UNIT-2

MICROENCAPSULATION

Points to be covered in this topic

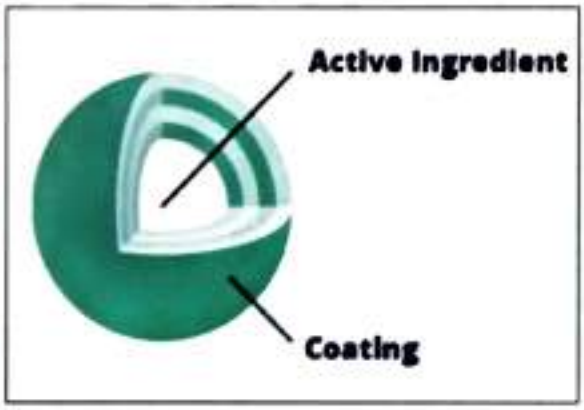
- ❑ INTRODUCTION
- ❑ ADVANTAGES
- ❑ DISADVANTAGES
- ❑ MICROPARTICLES, MICROSPHERES, MICROCAPSULES
- ❑ METHODS OF MICROENCAPSULATION
- ❑ APPLICATIONS

MICROENCAPSULATION

❑ INTRODUCTION

- Microencapsulation is defined as a **process of enclosing or enveloping solids, liquids or even gases** within second material With a continuous **coating of polymeric materials.**

- Ranging from **less than 1 micron** to several hundred microns in size.
- In this process, **small discrete solid particles** or **small liquid droplets** and dispersions are surrounded and **enclosed by applying thin coating**
- for the purposes of providing **environmental protection** and **controlling the release characteristics** or **availability of coated active ingredients.**
- Microencapsulation process is widely employed to **modify and delayed drug release** form different pharmaceutical dosage forms.
- The materials **enclosed or enveloped within the microcapsules** are known as **core materials** or pay-load materials or nucleus, and
- The **enclosing materials are known as coating materials** or wall material or shell or membrane.



❑ ADVANTAGES

- ✓ Providing **environmental protection** to the encapsulated active agents or core materials.
- ✓ Liquids and gases can be **changed into solid particles** in the form of microcapsules.
- ✓ **Surface as well as colloidal characteristics** of various active agents can be changed.

- ✓ **Modify and delayed drug release** form different pharmaceutical dosage forms
- ✓ Formulation of **sustained controlled release dosage** forms can be done by **modifying or delaying release of encapsulated active agents** or core materials.

❑ DISADVANTAGES

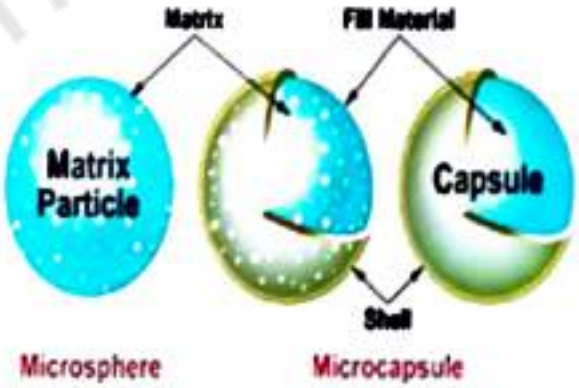
- ✓ **Expensive** techniques.
- ✓ This causes **reduction in shelf-life** of hygroscopic agents.
- ✓ Microencapsulation coating **may not be uniform** and this can influence the release of encapsulated materials.

❑ MICROPARTICLES:

- Refers to the particles having the **diameter range of 1-1000 µm,**
- Irrespective of the precise exterior and/or interior structures.

❑ MICROSPHERES:

- Refers to the **spherically shaped microparticles** within the broad Category of microparticles.



❑ MICROCAPSULES:

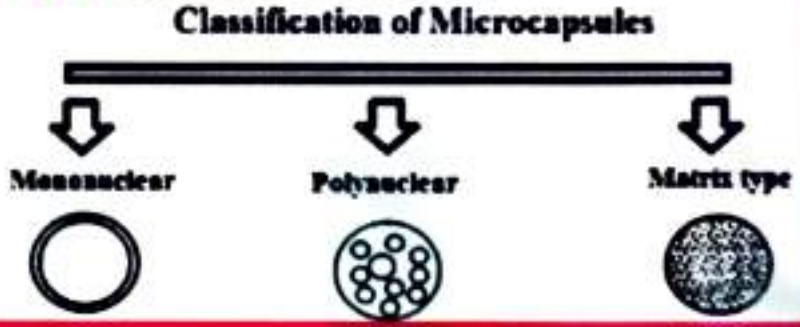
- Refers to microparticles having a **core surrounded by the coat.**
- Material distinctly different from that of the core.

Microcapsules can be classified on **three types**

i). Mononuclear: Containing the **shell around the core.**

ii). Polynuclear: Having **many cores** enclosed with in shell.

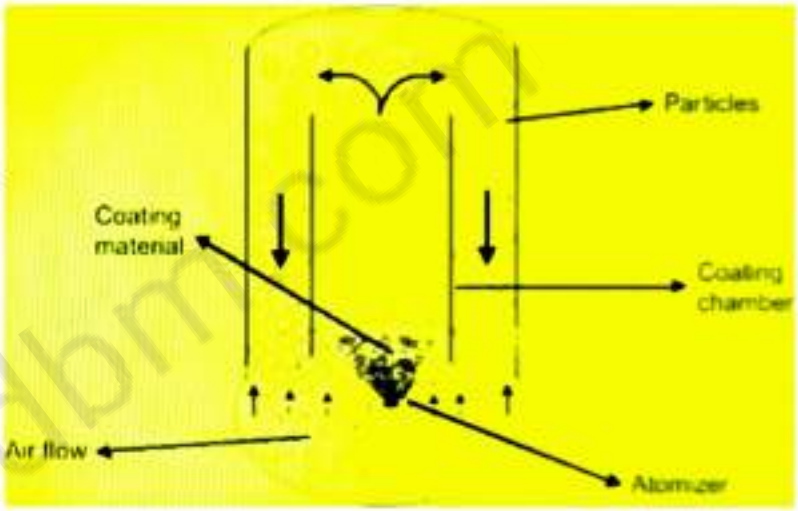
iii). Matrix type: **Distributed homogeneously** into the shell material.



❑ METHODS OF MICROENCAPSULATION:

❖ Air suspension:

- It consists of the **dispersing of core materials in a supporting air stream** and the **spray coating** on the air suspended particles.
- Within the coating chamber, particulate core materials are suspended on an **upward moving air stream.**
- The chamber design and its operating parameters influence a **re-circulating flow of the particles** through the coating-zone portion of the coating-chamber.
- During each pass through the coating-zone, the core material receives a coat and this cyclic process is repeated depending on the purpose of micro encapsulation.



- The supporting air stream also serves to **dry the product** while it is being encapsulated.

❖ Coacervation phase separation:

Coacervation phase separation method **consists of 3 steps:**

- **Formation of 3 immiscible phases**: a liquid manufacturing phase, a core material phase and a coating material phase.
- **Deposition** of the liquid polymer coating on the core material.
- **Rigidizing the coating** usually by thermal, cross linking or desolvation techniques to form microcapsules.

In many cases, physical or chemical changes in the coating polymer solutions can be induced so that phase separation of the polymers will occur.

Droplets of concentrated polymer solutions will form and coalesce to yield a two phase liquid-liquid system. When the coating material is an immiscible polymer, it may be added directly.

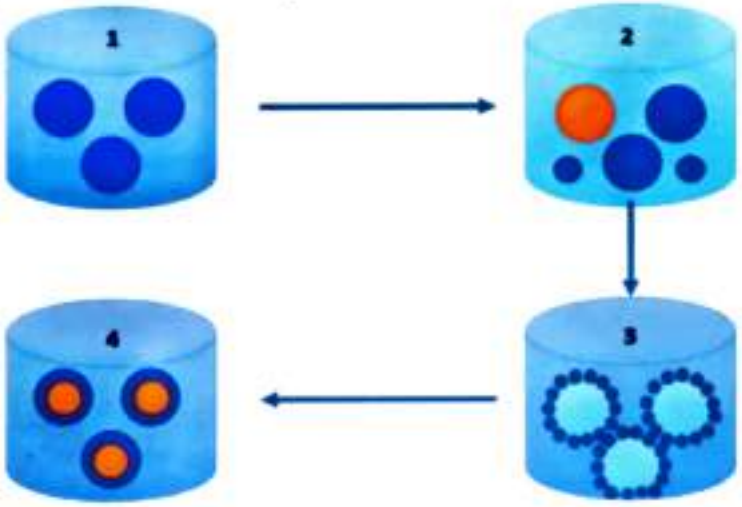
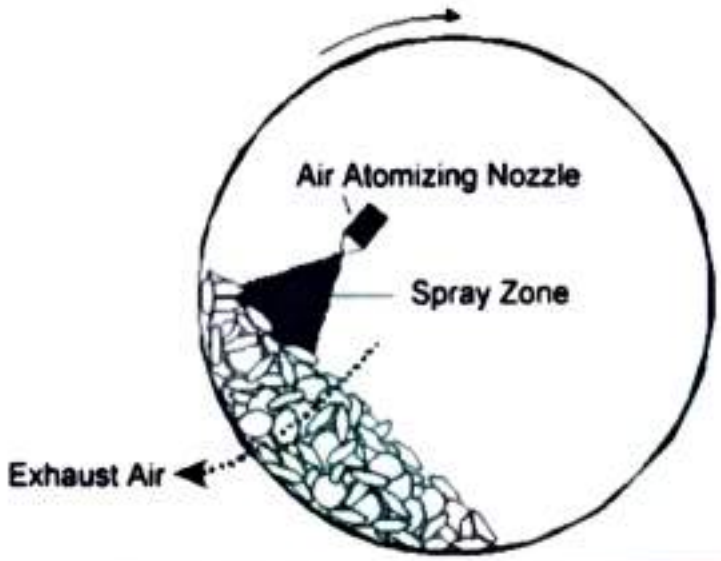


Fig. 1.dissolving polymer 2.formation of immiscible phases 3. depositing of liquid coating on core material 4. rigidizing of coating

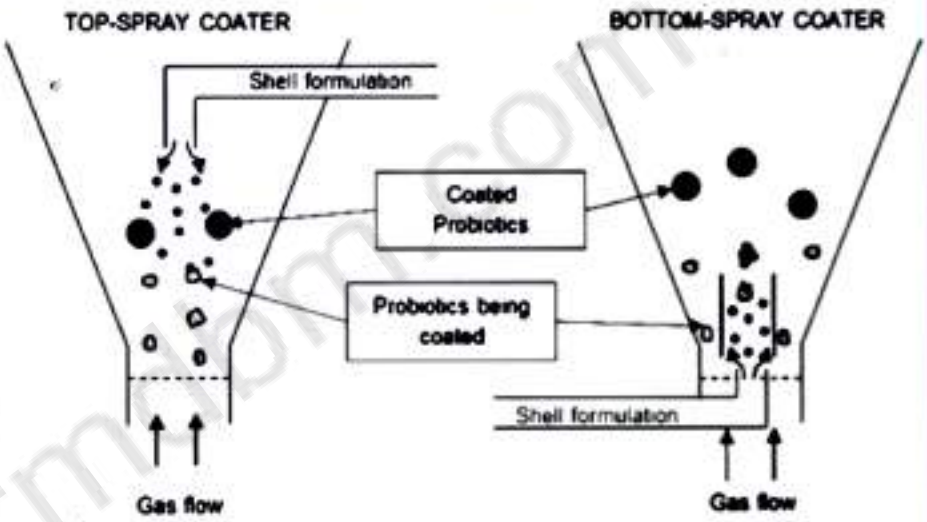
❖ Pan coating:

- For relatively large particles, which are greater than 600 μ in size, microencapsulation can be done by pan coating method,
- Which is being widely used in pharmaceutical industry for the preparation of **controlled release particulates**.
- In this method, various **spherical core materials**, such as nonpareil sugar seeds are coated with a variety of polymers.
- In practice, the **coating is applied as a solution or as an atomized spray** to the desired solid core material in the coating pan.



❖ Fluidized-bed technology

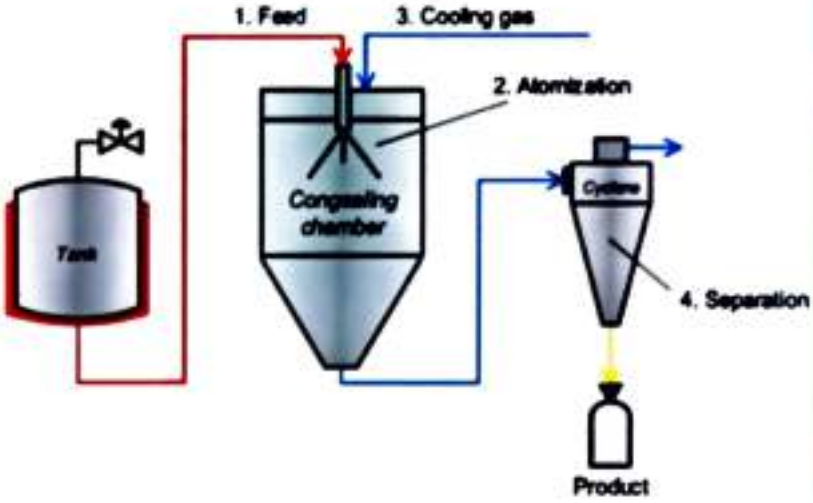
- Used for the encapsulation of **solid core materials**, including liquids absorbed into porous solids.
- Solid particles to be encapsulated are **suspended on a jet of air** and afterward, are **covered by a spray of liquid coating material.**
- The capsules are traveled to an area **where their shells are solidified by cooling or solvent vaporization.**
- The processes **of suspending, spraying, and cooling are repeated** until the attainment of the desired thickness of the capsule-wall.
- This is known as **wurster process** when the spray nozzle is located at the bottom of the fluidized-bed of particles.



❖ Spray drying and spray congealing:

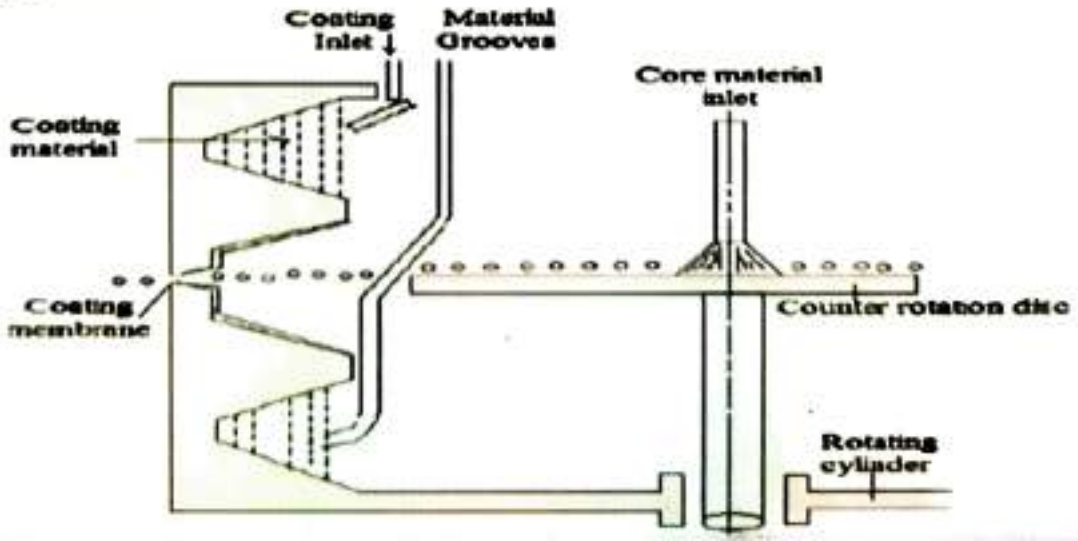
- Spray drying and spray congealing methods of microencapsulation are almost similar
- Both the methods entail the **dispersion of core material in a liquefied coating agent** and spraying **or introducing the core coating mixture** into some environmental condition,
- Whereby relatively **rapid solidification** of the coating is influenced
- The main difference in-between these two microencapsulation methods are the means by which the **coating solidification is carried out.**
- In spray drying method, the coating solidification is influenced by the **quick evaporation of a solvent,** in which the coating material is dissolved.

- In spray congealing method, the coating solidification is accomplished by the **thermal congealing of molten coating material** or solidifying a dissolved coating by introducing the coating core material mixture into a non-solvent.



❖ Multiorific-centrifugation

- Utilizes the **centrifugal forces** to hurl a core particle trough an **enveloping membrane.**
- Various processing variables of multiorific-centrifugation method include
  - ✓ Rotational speed of the cylinder,
  - ✓ Flow rate of the core and coating materials, and
  - ✓ 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

- 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. Most common method is the use of a **propeller style blade attached to a variable speed motor**

❖ Polymerization:

- The polymerization method of microencapsulation is used to **from protective microcapsule coatings**, in situ.
- The method involve the **reaction of monomeric units** positioned at the **interface existing in-between a core material and a continuous phase**, wherein the core material is dispersed.

❖ Interfacial cross-linking

- In interfacial cross-linking method of microencapsulation, the small bifunctional monomer containing active hydrogen atoms is replaced by a biosourced polymer, like a protein.
- When the reaction is performed at the interface of an emulsion, the acid chloride reacts with the various functional groups of the protein, leading to the formation of a membrane.
- Very versatile for pharmaceutical or cosmetic applications.

❑ APPLICATIONS:

- Microencapsulation can be used to formulate various sustained controlled release dosage forms.
- Can also be employed to formulate enteric-coated dosage forms, so that the drugs will be selectively absorbed in the intestine rather than the stomach.
- The taste of bitter drug candidates can be masked by these techniques.
- Liquids and gases can be changed into solid particles in the form of microcapsules.
- Microencapsulation can employed to aid in the addition of oily medicines to tableted dosage forms to overcome the problems of tacky granulations and in direct compression.
- Microencapsulation provides environmental protection to the encapsulated active agents.
- The hygroscopic characteristics of many core materials can be reduced.
- The separations of incompatible substances can be achieved. For example, pharmaceutical eutectics.

UNIT-2

MUCOSAL DRUG DELIVERY SYSTEM

Points to be covered in this topic

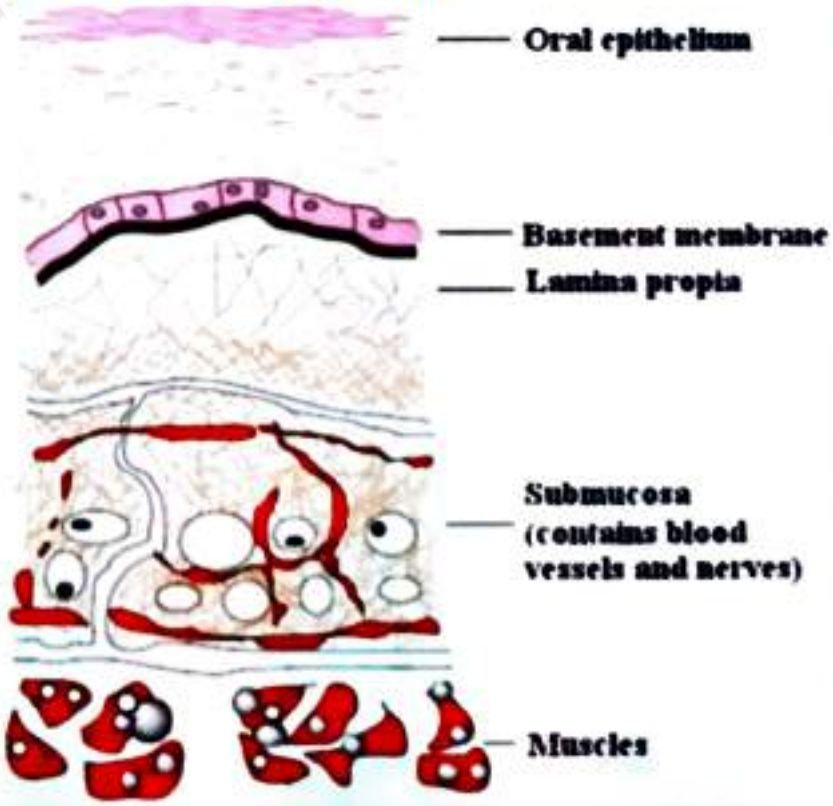
- ❑ INTRODUCTION
- ❑ PRINCIPLES OF BIOADHESION /MUCOADHESION
- ❑ ADVANTAGES AND DISADVANTAGES
- ❑ TRANSMUCOSAL PERMEABILITY
- ❑ FORMULATION CONSIDERATION OF BUCCAL DELIVERY SYSTEM

MUCOSAL DRUG DELIVERY SYSTEM

❑ INTRODUCTION

- Delivery of drugs via the **absorptive mucosa** in various easily accessible body cavities, like the **ocular, nasal, buccal, rectal and vaginal mucosae**, has the advantage of bypassing the **hepato-gastrointestinal first-pass elimination** associated with oral administration.
- Mucoadhesive drug delivery systems utilize the **property of bioadhesion of certain polymers** which become adhesive on hydration
- hence can be used for targeting a drug to a **particular region of the body** for extended periods of time.
- Different strategies have been adopted for **controlled mucosal delivery** and are based on:
  - ✓ Prolonging solely the duration of absorption process.
  - ✓ Developing unidirectional delivery systems
  - ✓ Preparing user-friendly mucosal delivery systems.
- The term 'bioadhesive' describes materials **that bind or adhere to the biological substrates.**

  'Bioadhesive' can be defined as a material that is capable of **interacting with biological material.**



Schematic diagram of buccal mucosa

❑ PRINCIPLES OF BIOADHESION /MUCOADHESION:

For bioadhesion /mucoadhesion, 3 stages are involved:

- ✓ An intimate **contact** in-between a **bioadhesive/mucoadhesive** and **a membrane** either from a good wetting of the bioadhesive/mucoadhesive and a membrane or from the swelling of bioadhesive/mucoadhesive.
- ✓ **Penetration** of the bioadhesive/mucoadhesive **into the tissue** takes place.
- ✓ **Inter penetration** of the chains of bioadhesives /mucoadhesives with **mucous takes place** and then, low chemical bonds can settle.

Several theories have been proposed to explain the fundamental mechanism of bioadhesion /mucoadhesion:

- ➢ **Wetting theory:** Ability of bioadhesive/mucoadhesive polymers to spread and develop immediate attachment with the mucous membranes.
- ➢ **Electronic theory:** Attractive electrostatic forces in-between glycoprotein mucin network and the bioadhesive/mucoadhesive polymers.
- ➢ **Adsorption theory:** Surface forces (covalent bonds, ionic bonds, hydrogen bonds, and vander Waal's forces) resulting in chemical bonding.
- ➢ **Diffusion theory:** Physical entanglement of mucin strands and the flexible polymeric chain.
- ➢ **Fracture theory:** Analyses the maximum tensile stress developed during detachment of mucoadhesive/bioadhesive drug delivery systems from the mucosal surfaces.

❑ ADVANTAGES AND DISADVANTAGES:

❖ Advantages:

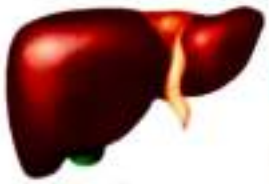
- These systems allow the developing of **contact in-between the dosage forms and the mucosa** (mucoadhesion/bioadhesion).

- **High drug concentration can be maintained** at the absorptive surface for a prolonged period.
- Dosage forms can **be immobilized specifically at any part** of the oral mucosa, buccal mucosa, sublingual or gingival mucosa, etc.

❖ Disadvantages:

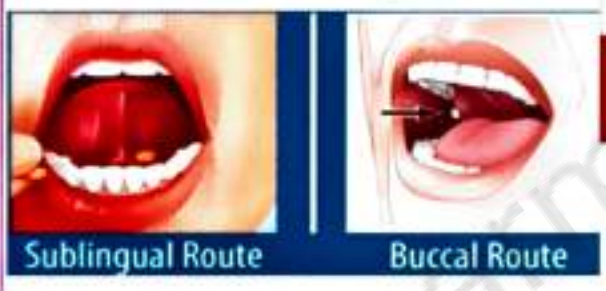
- Small mucosal surface for contact
- Lack of flexibility of dosage forms
- Difficult to achieve high drug release rates required for some drugs.
- Extent and frequency and frequency of attachment may cause local irritation.

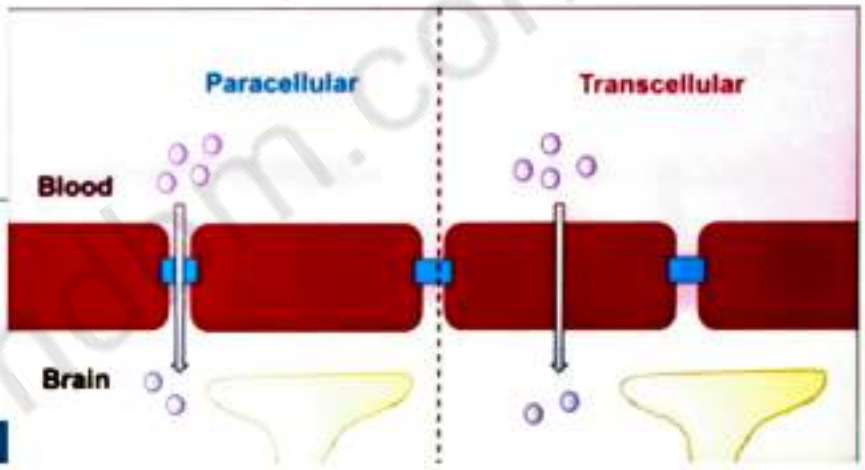
❑ TRANSMUCOSAL PERMEABILITY



- Mucosal routes provide the potential pathways to **bypass hepato-gastrointestinal first-pass elimination** following oral administration.
- Transmucosal drug delivery has the potential to **achieve greater systemic bioavailability** for orally metabolized drugs,
- Due to rich **blood supply, higher bioavailability, lymphatic drainage** and direct access to systemic circulation, the transmucosal route is suitable for drugs, which are generally **susceptible to acid-hydrolysis in the gastrointestinal tract** or extensively metabolized in liver.
- Facilitates an advantage **of retaining drug delivery systems** in contact with the absorptive mucosal surface for a longer period
- Optimizing **the drug concentration gradient** across the mucosal membrane.

- Certain **physiological features of the transmucosal route play significant roles in this process,** including pH, enzyme activity, fluid volume and the permeability of oral mucosa.
- The main mechanisms responsible for the penetration of various molecules include: **Simple diffusion (paracellular or transcellular), carrier-mediated diffusion, active transport, pinocytosis or endocytosis.**
- There are **two routes** potentially involved in drug permeation across epithelial membranes: **Transcellular route and Paracellular route**
- Drug delivery across the oral mucosal membranes is termed transmucosal drug delivery. divided into **three main categories.**
  - ✓ **Sublingual delivery**
  - ✓ **Buccal delivery**
  - ✓ **Local delivery**

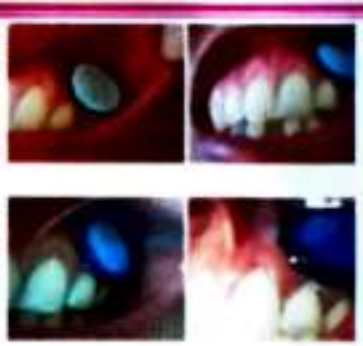




❑ FORMULATION CONSIDERATION OF BUCCAL DELIVERY SYSTEM:

- Drugs are delivered through mucosal membrane into systemic circulation by placing drug **in between cheeks and gums.**
- Classification of Buccal Bioadhesive Dosage Forms
  - ✓ Buccal Bioadhesive Tablets.
  - ✓ Buccal Bioadhesive semisolids.
  - ✓ Buccal Bioadhesive patch and films.
  - ✓ Buccal Bioadhesive Powders.

- **Buccal mucoadhesive tablets:** Buccal mucoadhesive tablets are **dry dosage forms that have to be moistened** prior to placing in contact with buccal mucosa.



- **Semisolids (ointments and gels):** Bioadhesive gels or ointments have **less patient acceptability than solid bioadhesive dosage forms**, and most of the dosage forms are used only for localized drug therapy within the oral cavity.
- **Buccal patches and films:** Buccal patches and films consist of **two laminates, with an aqueous solution of the adhesive polymer** being cast onto an impermeable backing sheet, which is then cut into the required round or oval shape.

❖ **The basic components of buccal bioadhesive drug delivery system are:**

- **Drug substance** - Drug used for rapid release/prolonged release and for local/systemic effect is a suitable candidate for buccal delivery
- **Bioadhesive polymers**- Play a major role in buccoadesive drug delivery systems of drugs. Polymers are also used in matrix devices in which the drug is embedded in the polymer matrix
- **Backing membrane**- Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane.
- **Penetration enhancers**- To increases the permeation rate of the membrane of co-administrated drug penetration enhancer are added.

❖ Advantages of buccal drug delivery systems

- Sustained drug delivery.
- Increased ease of drug administration.
- Excellent accessibility.
- Drug absorption through the passive diffusion.
- Improved patient compliance.
- Low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa, painless administration, easy drug withdrawal, facility to include permeation.
- Versatility in designing as multidirectional or unidirectional release systems for local or systemic actions, etc.
- The drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
- A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- Flexibility in physical state, shape, size and surface.
- Though less permeable than the sublingual area, the buccal mucosa is well vascularized, and drugs from the buccal systems can be rapidly absorbed into the venous system underneath the oral mucosa.
- Transmucosal delivery occurs is fewer variables between patients, resulting in lower inter-subject variability as compared to transdermal patches.

UNIT-2

IMPLANTABLE DRUG DELIVERY SYSTEM

Points to be covered in this topic

- ❑ INTRODUCTION
- ❑ ADVANTAGES AND DISADVANTAGES
- ❑ CONCEPT OF IMPLANTS
- ❑ OSMOTIC PUMPS

Implantable drug delivery system

❑ INTRODUCTION

- Implants are **small sterile solid masses** consisting of a **highly purified drug** made by **compression or molding or extrusion.**
- Implants are intended for **implantation in the body** (subcutaneous or intramuscular tissue) by a **minor surgical incision** or injected through a large bore needle.
- Implants are developed with a view to **provide continuous release of drug** into the bloodstream over long period of time without the repeated insertion of needles.
- Well suited for **insulin, steroids, chemotherapeutics, antibiotics, analgesics,** total parenteral nutrition and **heparin.**
- Allow targeted and localized drug delivery and may achieve a therapeutic effect with **lower concentrations** of drugs.
- It **avoids first pass metabolism** and chemical degradation in the stomach and intestine, thus, **increasing bioavailability.**

❑ ADVANTAGES AND DISADVANTAGES:

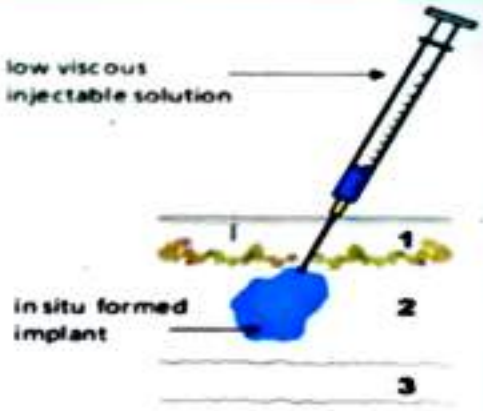
❖ Advantages:

1. More effective and more prolonged action.
2. Better control over drug release
3. A significantly small dose is sufficient.

❖ Disadvantages:

1. Chances of device failure
3. Limited to potent drugs
4. Biocompatibility issues

❑ CONCEPT OF IMPLANTS:



Implants for drug delivery are several types:

❖ In situ forming implants:

➢ In situ precipitating implants:

- These implants are formed from drug containing in a biocompatible solvent.
- The polymer solution form implants after subcutaneous (s.c.) or intramuscular (i.m.) injection and contact with aqueous body fluids via the precipitation of polymers.
- In situ precipitating implants are formulated to overcome some problems associated to the uses of biodegradable microparticles:
  - ✓ Requirement for the reconstitution before injection
  - ✓ Inability to remove the dose one injected.
  - ✓ Relatively complicated manufacturing procedures to produce a sterile, stable and reproducible product.

➢ In situ microparticle implants:

- This type of implants is formed to overcome the disadvantages associated with in situ precipitating implants.

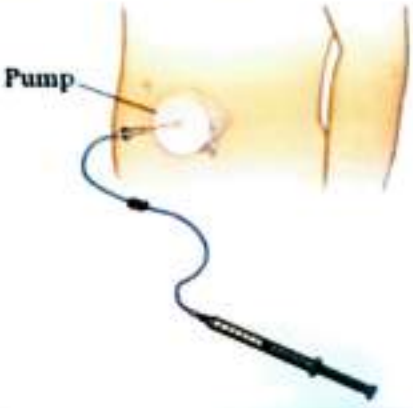
  These are:
  - ✓ High injection force.
  - ✓ Irregular shape of the implants.
  - ✓ Undesirable high initial burst release of drugs.
  - ✓ Potential solvent toxicity.
- These in situ implantable systems consist of internal phase and a continuous phase.
- The two phases are separately stored in dual-chambered syringes and mixed through a connector before administration.

❖ Solid implants:

- Solid implants are generally **cylindrical monolithic devices** implanted by a **minor surgical incision** or injected via a large bore needle into the s.c. or i.m. tissues.
- **Subcutaneous (s.c.) tissue is an ideal location** because of its easy access to implantation, poor infusion, slower drug absorption and low reactivity towards foreign materials.
- In these implants, **drugs may be dissolved, dispersed or embedded in a matrix of polymers** or waxes/lipids that control the releasing via dissolution and/or diffusion, bioerosion, biodegradation, or an activation process, such as hydrolysis or osmosis.
- These systems are generally prepared as implantable flexible/rigid molded or extruded rods, spherical pellets, or compressed tablets. Polymers used are silicone, polymethacrylates, elastomers, polycaprolactones, polylactide-co-glycolide, etc.
- Drugs generally presented in such implantable systems are **contraceptives, naltrexone, etc.**

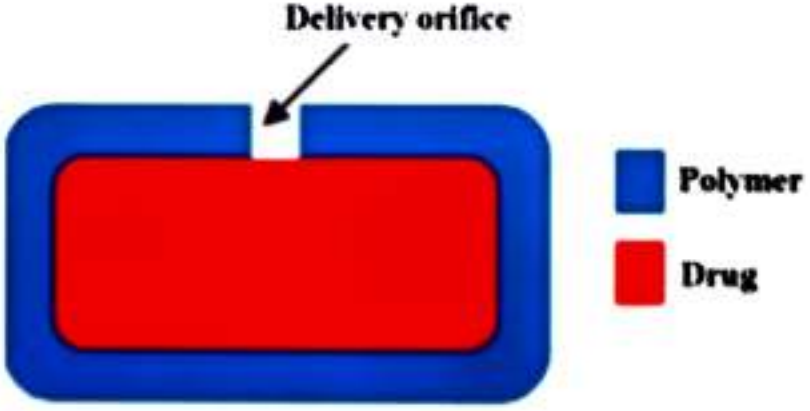
❖ Infusion devices:

- Infusion devices are intrinsically powered to **release the drugs at a zero order rate** and the drug reservoir can be replenished from time to time.
- Depending upon the mechanism by which these implantable pumps are power to release the drugs.
- These are 3 types:
  - ✓ Osmotic pressure activated drug delivery systems
  - ✓ Vapor pressure activated drug delivery systems
  - ✓ Battery powered drug delivery systems.



❑ OSMOTIC PUMPS:

- Osmotic pumps are designed mainly by a semi-permeable membrane that surrounds a drug reservoir.
- The membrane should have an orifice that will allow drug release.
- Osmotic gradients will allow a steady inflow of fluid within the implant.
- This process will lead to an increase in the pressure within the implant that will force drug release trough the orifice.
- This design allows constant drug release (zero order kinetics). This type of device allows a favorable release rate but the drug loading is limited.
- The historical development of osmotic systems includes seminal contributions such as the Rose-Nelson pump, the Higuchi- Leeper pumps, the Alzet and Osmet systems.



Osmotic pump