected by physical parameters(such as the configuration of the apparatus, stirring rate, volume ratio of the dispersed to continuous phase, and weight ratio of encapsulated core material to shell material),physicochemical parameters (such as interfacial tension, viscosities and densities of the dispersed and continuous phases), and chemical parameters (such as the types of polymer, drug, surfactant and solvent used in the emulsion reactor). The optimization of these parameters is material-specific, i.e., for different drug–polymer systems, the values of the parameters differ.

Supercritical Fluid

Supercritical fluids offer a wider scope of choices as solubilizing agents for core and/or shell materials. The ability of supercritical fluids to solvate core and shell materials can be altered by varying temperature and pressure conditions, the two key parameters in this particular microencapsulation technique. In addition to solvating the active principles, the use of supercritical fluids as extractants are also well documented. Therefore, if the starting solution is appropriately prepared, the final microencapsulated product can be obtained in one step that consists of two main processes: solvation of active principles by supercritical fluid in the rapid expansion of supercritical solutions (RESS) process and precipitation of compounds by the supercritical fluid in the supercritical anti-solvent crystallization (SAS) process

PHYSIO-MECHANICAL METHOD

Air suspension coating-

Air suspension:

Air-suspension coating, first described by Professor Dale Erwin Wurster at the University of Wisconsin in 1959' gives improved control and flexibility compared to pan coating. Microencapsulation by air suspension method consists of the dispersing of solids, particulate core materials in a supporting air stream and the spray coating on the air suspended particles (Figure 6). Within the coating chamber, particulate core materials are suspended on an upward moving air stream. The chamber design and its operating parameters influence a recirculating flow of the particles through the coating-zone portion of the coating-chamber, where a coating material is sprayed to the moving particles. During each pass through the coating-zone, the core material receives a coat and this cyclic process is repeated depending on the purpose of microencapsulation. The supporting air stream also serves to dry the product while it is being encapsulated. The drying rate is directly related to the temperature of the supporting air stream used.

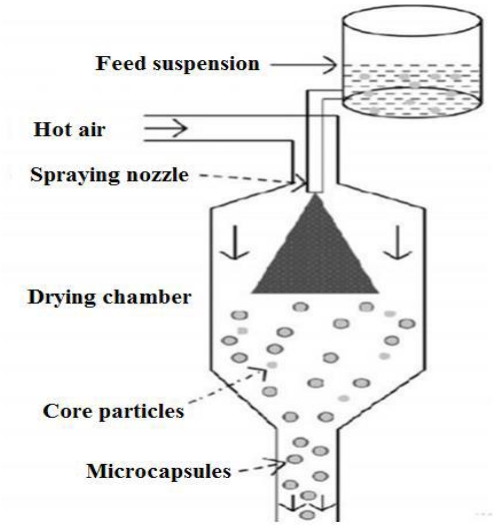

Figure. 6: Air suspension method for microencapsulation

Pan coating

The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly[12] with respect to microencapsulation, solid particles greater than 600 microns in size are generally considered

essential for effective coating, and the process has been extensively employed for the preparation of controlled - release beads. Medicaments are usually coated onto various spherical substrates such as nonpareil sugar seeds, and then coated with protective layers of various polymers .

In this method, solid particles are mixed with a dry coating material and the temperature is raised so that the coating material melts and encloses the core particles, and then is solidified by cooling; or, the coating material can be gradually applied to core particles tumbling in a vessel rather than being wholly mixed with the core particles from the start of encapsulation**.**

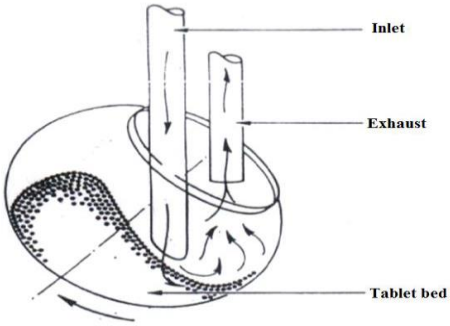

Figure 7: Pan coating method for microencapsulation

Centrifugal extrusion

This process possesses a number of commercial applications. Centrifugal extrusion processes generally produce capsules of a larger size, from 250 microns up to a few millimeters in diameter. The core and the shell materials, which should be immiscible with one another, are pushed through a spinning two-fluid nozzle. This movement forms an unbroken rope which naturally splits into round droplets directly after clearing the nozzle. The continuous walls of these droplets are solidified either by cooling or by a gelling bath, or chemical cross linking depending on the composition and properties of the coating material**.** Hepatocytes have been encapsulated in polyacrylonitrile77 by using this technique.

This process is excellent for forming particles 400–2,000 µm (16–79 mils) in diameter. Since the drops are formed by the breakup of a liquid jet, the process is only suitable for liquid or slurries. A high production rate can be achieved, up to 22.5 kg (50 lb) of microcapsules can be produced per nozzle per hour. Heads containing 16 nozzles are available.

Spray Drying

Spray drying is a relatively low cost, commercially viable method of microencapsulation. Current industrial applications of spray drying range from the encapsulation of flavors and fragrances by the food industry to paint pigments in manufacturing. During this process, the core

material is first emulsified or dispersed into a concentrated solution of the shell material. The mixture is then atomized into a heated chamber containing carrier gas where the solvent is rapidly removed to produce dry microparticles . A major advantage of spray drying is the ability to mass produce microparticles with relative ease and low cost. However, one major limitation is the restricted use of many solvents other than water due to flammability issues. This severely limits the types of shell materials to those soluble or at least dispersible in water.

Currently, other solvent options such an ethanol–water cosolvent system and methylene chloride are being explored. Another disadvantage of spray drying is the limited control over the geometries of the produced microparticles and the tendency for the microparticles to form aggregates. The viscosity and particle size distribution of the primary emulsion have significant impact on the morphology and size distribution of subsequent spray drying process. For example, if the viscosity is too high, elongated and large droplets may form. The concentration of wall forming materials in the solution has a direct impact on the microencapsulation efficiency of core materials. During spray drying, a number of processing parameters must be optimized in order to produce high quality microparticles. These parameters include feed temperature, air inlet and outlet temperatures, as well as the rate of emulsion mixture being delivered to the atomizer and rate of air flow. Optimization of these and many other factors that affect spray drying microencapsulation are mainly carried out by trial and error experimentation.

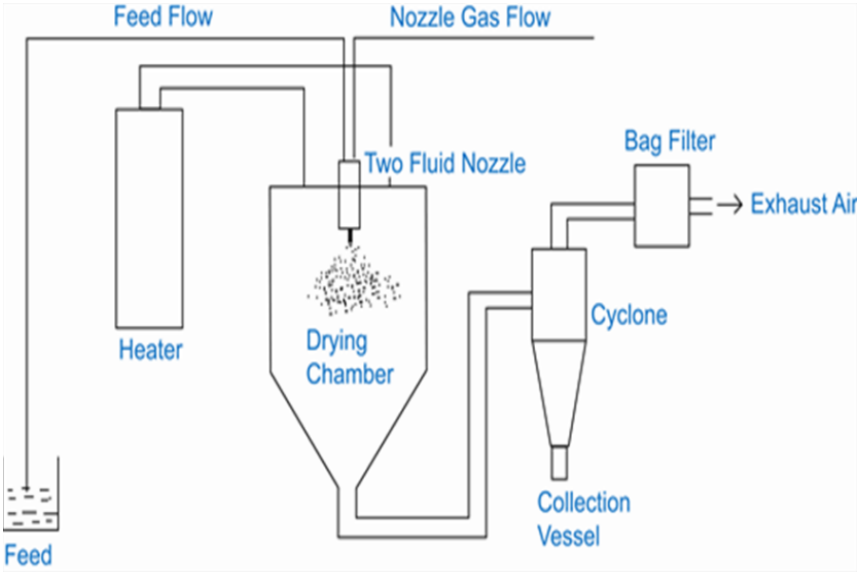

Figure 8: Spray drying method for microencapsulation

Multiorific-centrifugation

Multiorific-centrifugation method for microencapsulation utilizes the centrifugal forces to hurl a core particle trough an enveloping membrane. Various processing variables of multiorific-centrifugation method include (i) rotational speed of the cylinder, (ii) flow rate of the core and coating materials, and (iii) concentration, viscosity and surface tension of the core material. The multiorifice-centrifugal method is capable for microencapsulating liquids and solids of varied size ranges with diverse coating materials. The encapsulated product can be supplied as slurry in the hardening media or as dry powder.

Solvent Evaporation

Solvent evaporation method is appropriate for liquid manufacturing vehicle (O/W emulsion), which is prepared by agitation of two immiscible liquids. The solvent evaporation method involves dissolving microcapsule coating (polymer) in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material (drug) to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core–coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate sized microcapsules. Agitation of system is continued until the solvent partitions into the aqueous phase and is removed by evaporation. This process results in hardened microcapsules. Several techniques can be used to achieve dispersion of the oil phase in the continuous phase. The most common method is the use of a propeller style blade attached to a variable speed motor.

Various process variables namely rate of solvent evaporation for the coating polymer(s), temperature cycles and agitation rates influence the methods of forming dispersions. The most important factors that should be considered for the preparation of microcapsules by solvent evaporation method include choice of vehicle phase and solvent for the polymer coating, and solvent recovery systems. The solvent evaporation method for microencapsulation is applicable to a wide variety of liquid and solid core materials. The core materials may be either water soluble or water insoluble materials. A variety of film forming polymers can be used as coatings.

PHYSIOLOGICAL EVALUATION AND CHARACTERIZATION

Angle of contact

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This

thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200C within a minute of deposition of microspheres.

Sieve analysis

Separation of the microspheres into various size fractions can be determined by using a mechanical sieve shaker (Sieving machine, Retsch, Germany). A series of five standard stainless steel sieves (20, 30, 45, 60 and 80 mesh) are arranged in the order of decreasing aperture size. Five grams of drug loaded microspheres are placed on the upper-most sieve. The sieves are shaken for a period of about 10 min, and then the particles on the screen are weighed.

Viscosity of the polymer solutions

The absolute viscosity, kinematic viscosity, and the intrinsic viscosity of the polymer solutions in different solvents can be measured by a U-tube viscometer (viscometer constant at 40 °C) at 25 ± 0.1 °C in a thermostatic bath. The polymer solutions are allowed to stand for 24 h prior to measurement to ensure complete polymer dissolution.

Morphology of microspheres

The surface morphologies of microspheres are examined by a scanning electron microscope (XL 30 SEM Philips, Eindhoven, and The Netherlands). The microspheres are mounted onto a copper cylinder (10 mm in diameter, 10 mm in height) by using a double-sided adhesive tape. The specimens are coated at a current of 10 mA for 4 min using an ion sputtering device (JFC-1100E, Jeol, Japan).

Bulk density

The microspheres fabricated are weighed and transferred to a 10-ml glass graduated cylinder. The cylinder is tapped using an autotrap (Quantach- rome, FL, USA) until the microsphere bed volume is stabilised. The bulk density is estimated by the ratio of microsphere weight to the final volume of the tapped microsphere bed.

Atomic force microscopy (AFM)

A Multimode Atomic Force Microscope from Digital Instrument is used to study the surface morphology of the microspheres. The samples are mounted on metal slabs using double-sided adhesive tapes and observed under microscope that is maintained in a constant-temperature and vibration-free environment .

Particle size

Particle size determination approximately 30 mg microparticles is redispersed in 2–3 ml distilled water, containing 0.1% (m /m) Tween 20 for 3 min, using ultrasound and then transferred into the small volume recirculating unit, operating at 60 ml/s. The microparticle size can be determined by laser diffractometry using a Malvern Mastersizer X (Malvern Instruments, UK).

Density determination

The density of the microspheres can be measured by using a multi volume pychnometer. Accurately weighed sample in a cup is placed into the multi volume pychnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and density of the microsphere carrier is determined.

APPLICATIONS OF MICROCAPSULES AND MICROSPHERES

General Application

1. Cell immobilization:

In plant cell cultures, Human tissue is turned into bio-artificial organs, in continuous fermentation processes.

2. Beverage production
3. Protection of molecules from other compounds:
4. Quality and safety in food, agricultural and environmental sectors.
5. Soil inoculation.
6. In textiles**:** means of imparting finishes.
7. Protection of liquid crystals
8. Most flavoring is volatile; therefore encapsulation of these components extends the shelf-life of products by retaining within the food flavours that would otherwise evaporate out and be lost. Some ingredients are encapsulated to mask taste, such as nutrients added to fortify a product without compromising the product's intended taste

2. Controlled Release and Sustained Release Dosage Forms

1. To mask the bitter taste of drugs like Paracetamol, Nitrofurantoin etc.

2. To reduce gastric and other gastro intestinal (G.I) tract irritations, e.g., sustained release Aspirin preparations have been reported to cause significantly less G.I. bleeding than conventional preparations.

3. A liquid can be converted to a pseudo-solid for easy handling and storage e.g. eprazinone.

4. Hygroscopic properties of core materials may be reduced by microencapsulation e.g., Sodium chloride.

5. Carbon tetrachloride and a number of other substances have been microencapsulated to reduce their odor and volatility.

6. Microencapsulation has been employed to provide protection to the core materials against atmospheric effects, e.g., Vitamin-A Palmitate.

7. Separation of incompatible substance has been achieved by encapsulation

8. Physicochemical evaluation characterization: The characterization of the microparticulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier.

2. Medical application

1. Release of proteins, hormones and peptides over extended period of time.

2. Gene therapy with DNA plasmids and also delivery of insulin.

3. Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control.

4. Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intraarterial/ intravenous application.

5. Tumour targeting with doxorubicin and also treatments of leishmaniasis.

Magnetic microspheres can be used for stem cell extraction and bone marrow purging.

6. Used in isolation of antibodies, cell separation, and toxin extraction by affinity chromatography.

7. Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.

3. Radioactive microsphere's application

1. Can be used for radioembolisation of liver and spleen tumours.

2. Used for radiosynvectomy of arthiritis joint, local radiotherapy, interactivity treatement.

4. Cosmetics :

For cosmetic applications, organic acids are usually good solvents; chitin and chitosan have fungicidal and fungistatic properties. Chitosan is the only natural cationic gum that becomes viscous on being neutralized with acid. These materials are used in creams, lotions and permanent waving lotions and several derivatives have also been reported as nail lacquers.

5. Photography:

Chitosan has important applications in photography due to its resistance to abrasion, its optical characteristics, and film forming ability. Silver complexes are not appreciably retained by chitosan and therefore can easily be penetrated from one layer to another of a film by diffusion.

Introduction

Since the early 1980s, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology. Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface. The American Society of Testing and Materials has defined it as the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action or both. Mucoadhesive drug delivery systems prolong the residence time of the dosage form at the site of application or absorption. They facilitate an intimate contact of the dosage form with the underlying absorption surface and thus improve the therapeutic performance of the drug. In recent years, many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, rectal and vaginal routes for both systemic and local effects.

Dosage forms designed for mucoadhesive drug delivery should be small and flexible enough to be acceptable for patients and should not cause irritation. Other desired characteristics of a mucoadhesive dosage form include high drug loading capacity, controlled drug release (preferably unidirectional release), good mucoadhesive properties, smooth surface, tastelessness, and convenient application. Erodible formulations can be beneficial because they do not require system retrieval at the end of desired dosing interval. A number of relevant mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin-releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, have been delivered via the mucosal route, albeit with relatively low bioavailability (0.1–5%), owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the mucosa.

The development of sustain release dosage form can achieve the aim of releasing the drug slowly for a long period but this is not sufficient to get sustained therapeutic effect. They may be cleared from the site of absorption before emptying the drug content. Instead, the mucoadhesive dosage form will serve both the purposes of sustain release and presence of dosage form at the site of absorption.

Mucoadhesive drug delivery systems can be delivered by various routes:-

1. Buccal delivery system
2. Oral delivery system
3. Vaginal delivery system
4. Rectal delivery system
5. Nasal delivery system
6. Ocular delivery system

MUCOADHESIVE ORAL DRUG DELIVERY SYSTEMS

Oral route is the most preferred route for the delivery of any drug. Drug delivery via the membranes of the oral cavity can be subdivided as:-

1. Sublingual delivery: This is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.
2. Buccal delivery: This is drug administration through the mucosal membranes lining the cheeks (buccal mucosa)
3. **Local delivery:** This is drug delivery into the oral cavity.

Within the oral mucosal cavity, the buccal region offers an attractive route of administration for controlled systemic drug delivery. Buccal delivery is the administration of drugs through the mucosal membrane lining the cheeks. Although the sublingual mucosa is known to be more permeable than the buccal mucosa, the latter is the preferred route for systemic transmucosal drug delivery. This is because the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa, which makes it a more desirable region for retentive systems. Thus, the buccal mucosa is more appropriate for sustained direction of drug delivery.

Advantages of oral mucoadhesive drug delivery systems:

- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Excellent accessibility, rapid onset of action.
- Rapid absorption because of enormous blood supply and good blood flow rates.

- Drug is protected from degradation in the acidic environment in the git.
- Improved patient compliance.

Disadvantages of mucoadhesive drug delivery systems:

- Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property.
- One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.
- Patient acceptability in terms to taste and irritancy.
- Eating and Drinking is prohibited.

Physiology of the Oral Mucosa:

Structure: The cheeks, lips, hard and soft palates and tongue form the oral cavity. The main difference between the oral mucosa and skin as compared to the gastrointestinal (GI) tract lining lies in the organization of the different epithelia. While the latter has a single layer of cells forming the simple epithelium, the skin and the oral cavity have several layers of cells with various degrees of differentiation. Within the oral cavity, the masticatory mucosa has a keratinized or cornified epithelium, and covers the stress-enduring regions such as the gingival and the hard palate, providing chemical resistance and mechanical strength. It is divided into four layers: keratinized, granular, prickle-cell, and basal layer

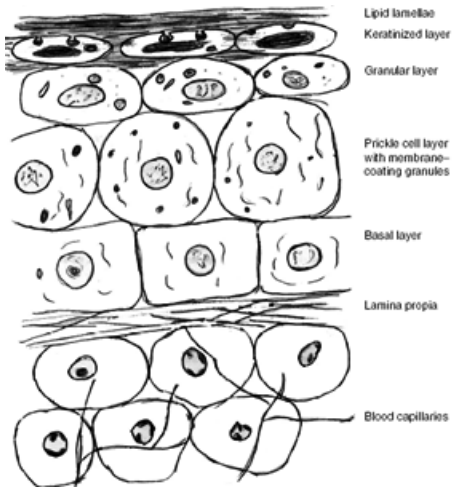

Figure. 1: structure of the mucosa

The lining mucosa, which provides elasticity, in contrast, is comprised of non-cornified surface epithelium covering the rest of the regions including the lips, cheeks, floor of the mouth, and soft palate. It also can be further divided into superficial, intermediate, prickle-cell, and basal layers. The third type of mucosa is the specialized mucosa consisting of both keratinized and non-

keratinized layers, and is restricted to the dorsal surface of the tongue. The intercellular spaces contain water, lipids, and proteins.

Physiological Importance of Mucins and Saliva: The mucosal tissues are further covered with mucus, which is negatively charged, and contains large glycoproteins termed mucins. These are thought to contribute significantly to the visco-elastic nature of saliva, and maintain a pH of 5.8–7.4. Mucin consists of a protein core, rich in O-glycosylated serine and threonine, containing many helix-breaking proline residues. The salivary glands secreting mucus also synthesize saliva, which offers protection to the soft tissues from chemical and mechanical abrasions. The average thickness of the salivary film in the mouth varies between 0.07 and 0.10 mm. Sustained adhesion of the dosage form (tablet, patch) to the mucosa is an important first step to successful buccal delivery. The mucus plays an important role during this mucoadhesive process by buccal drug delivery systems. The interaction between the mucus and mucoadhesive polymers generally used in most dosage forms can be explained by theories summarized in **Table 1**.

Theory of Adhesion	Mechanism of Adhesion
Adsorption	Secondary chemical bonds such as van der waal forces, hydrophobic interactions, electrostatic attraction, and hydrogen bonds between mucus and polymer.
Diffusion	Entanglements of the polymer chains in to mucus network.
Electronic	Attractive forces across electrical double layer formed due to electron transfer across polymer and mucus.
Wetting	Analyze the ability of past to spared over the biological surface and calculate the interfacial tension between the two. The tension is considered to proportional to X1 /2, where X is the polymer –polymer interaction parameter. Low values of these parameters correspond to structural similarities between polymers and an increased miscibility.
Fracture	Relates to the force necessary to separate to surfaces to the adhesive bond strength and it is often used to calculate fracture strength of adhesive bonds.

The mean total surface area of the mouth has been calculated to be 214.7+12.9 cm^2. The teeth, keratinized epithelium, and non-keratinized epithelium occupy about 20%, 50%, and 30% of this surface area, respectively. Drug delivery through the oral mucosa can be achieved via different

pathways: sublingual (floor of the mouth), buccal (lining of the cheeks), and gingival (gums). The sublingual mucosa is the most permeable followed by the buccal and then the palatal. This is due to the presence of neutral lipids such as ceramides and acylceramides in the keratinizedepithelia present on the palatal region, which are impermeable to water.

The non-keratinized epithelia contain water-permeable ceramides and cholesterol sulfate. A comparison of the various mucosae is provided in Table 2.The thickness of the buccal epithelium varies from 10 to about 50 cell layers in different regions because of serrations in connective tissue. In fact, the thickness of buccal mucosa has been observed to be 580 micron meter, the hard palate 310 micron meter, the epidermis 120 micron meter, and the floor of mouth mucosa 190 micron meter.

TABLE 2: suitability of various regions of the oral mucosa for the transmucosal drug delivery based on various tissue properties

	Permeability	**Blood flow**	**Residence time**
Buccal	+	++	+
Sublingual	++	--	--
Gingival	--	+	+
Palatal	--	--	++

Note ++ means very suitable; -- means least suitable.

Tissue Permeability: In comparison to the skin, the buccal mucosa offers higher permeability and faster onset of drug delivery; whereas the key features which help it score over the other mucosal route, the nasal delivery system, include robustness, ease of use, and avoidance of drug metabolism and degradation. The buccal mucosa and the skin have similar structures with multiple cell layers at different degrees of maturation. The buccal mucosa, however, lacks the intercellular lamellar bilayer structure found in the stratum corneum, and hence is more permeable. An additional factor contributing to the enhanced permeability is the rich blood supply in the oral cavity. The lamina propia, an irregular dense connective tissue, supports the oral epithelium. Though the epithelium is avascular, the lamina propia is endowed with the presence of small capillaries. These vessels drain absorbed drugs along with the blood into three major veins-lingual, facial, and retro-mandibular, which open directly into the internal jugular vein, thus avoiding first-pass metabolism. Numerous studies have been conducted comparing the blood supply of the oral cavity to the skin in animals. A thicker epithelium has been associated with a higher blood flow probably due to the greater metabolic demands of such epithelia. Gingiva and anterior and posterior dorsum of tongue have significantly higher blood flows than

all other regions; skin has a lower flow than the majority of oral regions; and palate has the lowest of all regions. In fact, the mean blood flow to the buccal mucosa in the rhesus monkey was observed to be 20.3 mL/min/100 g tissue as compared to 9.4 mL/min/100 g in the skin.

Barriers to Permeation : The main resistance to drug permeation is caused by the variant patterns of differentiation exhibited by the keratinized and non-keratinized epithelia. As mucosal cells leave the basal layer, they differentiate and become flattened. Accumulation of lipids and proteins also occurs. This further culminates in a portion of the lipid that concentrates into small organelles called membrane-coating granules (MCGs). In addition, the cornified cells also synthesize and retain a number of proteins such as profillagrin and involucrin, which contribute to the formation of a thick cell envelope. The MCGs then migrate further and fuse with the intercellular spaces to release the lipid lamellae. The lamellae then fuse from end to end to form broad lipid sheets in the extracellular matrix, forming the main barrier to permeation in the keratinized regions in the oral cavity. These lamellae were first observed in porcine buccal mucosa, and have been recently identified in human buccal mucosa. Though the non-keratinized epithelia also contain a small portion of these lamellae, the random placement of these lamellae in the non-cornified tissue the organized structure in the cornified tissue makes the former more permeable. Also, the non-keratinized mucosa does not contain acylceramides, but has small amounts of ceramides, glucosylceramides, and cholesterol sulfate. The lack of organized lipid lamellae and the presence of other lipids instead of acylceramides make the non-keratinized mucosa more water permeable as compared to the keratinized mucosa.

Physicochemical properties and routes of permeation: There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa:

1. Transcellular (intracellular, passing through the cell)
2. Paracellular (intercellular, passing around the cell)

Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intercellular lipids produced by membrane-coating granules. Although passive diffusion is the main mechanism of drug absorption, specialized transport mechanisms have been reported to exist in other oral mucosa (that of the tongue) for a few drugs and nutrients; glucose and cefadroxil were shown to be absorbed in this way. Figure 2 shows the two routes of permeation that can be used by drugs to pass through the buccal mucosa. The buccal mucosa is a potential site for the controlled delivery of hydrophilic macromolecular therapeutic agents (biopharmaceuticals) such as peptides, oligonucleotides and polysaccharides. However, these

high molecular weight drugs usually have low permeability leading to a low bioavailability, and absorption enhancers may be required to overcome this. The buccal mucosa also contains proteases that may degrade peptide-based drugs. In addition, the salivary enzymes may also reduce stability.

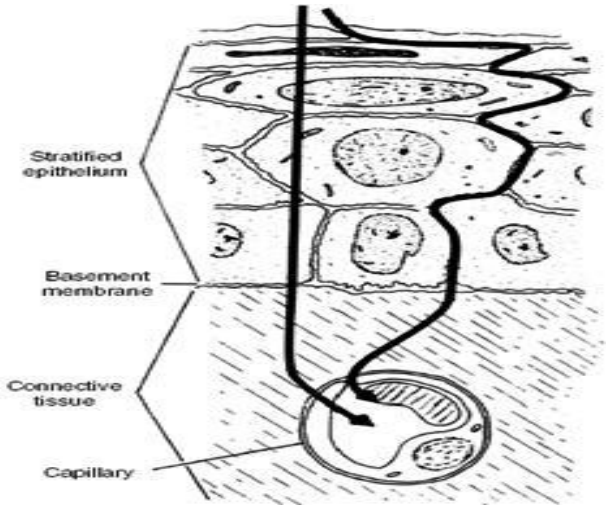

Figure . 2: *routes of transepithelial penetration: transcellular route versus paracellular route*
Disease states where the mucosa is damaged would also be expected to increase permeability. This would be particularly true in conditions that result in erosion of the mucosa such as lichen planus, pemphigus, viral infections and allergic reactions.

MECHANISM OF MUCOADHESION

The mucoadhesion can be defined as an interfacial phenomenon in which the two materials, in which one may be artificial such as mucoadhesive polymer and other may be the mucin layer of the mucosal tissue, are held together by means of interfacial forces of attraction. "Mucoadhesive" is defined as an artificial substance that is capable of interacting with mucus membrane and being retained on them or holding them together for extended or prolonged period of time. During the process of adhesion, generally the two stages have been identified are given below. These stages of mucoadhesion are also shown in Figure 3.

Contact stage:

During this stage, when the mucoadhesive material comes in contact with mucus membrane, an intimate wetting occurs between the mucoadhesive and mucous membrane. This wetting of the mucoadhesive is done by the mucus present in the mucosal membrane

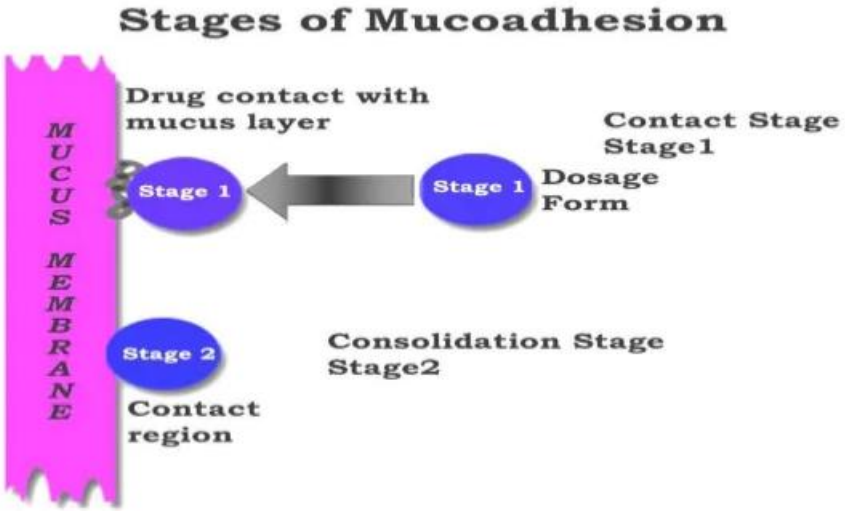

Figure 3: These stages of mucoadhesion

Consolidation stage:

By means of different physicochemical forces of attraction the mucoadhesive material gets joined to the mucus membrane and resulting in a long lasting mucoadhesion. This is called as the consolidation stage. After these two stages the process of mucoadhesion completes.

Theory of Mucoadhesion

The process of mucoadhesion is mainly based on formation of two types of bond between bio adhesive system and mucus membrane and they are:

Chemical bond

It may include covalent bonds, Weak secondary bonds, ionic bond and hydrogen bond etc

Mechanical bond

This bond can be arising from the physical connection between two surfaces. It is similar to that of the interlocking system. On the basis of nature and strength of these two kinds of bonds, there are following five theories of mucoadhesion that are been postulated.

Electronic theory

According to the electronic theory, there is difference in the electronic structure of mucin surfaces and bio adhesive system which results in attaining a electronic gradient. Due to presence this electronic structure difference the transfer of electrons occurs in these two systems (mucin surface and bioadhesive system) when they come in contact with each. As a result of this electron transfer there is the formation of an electronic bi-layer at the interface of the two

surfaces. This interfacial bi-layer exerts an attractive force in the interface of two surfaces that may produce an effective mucoadhesion

Adsorption theory

This theory describes the involvement of both type of chemical bond, that is, primary and secondary bond in the bio adhesion mechanism. Both the surface that is mucin and drug delivery system has their own surface energy. When they come in contact, the adhesion occurs due to the surface energy and results in the formation of two types of chemical bond. Primary chemical bond such as covalent bond, which is strong in nature, thus produces a permanent bonding, whereas secondary chemical bond involves Vander-Waals forces, hydrophobic interaction and hydrogen bonding, which are weak in nature, thus produces a semi-permanent bond.

Wetting theory

This theory is based on the mechanism of spreadability of drug dosage form across the biological layer. This theory is mainly applicable to liquids or low viscous mucoadhesive system. According to this theory, the active components penetrate in to the surface irregularities and gets harden it that finally results in mucoadhesion.

Diffusion interlocking theory

This theory describes the involvement of a mechanical bond between the polymeric chain of drug delivery system and polymeric chain of mucus membrane, that is, glycol proteins. When two surfaces are in intimate contact, the polymeric chain of drug delivery system penetrates in to the glycoprotein network. According to this theory, the bioadhesion basically depends on the diffusion coefficient of both polymeric chains. the other factors that may influence the inter movement of polymeric chain are molecular weight, cross linking density, chain flexibility and temperature in order to achieve a good bio adhesion, the bio adhesive medium should have a similar solubility with glycoprotein resulting in effective mucoadhesion.

Fracture theory

The fracture theory is mainly based on the fact that, the force required detaching the polymeric chain from the mucin layer is the strength of their adhesive forces. This strength may be also called as fracture strength. The fracture strength can be determined by using the formula given below

$$G = \left(E.\frac{e}{L}\right)^{1/2}$$

G-Fracture strength

E-Young's modules of electricity

e-Fracture energy

L-Critical crack length

Principles of Drug Absorption: The oral mucosa contains both hydrophilic and hydrophobic components and a combination of both keratinized and non-keratinized epithelia.

Passive diffusion is the most common route of permeation through the oral mucosa, and uses the Fick's first law of diffusion given by the general equation

$$P = \frac{DKp}{h}$$

The amount of drug absorbed A is given by;

$$A = PCSt = \frac{DKp}{h} CSt$$

Where,

P is the permeability coefficient

C is the free drug concentration in the delivery medium

D is the diffusion coefficient of the drug in the oral mucosa

Kp is the partition coefficient of the drug between the delivery medium and the oral mucosa

h is the thickness of the oral mucosa

S is the surface area of the delivery or the absorption site on the mucosa

t is the duration of time the drug stays in contact with the mucosa.

The thickness of the tissue, partition coefficient, and the diffusion coefficient are properties of the mucosa and cannot be altered. Designing appropriate formulations that need the necessary conditions can vary the surface area for delivery of the drug, time of contact, and the free drug concentration. The partitioning of the drug into the membrane will depend on its ratio of hydrophilicity and lipophilicity. Studies performed with amines and acids showed that their absorptions were proportional to their partition coefficients, thus also establishing the fact that the transcellular route was the primary route of absorption of these drugs. Similar results were obtained for b-adrenoreceptor-blocking drugs.

Since the drug will face different barriers through the paracellular and the transcellular routes, the flux of drug permeation through these routes will differ to some extent. The equation above can be modified to account for this difference. Hydrophilic compounds will tend to use the

paracellular route and permeate through the intercellular spaces, which present a smaller surface area. The flux of drug permeation through this pathway can be described as

$$\text{JH} = \frac{DH\varepsilon}{hH} CD$$

Where,

DH is the diffusion coefficient

hH is the length of the tortuous path followed in the paracellular route

CD is the concentration of the drug on the donor side

ε is the fraction of the surface area of the paracellular route.

A lipophilic drug will preferably use the transcellular route since it will be easier for it to partition into the lipophilic cell membrane. The path length here is shorter than for the paracellular route but the drug has to move through several types of barriers (cell membrane, the cytoplasm, as well as intercellular spaces). Thus the equation for flux through the transcellular route is given as

$$\text{JL} = \frac{(1-\varepsilon)DLKP}{hL} CD$$

Where Kp is the partition coefficient between the lipophilic regions (cell membrane) and the hydrophilic regions (cytoplasm, formulation vehicle, and the intercellular space).

Factors affecting Drug Absorption:

Besides the biochemical characteristics of the buccal and sublingual membranes, which are responsible for the barrier function and permeability, various factors of the drug molecule influence the extent of permeation through the membranes. The lipid solubility, degree of ionization, pKa of the drug, pH of the drug solution, presence of saliva and the membrane characteristics, molecular weight and size of the drug, various physicochemical properties of the formulation, and the presence or absence of permeation enhancers, all affect the absorption and the permeation of drugs through the oral mucosa.

Degree of Ionization, pH, and Lipid Solubility:

The permeability of unionizable compounds is a function of their lipid solubilities, determined by their oil–water partition coefficients demonstrated this dependence of water permeability on the lipid contents of keratinized and non-keratinized epithelia. The lipids present however

contribute to this effect more in the keratinized epithelia (more total lipid content, non-polar lipids, ceramides) than in the non-keratinized epithelia where permeability seems to be related to the amount of glycosylceramides present.

The absorption of drug through a membrane depends upon its lipophilicity, which in turn depends on its degree of ionization and partition coefficient. The higher the unionized fraction of a drug, the greater is its lipid solubility. The degree of ionization in turn depends on the pH of the mucosal membrane and the pKa of the drug. Buccal absorption of basic drugs over a range of concentration, pH, and the use of different drug combinations (alone and mixtures). The resultant pH–absorption curves showed that the percentage of drug absorbed increased as the concentration of drug in the unionized form increased.

Also, the shapes of the absorption curves were a function of the pKa values and the lipid solubility of their unionized form. A study conducted with fentanyl, a weak base with a pKa of 8.2, further demonstrated the relationship between the pH and the absorption across oral mucosa. When the pH of the delivery solution was increased, more of the drug was present in the unionized form, with the drug being 2.45% unionized at pH 6.6, 9.1% unionized at pH 7.2, and 24% unionized at pH 7.7. The fentanyl solutions with a pH range of 6.6 to 7.7 showed a three- to fivefold increase in peak plasma concentration, bioavailability, and permeability coefficients.

Similar studies conducted with sublingual administration of opioids such as buprenorphine, methadone, and fentanyl showed increased absorption with increase in pH, where the drug was predominantly present in the unionized form. However, absorption of other opioids such as levorphanol, hydromorphone, oxycodone, and heroin under similar conditions did not improve. These drugs, however, were more hydrophilic as compared to the earlier set of opioids. Thus, pH modifiers can be used to adjust the pH of the saliva prior to drug administration to increase the absorption of such drugs through the mucosal membranes. However, the nature of the buccal and sublingual membrane complicates the above condition since the pH may vary depending on the area of the membrane and also on the layer of the membrane that is considered. The pH of the mucosal surface may be different from that of buccal and sublingual surfaces throughout the length of the permeation pathway. Thus, the drug in its unionized form may be well absorbed from the surface of the membrane, but the pH in the deeper layers of the membrane may change the ionization and thus the absorption. Also, the extent of ionization of a drug reflects the partitioning into the membrane, but may not reflect the permeation through the lipid layers of the mucosa. Henry *et al*., studied the buccal absorption of propranolol followed by repeated rinsing

of the mouth with buffer solutions and recovered much of this drug in the rinsing. In addition, the effect of lipophilicity, pH, and pKa will depend on the transport pathway used by the drug. Studies conducted with busiprone showed that the unionized form of the drug used the more lipophilic pathway, the transcellular route, but an increase in the pH increased the ionization of the drug and subsequently the absorption. It was concluded that this transport of the ionized form of the drug was through the more hydrophilic paracellular pathway. Therefore, at neutral pH the preferred pathway was found to be transcellular, but at acidic pH, the ionized species of the drug also contributed to the absorption across the membrane.

Molecular Size and Weight: The permeability of a molecule through the mucosa is also related to its molecular size and weight, especially for hydrophilic substances. Molecules that are smaller in size appear to traverse the mucosa rapidly. The smaller hydrophilic molecules are thought to pass through the membrane pores, and larger molecules pass extracellularly. Increases in molar volume to greater than 80 mL/mol produced a sharp decrease in permeability. Due to the advantages offered by the buccal and the sublingual route, delivery of various proteins and peptides through this route has been investigated.

$$P = \frac{\%\ Permeated\ \times Vd}{A \times t \times 100}$$

Where P is the permeability coefficient (cm/s), A is the surface area for permeation, Vd is the volume of donor compartment, and t is the time. This equation assumes that the concentration gradient of the drug passing through the membrane remains constant with time, as long as the percent of drug absorbed is small.

Types of Penetration Enhancers:

- Bile salts
- Fatty acids and their salts and Esters
- Azones
- Surfactants
- Complexing Agents
- Co-solvents
- Miscellaneous

Bile Salts: Bile salts are steroids with surfactant-like properties that form associations in water. Their physiological role is to emulsify lipids in food stuff passing through the intestine to enable fat digestion and absorption through the intestinal wall. Bile salts are used as permeation

enhancers and have been extensively employed to enhance the absorption of drugs through various epithelia. They are believed to act on both the transcellular and paracellular routes by a variety of mechanisms including solubilization and micellar entrapment of intercellular lipids, denaturation and extraction of proteins, enzyme inactivation, tissue swelling, the extraction of lipids or proteins from the cell wall, membrane fluidization, and reverse membrane micellation. Bile salts used in permeation enhancement studies include the trihydroxy salts sodium cholate, sodium glycocholate, and sodium taurocholate and the dihydroxy salt sodium deoxycholate, sodium glycodeoxycholate, and sodium taurodeoxycholate.

Fatty acids and their salts and esters : Fatty acids include oleic acid, lauric acid, and cod liver oil extract, whereas fatty acid salts include sodium laurate and sodium caprate, and esters include glyceryl monostearate, diethy lene glycol monoethyl ether, and various sucrose fatty acid esters. These are generally lipophilic in nature with limited water solubility. The unsaturated fatty acids such as oleic acid act by reducing lipid order and increasing fluidity in the skin due to their ‘‘kinked’’ molecular conformation arising from the double bond in the hydrocarbon chain, and they should have a similar effect on oral mucosa.

Oleic acid has been reported to be a good adsorption enhancer for insulin. Unionized ergotamine absorption was enhanced in the presence of 5% cod liver oil extract, which contained oleic acid as one of its major components. The distribution of the drug within the lipid-rich region of the buccal mucosa and the resultant reduction in the barrier structure were correlated with its permeation enhancing effects (although at higher concentrations [7%–10%] permeation was seen to apparently decrease). Fatty acid esters would be predicted to have little irritation or toxic effects.

Azone: Azone (laurocapram) is used extensively as a transdermal permeation enhancer, and has also found use in buccal drug delivery. It is a lipophilic surfactant in nature. Permeation of salicylic acid was enhanced by the pre-application of an Azone emulsion in vivo in a keratinized hamster cheek pouch model. Octreotide and some hydrophobic compounds’ absorption have also been improved by the use of Azone. Azone was shown to interact with the lipid domains and alter the molecular moment on the surface of the bilayers. In skin it has been proposed that Azone was able to form ion pairs with anionic drugs to promote their permeation.

Surfactants: The other surfactants include sodium dodecyl (lauryl) sulfate, the polysorbates, the laureths, Brijs and benzalkonium chloride. These are predominantly water soluble and can form associations (micelles) in aqueous solution. They are believed to enhance the transbuccal

permeation by a mechanism that is similar to that of bile salts, namely, extraction of lipids, protein denaturation, inactivation of enzymes and swelling of tissues. Sodium dodecyl sulfate is reported to have a significant absorption enhancing effect but may also produce damage to the mucosa. The effect of Sodium dodecyl sulfate on the in vitro buccal permeability of caffeine and estradiol has been evaluated using porcine buccal tissue.

Complexing Agents: The complexing agents include cyclodextrins and sodium edetate. Cyclodextrins are enzymatically modified starches, forming rings of 6-8 units. The outer surface of the ring is polar whereas the internal surface is non-polar. Hence, the center of the cyclodextrin can be used to carry water-insoluble molecules in an aqueous environment by forming inclusion complexes. Effective buccal absorption of steroidal hormones using two different hydrophilic cyclodextrin derivatives, namely, 2-hydroxypropyl β-cyclodextrin and poly β-cyclodextrin, was reported. The effect of cyclodextrins (5%) on the buccal absorption of interferon has also been described. Chelators such as EDTA, sodium citrate, and also the polyacrylic acids to have an absorption enhancing effect by interfering with calcium ions.

Co-solvents: Co-solvents include water-miscible solvents such as ethanol and propylene glycol. The use of vehicles that enhance absorption has been considered in transdermal drug delivery, and would also be of use in buccal delivery. They work by changing the thermodynamic activity of the drug in solution, increasing its concentration and facilitating partition of the drug into the membrane, and promoting passive diffusion.

As ethanol and propylene glycol penetrate into mucosa, drugs dissolved in these co-solvents are expected to be carried with them. In most studies, the vehicle is used in combination with a permeation enhancer to further increase absorption. A combination of oleic acid (1%) and polyethylene glycol 200 (PEG, 5% and 10%) appreciably enhanced the ex vivo permeation of a model peptide across porcine buccal mucosa.

Miscellaneous: Lecithin (phosphatidylcholine) is a phospholipid, which may be isolated from either egg yolk or soybeans. It is commercially available in high purity for medical uses and has been used to enhance the absorption of insulin *in vivo*. The antibiotic sodium fusidate, a steroid similar in molecular structure to bile salts has also been shown to have permeation enhancing properties for insulin *in vitro*. Chitosan, a polysaccharide containing glucosamine and acetyl glucosamine units, has been shown to have permeation-enhancing activity. Solutions and gels of chitosan were found to be effective absorption enhancers by their transient widening of the tight junctions within the mucosa. It was found to promote the transport of mannitol and fluorescent-

labeled dextrans across a tissue culture model of the buccal epithelium, chitosan glutamate being particularly effective. Chitosan has been shown to be an effective permeation enhancer for peptide absorption across porcine buccal mucosa without producing any histological evidence of tissue damage.

Sr. no	Permeation Enhancers	Permeation Enhancers
1	2, 3-Lauryl ether	Phosphatidylcholine
2	Aprotinin	Polyoxyethylene
3	Azone	Polysorbate 80
4	Benzalkonium chloride	Polyoxyethylene
5	Cetylpyridinium chloride	Phosphatidylcholine
6	Cetyltrimethyl ammonium bromide	Sodium EDTA
7	Cyclodextrin	Sodium glycocholate
8	Dextran sulfate	Sodium glycodeoxycholate
9	Glycol	Sodium lauryl sulfate
10	Lauric acid	Sodium salicylate
11	Lauric acid/Propylene	Sodium taurocholate
12	Lysophosphatidylcholine	Sodium taurodeoxycholate
13	Menthol	Sulfoxides

Structure and Design of Oral mucosal Dosage Form

1. Matrix type: The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together

2. Reservoir type: The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.

Additionally, the patch can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.

Oral mucosal drug delivery systems can be bi-directional or unidirectional. Bi-directional patches release drug in both the mucosa and the mouth while, Unidirectional patches release the drug only into the mucosa.

Mechanisms of Mucoadhesion:

The mechanistic processes involved in mucoadhesion between hydrogels and mucosa can be described in three steps:

1. Wetting and swelling of the polymer to allow for intimate contact with the biological tissue.
2. Interpenetration of the bioadhesive polymer chains and entanglement of polymer and mucin chains, and
3. Formation of weak chemical bonds between entangled chains

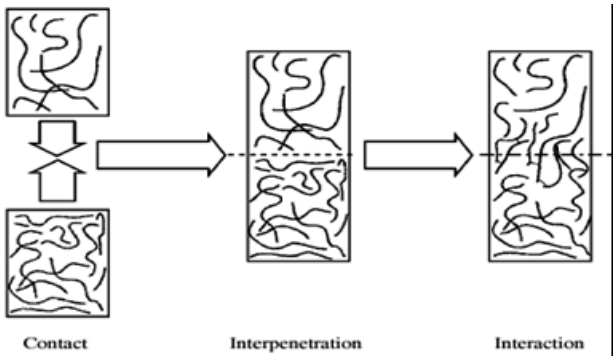

Figure 4: Three stages in the interaction between a mucoadhesive polymer and mucin glycoprotein according to the interpenetration theory

Dosage Forms :

A wide range of formulations have been developed and tested for buccal and sublingual administration. Various advances have been made over the years, which counteract the problems faced in delivering drugs through the sublingual and buccal mucosae to the systemic circulation. The primary challenges for these routes of delivery are:

1. The varying structure of the mucosal membrane in different parts of the oral cavity and the reduced permeation due to the barrier presented by the mucosal epithelial layers
2. The constant presence of saliva, which prevents the retention of the formulation in one area of the oral cavity leading to shorter contact time
3. Person to person variability caused by differences in tongue movements, saliva amounts, and saliva content
4. The limited surface area available for absorption
5. Ensuring patient comfort with a dosage form small and flexible enough to fit comfortably in the oral cavity, easy to install and remove, and not causing any local reactions, discomfort, or erythema.

Buccal and sublingual deliveries have been used in various clinical applications such as cardiovascular, smoking cessation, sedation, analgesia, antiemesis, diabetes, and hormonal therapy. The specific drugs will be discussed in relation to the dosage form category. Buccal delivery has also been actively researched for the delivery of peptides, since these molecules are sensitive to the acidic and proteolytic environment of the GI tract and are subjected to first-pass metabolism.

Chewing Gums: Gums are now considered pharmaceutical dosage forms, and have been used to deliver drugs for buccal absorption. These formulations consist of a gum base, which primarily consists of resins, elastomers, waxes, and fats. Emulsifiers such as glycerol monostearate and lecithin are added to facilitate and enhance the uptake of saliva by the gum. Resin esters and polyvinyl acetate (PVA) are added to improve texture and decrease sticking of the gum to teeth. Additives such as sweeteners, glycerol (to keep the gum soft and flexible), and flavors can be added as desired. These chewing gums move about in the oral cavity, and the process of chewing mixes it with the saliva where the drug is rapidly released, partitioned, and then absorbed into the mucosal membrane. Thus, the solubility of the drug in saliva is an important factor in increasing the amount of drug released and absorbed.

Intersubject variation such as the intensity of chewing, amount of saliva produced, and inconsistent dilution of the drug influence the amount of drug released. Also, the saliva can be swallowed, leading to disappearance of an often unknown amount of drug. Gum formulations containing caffeine showed rapid release and absorption of the agent with comparable bioavailability to the capsule form. Various gum formulations with vitamin C, diphenhydramine, methadone, and verapamil have been developed and tested. Recently, sustained release of catechins from chewing gums has been achieved by using a special procedure involving granulation of the active principles with PVA followed by coating of the pellets with acrylic insoluble polymer. One of the most important and successful applications for chewing gum as a dosage form is that for nicotine replacement therapy (NRT). Nicorette (GlaxoSmithKline, USA), a chewing gum containing nicotine, is available in regular strength (2mg) and extra strength (4mg) and has a specially recommended chewing technique to maximize efficacy.

Lozenges: Lozenges can be used as an alternative dosage form to tablets and capsules when patients are unable to swallow. The use of lozenges has been reported for systemic drug delivery but it is more usual to see this dosage form used to bathe the oral cavity or the throat areas. While sublingual lozenges may be impractical due to their size, buccal lozenges have been

extensively used, and are kept between the cheek and the gums. Though the lozenge usually dissolves in about 30 min, the patient controls the rate of dissolution and absorption because the patient sucks on the lozenge until it dissolves. This process can result in high variability of amounts delivered each time the lozenge is administered. Increase in the amount of sucking and production of saliva may also lead to increased dilution of the drug and often accidental swallowing. There was a noticeable intrasubject variation in residence time (from 2 to 10 min) of unflavored buccal lozenges. They also found that stronger lozenges prolonged the buccal residence time, a factor which can be used as an advantage in local delivery of agents from lozenges.

Despite their drawbacks and an additional requirement of palatability, lozenges have had considerable success in the market. For example, zinc lozenges have been studied and used extensively in the treatment of common colds. A study utilizing NRT was conducted with 2 and 4 mg lozenges. It was found that the lozenges achieved better abstinence from smoking in low- and high-dependent smokers compared to those patients receiving an identical dose in a chewing gum. Oral mucosal administration of fentanyl citrate, a medication for breakthrough pain, resulted in a bioavailability substantially greater than oral administration and led to faster achievement of peak plasma concentration.

Buccal and Sublingual Tablets: These tablets are placed and held between the cheek and gum or the lip and gum (buccal) or under the tongue (sublingual) until they dissolve. Nitroglycerin tablets have been used extensively in the form of buccal and sublingual tablets for the fast onset and quick relief from angina. Similarly isosorbide dinitrate is available in the form of sublingual tablets to be placed under the tongue or chewable tablets where the tablet has to be chewed in the mouth for 2 min before swallowing, and the drug is adsorbed through the oral mucosa. Other formulations that have been used are nifedipine (sublingual capsules), sublingual misoprostol for labor induction, methyl testosterone (buccal and sublingual tablets), buprenorphine (sublingual and buccal), and selegiline for monoamine oxidase-B inhibition.

Mucoadhesive Systems: One of the primary problems in oral mucosal drug delivery is the retention of the device on the desired area of the membrane for a sufficiently long period of time to allow for absorption of the drug and hence achievement of the desired blood levels. To assist in this, bioadhesive systems have been designed to stay and maintain intimate contact with the mucous membrane that covers the epithelium. These systems are referred to as ‘‘mucoadhesive,’’ and they isolate the delivery of the drug from environmental factors in the

cavity and allow the drug to be absorbed only from a specific (buccal or sublingual) region. This result in prolonged contact and these systems can also be designed to control the release rate of the drug.

Mucoadhesives are generally macromolecular organic polymers made from natural (gelatin, agarose, chitosan, hyaluronic acid) or synthetic polymers (polyvinylpyrrolidone (PVP), polyacrylates, polyvinyl alcohol, cellulose derivates). They possess hydrophilic groups that can form hydrogen bonds such as carboxyl, hydroxyl, amide, and amine groups. These mucoadhesives are called ‘‘wet’’ adhesives and need to be in the presence of water in order to hydrate and swell. The amount of water uptake by the system depends on the number of hydrophilic groups in the polymer, and the degree of adhesion in turn depends on the amount of hydration. Upon hydration and swelling, they adhere nonspecifically to the mucosal surfaces. Mucoadhesives can also be used in the dry or partially hydrated forms. Hypotheses have described the mucoadhesion process as initial establishment of contact with the substrate and the subsequent formation of chemical bonds. The attachment to the substrate can be governed by covalent interaction, electrostatic interaction, hydrogen bonding, or hydrophobic interactions. The result is the formation of a tight and intimate contact between the mucosal surface and the polymeric chains of the mucoadhesive, and this ‘‘intertangling’’ between the two surfaces leads to adhesiveness. The mucoadhesion achieved depends on various polymer properties, such as molecular weight, chain length, conformation, and chain flexibility. Effective mucoadhesion has been used to design different formulations, some of which are discussed below.

Films and Patches: Patches are flexible dosage forms that adhere to a specific region of the mucosa and provide either a unidirectional flow or a bidirectional flow of drug, depending on the type of delivery intended (local or systemic). The permeation of the drug into the membrane will depend on the surface area of the patch. Different patches are designed to achieve objectives such as local and systemic drug delivery, varying duration of action and varying rates of release. In general, most patches contain either a ‘‘matrix system’’ in which the drug is dispersed along with excipients or the mucoadhesive, or a ‘‘reservoir system.’’ The mucoadhesive can be dispersed in the drug matrix as described above or as a separate layer. The patches may incorporate a backing layer that protects it from the surrounding oral cavity if strictly Oral mucosal delivery is required. Otherwise, the backing layer is omitted. The polymer within the mucoadhesive layer swells, and a network is produced through which the drug diffuses into the membrane. Combinations of the above factors have been used to design and develop three kinds

of patches: patches with a dissolvable matrix, patches with a non-dissolvable backing, and patches with a dissolvable backing. Patches with a dissolvable matrix release the drug into the entire oral cavity, but the presence of a mucoadhesive layer prolongs this release. Patches with a non-dissolvable backing provide a unidirectional flow of the drug through the mucosa for a long period of time, whereas patches with a dissolvable backing are short acting as the backing layer dissolves fairly rapidly in the oral cavity.

Hydrogels: Hydrogels are three-dimensional, hydrophilic, polymeric networks that can take up large amounts of water or other biological fluids. The networks consist of homopolymers or copolymers having physical or chemical cross-links that make them insoluble, which are responsible for the integrity of the network. Depending on their chemical side groups, hydrogels can be neutral or ionic. For a hydrogel to possess mucoadhesive properties, the polymer chains have to be mobile to facilitate the interpenetration into the mucous layer and formation of bonds leading to mucoadhesion.

Also, gels containing more hydrophilic groups will swell more as compared with those containing more hydrophobic groups. Swelling of physiologically responsive hydrogels is affected by various external factors such as pH, ionic strength, temperature, and electromagnetic radiation. The drug can be either present in a matrix core anchored by a hydrogel to the mucosa or it can be dispersed into the mucoadhesive matrix. In the second case, swelling will play a primary role in the release of the drug from the system.

Liposomes: Liposomes have been used in the local delivery of drugs to the oral mucosa. The biodistribution of dexamethasone sodium phosphate (DSP) encapsulated in multilamellar vesicle (MLV) liposomes labeled with 99mTc in ulcerated and intact oral mucosae of rats. The liposomes were found to localize the drug in the ulcerated area and increase local drug concentration while decreasing systemic concentration.

Nanoparticles: In an effort to develop an effective bioadhesive system for buccal administration, insulin was encapsulated into polyacrylamide nanoparticles by the emulsion solvent evaporation method. Though nanoparticle formation ensures even distribution of the drug, pelleting of the nanoparticles was performed to obtain three-dimensional structural conformity. In addition, it was hypothesized that the pelletized particles will remain adhered to the mucosa, leading to good absorption. While studying bioadhesion and drug release profiles, it was found that the system showed a sustained drug release profile that was mainly governed by

polymer concentration. A significant and non-fluctuating hypoglycemic response with this formulation was observed after 7 h in diabetic rats.

Microparticulate Delivery Systems: Microparticulate delivery systems containing piroxicam in amorphous form were designed to improve the drug dissolution rate via the sublingual route. Two low-swellable mucoadhesive methacrylic copolymers, namely Eudragit1 L sodium salt (EuLNa) and Eudragit1 S sodium salt (EuSNa), were chosen as carriers for the preparation of the microparticles. The microparticles of piroxicam and the copolymer improved the piroxicam dissolution rate in comparison with that of micronized piroxicam in cubic form. Also, the drug released from the microparticles reached a plateau within 12 min, and the concentrations were always higher than the maximum solubility of piroxicam in the cubic form.

Iontophoresis: Iontophoresis is the process of delivering drugs or other charged molecules across a membrane using a small electrical charge. The ‘‘like-repels-like’’ phenomenon is applied here to drive charged molecules that are repelled by similarly charged electrodes into a tissue. Besides its use in transdermal delivery, this method has also been used to enhance oral mucosal drug delivery. iontophoresis to enhance the absorption of atenelol into porcine buccal mucosa. A newly designed *in- vitro* three-chamber iontophoretic permeation cell was used to measure the permeability of the drug over a period of 8 h. High enhancement ratios were obtained, and were found to be a factor of the electric current rather than the concentration gradient. Though this method can be used to increase the penetration of drugs, the inconvenience and accessibility issues faced in administration to the oral mucosa limit its applications.

Introduction

Implantable drug delivery systems are placed under the skin and designed to release drugs into the bloodstream without the repeat insertion of needles. It is “A sterile drug delivery device for subcutaneous implantation having the ability to deliver the drugs at a controlled rate over a prolonged period of time, comprising a rod shaped polymeric inner matrix with an elongated body and two ends. Implantation is typically done in subcutaneous or intramuscular tissue, with the aid of special implantation devices, needles, or the use of surgery . Subcutaneous tissue or intramuscular tissue are ideal locations for implantation of drug-depot devices, due to high fat content that facilitates slow drug absorption, minimal innervation, good hemoperfusion, and a lower possibility of localized inflammation (low reactivity to the insertion of foreign materials). From these early beginnings, the potential of this mode of delivery in overcoming problems

associated with oral administration, such as drug bioavailability, stability, toxicity, and duration of release, was recognized. Implant delivery systems have been subsequently designed to reduce the frequency of dosing, prolong duration of action, increase the patient compliance, and reduce the systemic side effects.

IDDSs are very attractive for a number of classes of drugs, particularly those that cannot be delivered via the oral route, are irregularly absorbed via the gastrointestinal tract, or that benefit from site-specific dosing. Examples include steroids, chemotherapeutics, antibiotics, analgesics and contraceptives, and biologics such as insulin or heparin. Implantable drug delivery should be environmentally stable, biocompatible, easy to sterilize, rate controlled release of drug, improve patient compliance by reducing the frequency of the drug administration over the entire period of treatment, easy to manufacture & relatively inexpensive, good mechanical strength and free from surgical procedure.

History

The concept of implantable drug delivery systems (IDDSs) in modern medicine may be traced to Deansby and Parkes who, in 1938, subcutaneously (SC) implanted compressed pellets of crystalline estrone to study their effect up on castrated male chickens. Folkman and Long pioneered implantable formulations, with drug release rates controlled by a polymeric membrane, in the 1960s. They investigated the use of silicone rubber (Silastic) for long-term drug delivery at a systemic level. In the year 1861, Lafarge introduced the concept of implantable system for sustained release drug administration. In the very beginning it was first introduced to produce the **solid implants** containing steroid hormones implantable system for long term delivery

Advantage of Implantable drug delivery systems

Localized delivery: - Drug(s) are released in immediate vicinity of implant. Action may be diffusion, limited to the specific location of implantation

Improved patient Compliance: - Patient does not need to comply with repeated and timely intake of medication throughout the implantation period. Compliance is limited to one-time implantation (and potential removal in the case of non-biodegradable implants)

Minimized systemic side effects: - Controlled release for extended periods of time and localized dosing possible with at site of action; adverse effects away from site of action are minimized; peaks and valleys in plasma drug concentration from repeated intermediate release dosing are avoided

Lower dose: - Localized implantation of site specific drugs can avoid first pass hepatic effects, thereby reducing dose required to ensure systemic bioavailability

Improved drug stability: - Protection of drug undergoing rapid degradation in the gastrointestinal and hepatobiliary system

Suitability over direct Administration: - Hospital stay or continuous monitoring by healthcare staff may not be required for chronic illnesses

Facile termination of drug delivery: - If allergic or other adverse reaction to drug is experienced, discontinuation of therapy by implant removal is possible

Potential for intermittent release: Extremely programmable pumps can facilitate intermittent release in response to various factors such as cardiac rhythm, metabolic needs etc.

Flexibility: Various types of flexibilities like materials, method of manufactures etc. are available in case of implants. Controlled delivery of both hydrophilic and lypophillic drugs can be obtained from here.

Disadvantage of Implantable drug delivery systems

Invasive: For the insertion of the implants patient has to face either a major or a minor surgical procedure.

Termination: non-biodegradable polymeric implants can be terminated from the body also with the help of a surgical method at the end of the treatment.

Danger of device failure: If due to some reason the device fails to operate properly during the treatment then again surgical steps should be taken for removal of the device from the patient's body.

Limited to potent drug: The size of the device is very small to reduce the patient's discomfort, therefore only the potent drugs which are very small in amount can only be used in this system.

Adverse reaction: As a high concentration of drug is delivered to the implantation site with the help of the device therefore there is always a chance of adverse reaction due to this local high concentration.

Mechanism of Drug Release from Implantable Therapeutic System

Rate pre-programmed drug delivery system

The recent advances in smart drug delivery systems with rate-programmed drug delivery systems have been achieved by functionalization of rate-controlling surface. The transdermal drug delivery have been achieved a new rate pre-programmed drug delivery system, transdermal patch which delivers a particular concentration of drugs to the blood circulation via the skin. It release

of drug molecules from the rate controlling membrane system has been preprogrammed at particular rate kinetics. The rate controlling membranes made from natural and semi-synthetic polymeric material and proves their ability to use as a rate controlling membranes in any dosage form even nano to microscale level particle embedded matrixes or implantable or transdermal patches. Optimizing the system design, determines the diffusivity of active agents across the membrane. This rate-programmed drug delivery system can be categorized by various controlling dependencies, such as membrane permeation-controlled, diffusion-controlled, membrane/matrix hybrid type and reservoir partition-controlled systems. The whole mechanism of drug release from implantable therapeutic system approaches are designed as follows

1. Polymer membrane permeation controlled drug delivery system

In this controlled drug delivery device, drug reservoir is totally encapsulated within a capsule shaped or spherical compartment. This total system is covered with a rate controlling polymeric membrane. The drug reservoir can be either solid particles or the dispersion of the solid particles in a liquid or solid dispersing medium. The encapsulation of the drug reservoir system inside the polymeric membrane can be done by the encapsulation, microencapsulation, molding, extrusion etc. Example: Norplant subdermal implant. So in this system, the drug reservoir is sandwiched between a drug-impermeable backing laminate and a rate controlling polymeric membrane. The drug is allowed to permeate only through the rate controlling membrane. The drug solids are homogeneously dispersed in a solid polymer matrix, suspended in an unleachable, viscous liquid medium e.g. silicone fluid to form a paste like suspension or dissolved in a releasable solvent e.g. alkyl alcohol to a clear drug solution.

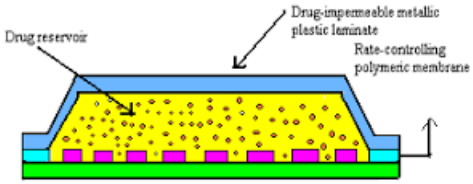

Figure 1 :Cross-sectional view of polymer membrane permeation-controlled TDD systems.

The rate controlling membrane can be either a micro-porous or a nonporous polymeric membrane e.g. ethylene-vinyl acetate copolymer, with specific drug permeability. On the external surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic pressure sensitive adhesive polymer e.g. silicone adhesive may be applied to provide intimate contact of TDDS with the skin surface. Varying the composition of drug reservoir formulation,

the permeability coefficient and thickness of rate controlling membrane can alter the drug release rate. E.g. Some FDA approved systems – Transderm-Nitro for angina pectoris, Transderm-Scop for motion sickness, Catapres-TTS system for hypertension. The intrinsic rate of drug release from this type of TDD system is defined by

$$\frac{dQ}{dt} = \left[\frac{\frac{Km}{r}\frac{Ka}{m}Dahm}{\frac{Km}{r}Dmha + \frac{Ka}{m}Da\,hm}\right] C_R$$

Where, C_R is drug concentration in reservoir compartment.

Km/r the partition coefficient for the interfacial partitioning of drug from the reservoir to the membrane.

Ka/m the partition coefficient for the interfacial partitioning of drug from membrane to adhesive.

Da diffusion coefficient in rate controlling membrane.

Dm diffusion coefficient in adhesive layer.

ha thickness of rate controlling membrane.

hm thickness of adhesive layer

2. Polymer matrix diffusion controlled drug delivery system

In this implantable device the reservoir is formed by dispersion of the solid particles throughout a lipophilic or hydrophilic polymer matrix. This dispersion can be obtained by dispersing the solid drug dosage form in the liquid or semisolid polymer matrix at the room temperature followed by cross linking of the polymer chains. The drug polymer dispersions are then molded or extruded to form drug delivery devices of various shapes. It can also be prepared by dissolving the drug solid or the polymer in an organic solvent followed by conservation or solid evaporation at an elevated temperature under a vacuum to form microsphere. Example: Compudose implant.

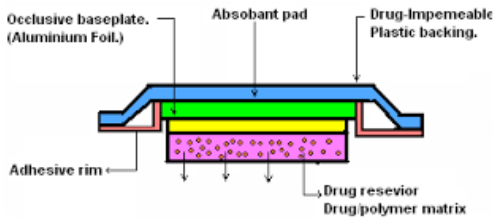

Figure 2: Cross-sectional view of polymer matrix diffusion controlled TDD systems

This drug reservoir containing polymer disk is then mounted on occlusive baseplate in a compartment fabricated from a drug-impermeable plastic backing. Instead of coating adhesive polymer directly on the surface of medicated disk, it is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disk. E.g. Nitro-Dur system and NTS system for angina pectoris . The rate of release from polymer matrix drug dispersion-type is

$$\frac{dQ}{dt} = \left[\frac{LdCpDP}{2t}\right] 1/2$$

Where, Ld is drug loading dose initially dispersed in polymer matrix.

CP is solubility of drug in polymer matrix.

DP is diffusivity of drug in polymer matrix. Only drug dissolved in polymer matrix can diffuse, CP is practically equal to CR

3. Membrane-matrix hybrid type drug delivery system

This type drug delivery system is actually a hybrid form of polymer membrane permeation controlled drug delivery system and the polymer matrix permeation controlled drug delivery system. It follows the constant drug release kinetics just like the polymer membrane permeation Controlled drug delivery system. Therefore it will reduce the chances of dose dumping from the reservoir compartment. Just like the matrix diffusion system the drug reservoir is also prepared by the homogeneous dispersion of the drug solid particles throughout a polymer matrix. But in case of this implantable drug delivery, the total reservoir is encapsulated within a rate controlling polymeric membrane. This is actually a sandwich type implantable device, Example: Norplant II subdermal implant.

4. Micro reservoir partition controlled drug delivery system

In this controlled release drug delivery device the drug reservoir is a suspension of drug crystals in an aqueous solution of water miscible polymer & it also forms a homogeneous dispersion. Micro dispersion is obtained by the high energy dispersion technique. Different size and shapes of drug delivery devices can be obtained with the help of extrusion and molding. According to the physicochemical properties of the drug, the device can be further coated with a layer of biocompatible polymer to modify the mechanism & the rate of drug release. Example: Syncromate implant. Micro dispersion of an aqueous suspension of drug using a high-energy dispersion technique in a bio-compatible polymer,(Eg. silicone elastomers), forms a homogenous

dispersion of many discrete, unleachable, microscopic drug reservoirs. Device can be further coated with a layer of biocompatible polymer to modify the mechanism and the rate of drug release. e.g Nitro-glycerin in silicone elastomer 0.5mg/cm^2 for once-a-day 17.

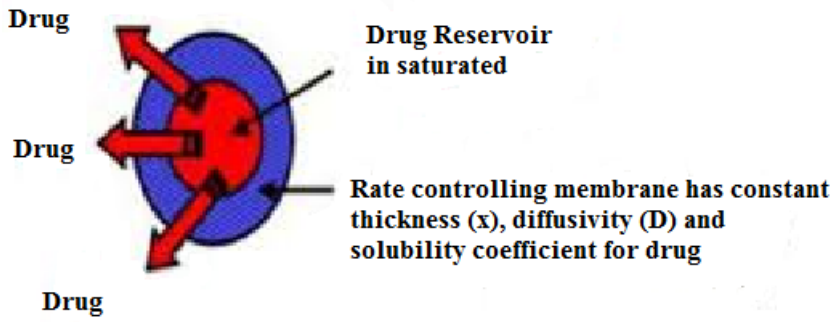

Figure 3: Reservoir type drug delivery system

Osmotic Drug Delivery System

Osmotic devices are most promising strategy-based systems for controlled drug delivery [7–9]. Osmosis can be defined as the net movement of water across a selectively permeable membrane driven by a difference in osmotic pressure across the membrane. It is driven by a difference in solute concentrations across the membrane that allows passage of water, but rejects most solute molecules or ions. Osmosis is exploited for development of ideal controlled drug delivery system. Osmotic pressure created by osmogen is used as driving force for these systems to release the drug in controlled manner.

These systems can be used for both route of administration, that is, oral and implantation. Osmotic pump offers many advantages over other controlled drug delivery systems, that is, they are easy to formulate and simple in operation, improved patient compliance with reduced dosing frequency and more consistence, and prolonged therapeutic effect with uniform blood concentration. Moreover they are inexpensive and their production scaleup is easy .

Osmotic drug-delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semipermeable membrane coating. This coating has one or more delivery ports through which a solution or suspension of the

drug is released over time. The core consists of a drug formulation that contains an osmotic agent and a water swellable polymer. The rate at which the core absorbs water depends on the osmotic pressure generated by the core components and the permeability of the membrane coating. As the core absorbs water, it expands in volume, which pushes the drug solution or suspension out of the tablet through one or more delivery ports.

The key distinguishing feature of osmotic drug delivery systems (compared with other technologies used in controlled-release formulations) is that they release drug at a rate that is independent of the pH and hydrodynamics of the external dissolution medium. The result is a robust dosage form for which the in vivo rate of drug release is comparable to the in vitro rate, producing an excellent in vitro/in vivo correlation. Another key advantage of the present osmotic systems is that they are applicable to drugs with a broad range of aqueous solubilities .

The historical development of osmotic systems includes seminal contributions such as the Rose-Nelson pump, the Higuchi-Leeper pumps, the Alzet and Osmet systems , the elementary osmotic pump, and the push-pull or GITSR system. Recent advances include the development of the controlled porosity osmotic pump, systems based on asymmetric membranes, and other approaches.

The following are the materials used in formulation of osmotically regulated system.

(1) Semipermeable Membrane

Since the membrane in osmotic systems is semipermeable in nature, any polymer that is permeable to water but impermeable to solute can be selected . Cellulose acetate is a commonly employed semipermeable polymer for the preparation of osmotic pumps. It is available in different acetyl content grades. Particularly, acetyl content of 32% and 38% is widely used. Acetyl content is described by the degree of substitution (DS), that is, the average number of hydroxyl groups on the anhydroglucose unit of the polymer replaced by substituting group. Some of the polymers that can be used for above purpose include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, and cellulose ethers like ethyl cellulose. Apart from cellulose derivatives, some other polymers such as agar acetate, amylose triacetate, betaglucan acetate, poly(vinyl methyl) ether copolymers, poly(orthoesters), poly acetals and selectively permeable poly(glycolic acid), poly(lactic

acid) derivatives, and Eudragits can be used as semipermeable film-forming materials. The permeability is the important criteria for the selection of semipermeable polymers.

(2) Hydrophilic and Hydrophobic Polymers

These polymers are used in the formulation development of osmotic systems for making drug containing matrix core. The highly water soluble compounds can be coentrapped in hydrophobic matrices and moderately water soluble compounds can be coentrapped in hydrophilic matrices to obtain more controlled release. Generally, mixtures of both hydrophilic and hydrophobic polymers have been used in the development of osmotic pumps of water-soluble drugs. The selection is based on the solubility of the drug as well as the amount and rate of drug to be released from the pump. The polymers are of either swellable or nonswellable nature. Mostly, swellable polymers are used for the pumps containing moderately water-soluble drugs. Since they increase the hydrostatic pressure inside the pump due to their swelling nature, the nonswellable polymers are used in case of highly water-soluble drugs . Ionic hydrogels such as sodium carboxymethyl cellulose are preferably used because of their osmogenic nature. More precise controlled release of drugs can be achieved by incorporating these polymers into the formulations. Hydrophilic polymers such as hydroxy ethyl cellulose, carboxy methylcellulose, hydroxy propyl methylcellulose, high-molecular-weight poly(vinyl pyrrolidone), and hydrophobic polymers such as ethyl cellulose and wax materials can be used for this purpose.

(3) Wicking Agents

A wicking agent is defined as a material with the ability to draw water into the porous network of a delivery device. The wicking agents are those agents which help to increase the contact surface area of the drug with the incoming aqueous fluid. The use of the wicking agent helps to enhance the rate of drug released from the orifice of the drug. A wicking agent is of either swellable or nonswellable nature. They are characterized by having the ability to undergo physisorption with water. Physisorption is a form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via Van der Waals interactions between the surface of the wicking agent and the adsorbed molecule. The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of

increased surface area. The examples are colloidal silicon dioxide, PVP and Sodium lauryl sulfate.

(4) Solubilizing Agents

For osmotic drug delivery system, highly water-soluble drugs would demonstrate a high release rate that would be of zero order. Thus, many drugs with low intrinsic water solubility are poor candidates for osmotic delivery. However, it is possible to modulate the solubility of drugs within the core. Addition of solubilizing agents into the core tablet dramatically increases the drug solubility.

Nonswellable solubilizing agents are classified into three groups

(i) Agents that inhibit crystal formation of the drugs or otherwise act by complexation with the drugs (e.g., PVP, poly(ethylene glycol) (PEG 8000) and β-cyclodextrin)

(ii) a micelle-forming surfactant with high HLB value, particularly nonionic surfactants (e.g., Tween 20, 60, and 80, polyoxyethylene or poly ethylene containing surfactants and other long-chain anionic surfactants such as SLS)

(iii) citrate esters (e.g., alkyl esters particularly triethyl citrate) and their combinations with anionic surfactants. The combinations of complexing agents such as polyvinyl pyrrolidone (PVP) and poly(ethylene glycol) with anionic surfactants such as SLS are mostly preferred.

(5) Osmogens

Osmogens are essential ingredient of the osmotic formulations. Upon penetration of biological fluid into the osmotic pump through semipermeable membrane, osmogens are dissolved in the biological fluid, which creates osmotic pressure buildup inside the pump and pushes medicament outside the pump through delivery orifice. They include inorganic salts and carbohydrates. Mostly, potassium chloride, sodium chloride, and mannitol used as osmogens.

(6) Surfactants

Surfactants are particularly useful when added to wall-forming material. They produce an integral composite that is useful for making the wall of the device operative. The surfactants act by regulating the surface energy of materials to improve their blending into the composite and maintain their integrity in the environment of use during the drug release period. Typical surfactants such as poly oxyethylenated glyceryl recinoleate,

polyoxyethylenated castor oil having ethylene oxide, glyceryl laurates, and glycerol (sorbiton oleate, stearate, or laurate) are incorporated into the formulation.

(7) Coating Solvents

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core and other materials. The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, and water. The 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) can be used.

(8) Plasticizers

In pharmaceutical coatings, plasticizers, or low molecular weight diluents are added to modify the physical properties and improve film-forming characteristics of polymers. Plasticizers can change visco elastic behavior of polymers significantly. Plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. Plasticizers lower the temperature of the second order-phase transition of the wall or the elastic modules of the wall and also increase the workability, flexibility, and permeability of the coating solvents. Generally from 0.001 to 50 parts of a plasticizer or a mixture of plasticizers are incorporated into 100 parts of costing materials. PEG-600, PEG-200, triacetin (TA), dibutyl sebacate, ethylene glycol monoacetate, ethylene glycol diacetate, triethyl phosphate, and diethyl tartrate used as plasticizer in formulation of semipermeable membrane.

(9) Pore-Forming Agents

These agents are particularly used in the pumps developed for poorly water-soluble drugs and in the development of controlled porosity or multiparticulate osmotic pumps. These pore-forming agents cause the formation of microporous membrane. The microporous wall may be formed in situ by a pore-former by its leaching during the operation of the system. The pore-formers can be inorganic or organic and solid or liquid in nature. For example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate, and so forth,

alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, and mannitol, and diols and polyols such as poly hydric alcohols, polyethylene glycols, and polyvinyl pyrrolidone can be used as pore-forming agents. Triethyl citrate (TEC) and triacetin (TA) are also used to create pore in the membrane. Membrane permeability to the drug is further increased addition of HPMC or sucrose.

4. Creation of delivery orifice

Osmotic delivery systems contain at least one delivery orifice in the membrane for drug release. The size of delivery orifice must be optimized in order to control the drug release from osmotic systems. On the other hand, size of delivery orifice should not also be too large, otherwise, solute diffusion from the orifice may take place. If the size of delivery orifice is too small, zero-order delivery will be affected because of development of hydrostatic pressure within the core. This hydrostatic pressure may not be relieved because of the small orifice size and may lead to deformation of delivery system, thereby resulting in unpredictable drug delivery. Optimum orifice diameter is in the range of 0.075–0.274 mm. At orifice size of 0.368 mm and above, control over the delivery rate is lost.

Delivery orifices in the osmotic systems can be created with the help of a mechanical drill . Laser drilling is one of the most commonly used techniques to create delivery orifice in the osmotic tablet. Laser beam is fired onto the surface of the tablet that absorbs the energy of the beam and gets heated ultimately causing piercing of the wall and, thus forming orifice. It is possible to control the size of the passageway by varying the laser power, firing duration (pulse time), thickness of the wall, and the dimensions of the beam at the wall.

In some of the oral osmotic systems, there is in situ formation of delivery orifice. The system described consists of a incorporation of pore-forming agents into the coating solution. Pore-forming agents are water soluble: upon contact with the aqueous environment, they dissolve in it and leach out from membrane, creating orifice.

5.1. Rose-Nelson Pump

Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. In 1955, they developed an implantable pump for the delivery of drugs to the sheep and cattle gut [16].

The Rose-Nelson implantable pump shown in Figure 2 is composed of three chambers: a drug chamber, a salt chamber holding solid salt, and a water chamber. A semipermeable membrane separates the salt from water chamber. The movement of water from the water chamber towards salt chamber is influenced by difference in osmotic pressure across the membrane. Conceivably, volume of salt chamber increases due to water flow, which distends the latex diaphragm dividing the salt and drug chambers: eventually, the drug is pumped out of the device.

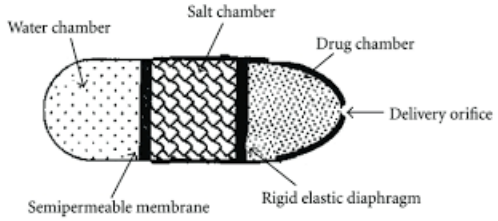

Figure 4: Rose and Nelson

The kinetics of pumping from Rose Nelson pump is given by the following equation:

$$\frac{dMt}{dt} = \left(\frac{dV}{dt}\right) C$$

Where

dMt/dt is the drug release rate,

dV/dt is the volume flow of water into the salt chamber, and

C represents the concentration of drug in the drug chamber.

$$\frac{dMt}{dt} = A\theta\Delta\Pi\frac{C}{l}$$

where,

A is the area of semi permeable membrane,

$\Delta\pi$ is the osmotic pressure gradient,

θ is the permeability of semipermeable membrane, and

l is the thickness of semi permeable membrane.

These basic equations are applicable to the osmotically driven controlled drug delivery devices. The saturated salt solution created a high osmotic pressure compared to that pressure required for pumping the suspension of active agent. Therefore, the rate of

water entering into the salt chamber remains constant as long as sufficient solid salt is present in die salt chamber to maintain a saturated solution and thereby a constant osmotic pressure driving force is generated.

The major problem associated with Rose-Nelson pumps was that the osmotic action began whenever water came in contact with the semipermeable membrane. This needed pumps to be stored empty and water to be loaded prior to use.

Higuchi-Leeper Osmotic Pump

Higuchi and Leeper have proposed a number of variations of the Rose-Nelson pump and these designs have been described in US patents which represent the first series of simplifications of the Rose-Nelson pump made by the Alza Corporation. One of these pumps is illustrated in Figure 5 .

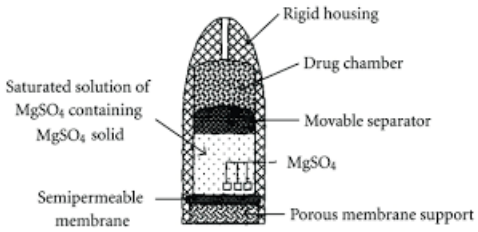

Figure 5: Higuchi-Leeper pump

The Higuchi-Leeper pump has no water chamber, and the activation of the device occurs after imbibition of the water from the surrounding environment. This variation allows the device to be prepared loaded with drug and can be stored for long prior to use. Higuchi-Leeper pumps contain a rigid housing and a semi permeable membrane supported on a perforated frame; a salt chamber containing a fluid solution with an excess of solid salt is usually present in this type of pump. Upon administration/implantation, surrounding biological fluid penetrates into the device through porous and semipermeable membrane and dissolves the MgSO4, creating osmotic pressure inside the device that pushes movable separator toward the drug chamber to remove drug outside the device. It is widely employed for veterinary use. This type of pump is implanted in body of an animal for delivery of antibiotics or growth hormones to animals.

Pulsatile delivery could be achieved by using Higuchi Leeper pump; such modifications are described and illustrated in Figure 6.

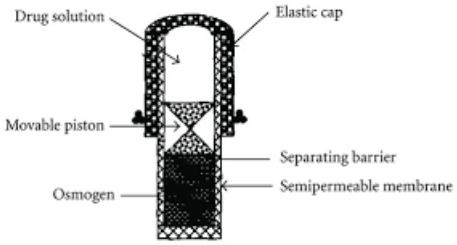

Figure 6: Pulsatile release osmotic pump

The Pulsatile release of drug is achieved by drilling the orifice in elastic material that stretches under the osmotic pressure. Pulse release of drug is obtained after attaining a certain critical pressure, which causes the orifice to open. The pressure then reduces to cause orifice closing and the cycle repeats to provide drug delivery in a pulsatile fashion. The orifice should be small enough to be substantially closed when the threshold level of osmotic pressure is not present.

Higuchi-Theeuwes Osmotic Pump

Higuchi and Theeuwes in early 1970s developed another variant of the Rose-Nelson pump, even simpler than the Higuchi-Leeper pump. This device is illustrated in Figure 7

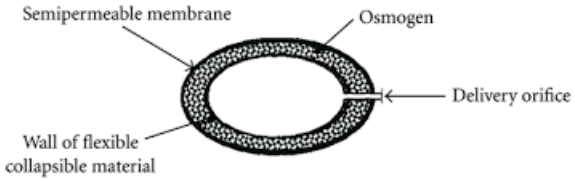

Figure 7: Higuchi-Theeuwes Osmotic Pump

In this device, the rigid housing consisted of a semipermeable membrane. This membrane is strong enough to withstand the pumping pressure developed inside the device due to imbibition of water. The drug is loaded in the device only prior to its application, which extends advantage for storage of the device for longer duration. The release of the drug from the device is governed by the salt used in the salt chamber and the permeability characteristics of the outer membrane .

Small osmotic pumps of this form are available under trade name Alzet made by Alza Corporation in 1976. They are used frequently as implantable controlled release delivery systems in experimental studies requiring continuous administration of drugs. Such a implantable Alzet pump is shown in Figure 8

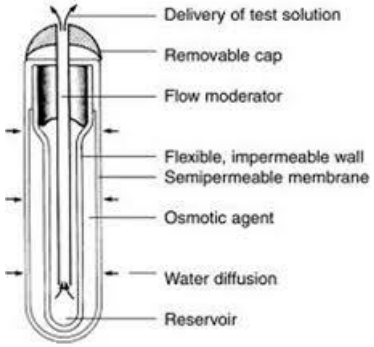

Figure 8: Alzet Osmotic Pump

Elementary Osmotic Pump (EOP)

Rose-Nelson pump was further simplified in the form of elementary osmotic pump, which made osmotic delivery as a major method of achieving controlled drug release. Elementary osmotic pump shown in Figure 9 was invented by Theeuwes in 1974 and it essentially contains an active agent having a suitable osmotic pressure; it is fabricated as a tablet coated with semi permeable membrane, usually cellulose acetate. A small orifice is drilled through the membrane coating. When this coated tablet is exposed to an aqueous environment, the osmotic pressure of the soluble drug inside the tablet draws water through the semi permeable coating and a saturated aqueous solution of drug is formed inside the device. The membrane is nonextensible and the increase in volume due to imbibition of water raises the hydrostatic pressure inside the tablet, eventually leading to flow of saturated solution of active agent out of the device through a small orifice.

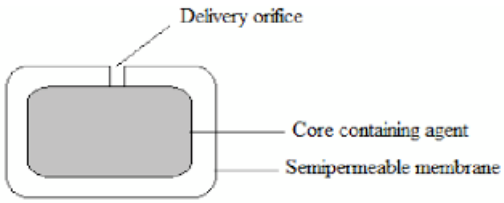

Figure 9: Elementary Osmotic Pump (EOP)

The pump initially releases the drug at a rate given by the following equation

$$\frac{dMt}{dt} = \left(\frac{dV}{dt}\right) C_S$$

Where

dV/dt depicts the water flow into the tablet and

Cs is the solubility of the agent inside the tablet.

Push-Pull Osmotic Pump (PPOP)

Push-pull osmotic pump is a modification of EOP (Figure 10). Push-pull osmotic pump is delivered both poorly water soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. One layer (the upper layer) contains drug in a formulation of polymeric, osmotic agent, and other tablet excipients. This polymeric osmotic agent has the ability to form a suspension of drug in situ. When this tablet later imbibes water, the other layer contains osmotic and colouring agents, polymer and tablet excipients. These layers are formed and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with semipermeable membrane. After the coating has been applied, a small hole is drilled through the membrane by a laser or mechanical drill on the drug layer side of the tablet. When the system is placed in aqueous environment, water is attracted into the tablet by an osmotic agent in both the layers. The osmotic attraction in the drug layer pulls water into the compartment to form in situ a suspension of drug. The osmotic agent in the nondrug layer simultaneously attracts water into that compartment, causing it to expand volumetrically, and the expansion of nondrug layer pushes the drug suspension out of the delivery orifice

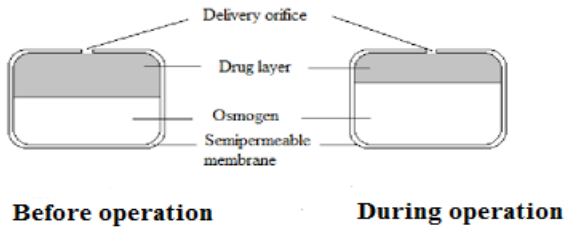

Figure 10: Push-pull osmotic pump

Controlled Porosity Osmotic Pump (CPOP)

Figure 11 represents the controlled porosity osmotic pump (CPOP). It is an osmotic tablet wherein the delivery orifices (holes) are formed in situ through leaching of water soluble pore-forming agents incorporated in semipermeable membrane (SPM) (e.g., urea, nicotinamide, sorbitol, etc.). Drug release rate from CPOP depends on various factors like coating thickness, solubility of drug in tablet core, level of leachable pore-forming agent(s) and the osmotic pressure difference across the membrane.

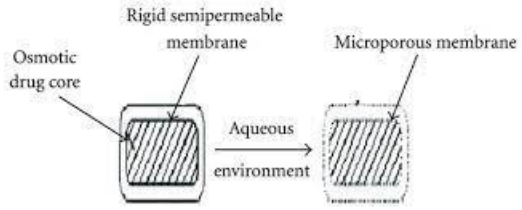

Figure 11: controlled porosity osmotic pump

There are several obvious advantages inherent to the CPOP system. The stomach irritation problems are considerably reduced, as drug is released from the whole of the device surface rather from a single hole. Further, no complicated laser-drilling unit is required because the holes are formed *in situ*. Scheme describes the drug release phenomenon from a typical CPOP.

Liquid-Oral Osmotic (L-OROS) System

Various L-OROS systems available to provide controlled delivery of liquid drug formulations include L-OROS hardcap, L-OROS softcap, and a delayed liquid bolus delivery system. Each of these systems includes a liquid drug layer, an osmotic engine or push layer, and a semipermeable membrane coating. When the system is in contact with the aqueous environment, water permeates across the rate-controlling membrane and activates the osmotic layer (Figure 12).

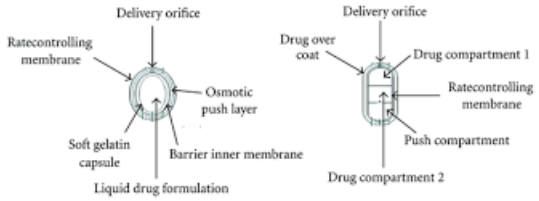

Figure 12: Liquid-Oral Osmotic (L-OROS) System

The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered at the delivery orifice. Whereas L-OROS hardcap and L-OROS softcap systems are designed to provide continuous drug delivery, the L-OROS delayed liquid bolus delivery system is designed to deliver a pulse of liquid drug.

The delayed liquid bolus delivery system comprises three layers: a placebo delay layer, a liquid drug layer, and an osmotic engine, all surrounded by a rate-controlling semipermeable membrane (SPM). The delivery orifice is drilled on the placebo layer end of the capsule shaped device. When the osmotic engine expands, the placebo is released first, delaying release of the drug layer. Drug release can be delayed from 1 to 10 hours, depending on permeability of the rate-controlling membrane and the size of placebo.

Sandwiched Osmotic Tablet (SOT)

Figure 13 shows that sandwiched osmotic tablet is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment, the middle push layer containing the swelling agents' swells and the drug is released from the two orifices situated on opposite sides of the tablet; thus sandwiched osmotic tablets (SOTS) can be suitable for drugs prone to cause local irritation of the gastric mucosa

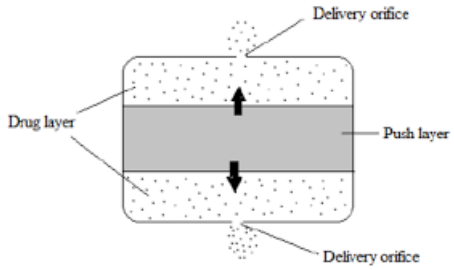

Figure 13: Sandwiched Osmotic Tablet (SOT)

Table 1: Market product

Product name	Active pharmaceutical ingredient	Design of pump
Acutrim	Phenylpropanolamine	Elementary pump osmotic pump
Alpress LP	Prazosin	Push-pull osmotic pump
ChronogesicTM	Sufentanil	Implantable osmotic system
Covera HS	Verapamil	Push-pull osmotic pump with time delay
Dynacirc CR	Isradipine	Push-pull osmotic pump
Efidac 24	Chlorpheniramine meleate	Elementary pump osmotic pump
Glucotrol XL	Glipizide	Push-pull osmotic pump
Invega	Paliperidone	Push-pull osmotic pump
Minipress XL	Prazocine	Elementary osmotic pump
Procadia XL	Nifedipine	Push-pull osmotic pump

Sudafed 24	Pseudoephedrine	Elementary osmotic pump
Viadur	Leuprolide acetate	Implantable osmotic system

THERAPEUTIC APPLICATIONS:

1. **Ocular disease:** Numerous different implantable systems have been estimated to deliver sustained ocular delivery. These comprise membrane-controlled devices, implantable infusion systems and implantable silicone devices. Ocular insert (ocusert) having pilocarpine base and alginic acid in a drug reservoir surrounded by a release-rate controlling ethylene-vinyl acetate membrane is an example of the membrane-controlled system.
2. **Contraception:** Norplant a sub-dermal implant for long-lasting transport of the contraceptive agent levonorgestrel recently been approved for marketing by the FDA. The device consists of six silicone membrane capsules each having about 36 mg of levonorgestrel. The capsules are placed sub-dermally on the inside of the upper arm or the forearm in a fan-shaped pattern through a trocar from a single trocar entry point.
3. **Dental application:** For numerous dental applications including local prolonged administration of fluoride antibacterial and antibiotics, polymeric implants have been evaluated. Stannous fluoride was integrated into different dental cements for sustained release fluoride delivery.
4. **Immunization:** Polymeric implants are being evaluated for better immune response to antigens. The concept here is to offer pulsatile or continuous administration of the antigen over a prolonged period of time. Immunization efficiency of ethylene-vinyl acetate copolymer pellets having bovine serum albumin as model antigen.
5. **Cancer:** Silicone rod implants analogous to those used for delivery of levonorgestrone have been evaluated for delivery of ethinyl estradiol or testosterone propionate in persons with prostate cancer. Lupron depot produced by Takeda chemical industries is an implantation system providingone month depot release of leuprolide acetate, a synthetic analogue of the gonadotropin-releasing hormone (GhRH).
6. **Narcotic antagonists:** Naltrexone has been comprehensively evaluated in implant from long term delivery of narcotic antagonists. Naltrexone freebases its hydrochloride or the pamoate acid salt has been formulated in a various polymers and dosage forms for prolonged narcotic antagonist activity.

QUESTION BANK

SHORT QUESTIONS (2MARKS)

1. Define microspheres and microcapsules.
2. Enlist different methods of microencapsulation.
3. Enlist different evaluation tests for microparticles.
4. What are the various applications of microprticles.
5. Name the two polymerization techniques.

6. Define microsphere and microcapsules
7. What are the stages in mucoadhesion
8. What are the drug release mechanisms in implants
9. Give examples of mucoadhesive formulations
10. Enlist advantages of implantable drug delivery system
11. Write the types of microencapsulation method
12. Write the role of saliva and mucus in mucosal drug delivery

LONG QUESTIONS (5MARKS)

1. Write in detail about the microencapsulated drug delivery system.
2. Describe solvent evaporation methods to prepare microencapsulation.
3. Explain evaluation of microparticulate DDS.
4. Explain the types, advantages and disadvantages of implantable drug delivery system
5. Describe various theories of mucoadhesion with their significance in designing mucoadhesive products.

VERY LONG QUESTIONS (10MARKS)

1. Explain in detail about various types of osmotic pumps
2. Explain the types, advantages and disadvantages of mucoadhesive formulations
3. Explain in details of implantable drug delivery system and their drug release mechanisms
4. Write about factors affecting designing and development of mucoadhesive dosage forms.
5. Explain in detail about the evaluation of mucoadhesive formulations
6. Write about concept of mucoadhesion
7. Write in details about the microencapsulated drug delivery systems
8. Describe about mucosa and drug permeation across it
9. Explain types, advantages and disadvantages of microparticulate drug delivery systems.
10. Write the basic components in buccal drug delivery system.
11. Explain in detail about types of microparticulate drug delivery systems and their Evaluation
12. Write note on applications of mucoadhesion in development of pharmaceutical products