UNIT-2 MICROENCAPSULATION

Points to be covered in this topic

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

MICROENCAPSULATION

INTRODUCTION

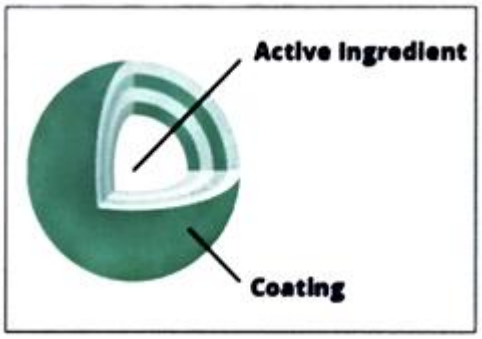
• Microencapsulation is defined as a **process of enclosing or enveloping solids, liquids or even gases within second material** with a continuous **coating of polymeric materials**.

• 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** from 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** from 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**.

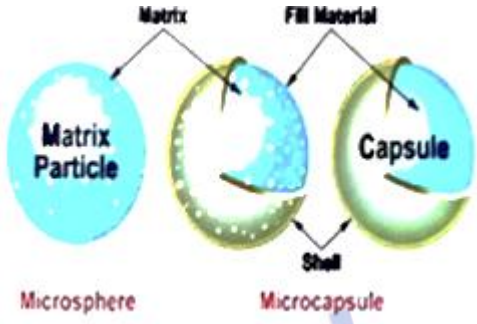
✓ Microencapsulation coating **may not be uniform** and this can influence the **release of encapsulated materials**.

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**.

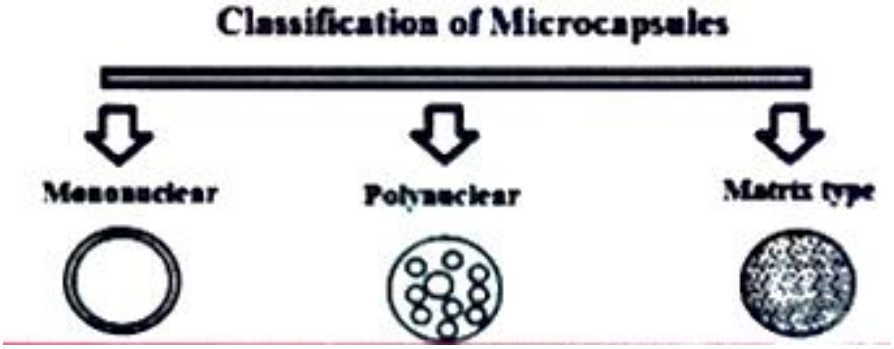
• Material distinctly **different from that of the core**.

Microcapsules can be classified on three types

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

ii) **Polynuclear**: Having **many cores enclosed within shell**.

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



METHODS OF MICROENCAPSULATION

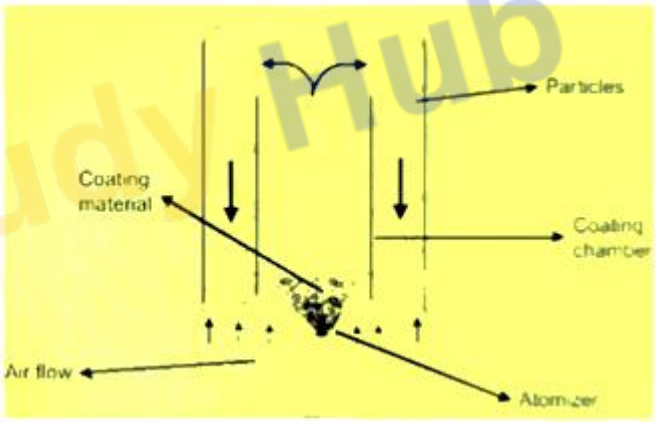
1. Air suspension

• 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 **recirculating 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 microencapsulation.



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

2. 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.

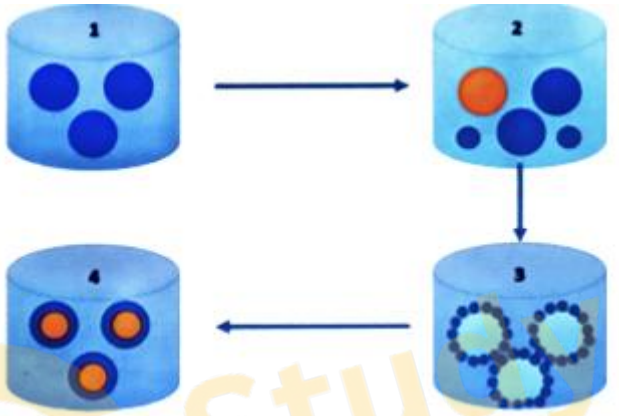
• **Deposition of the liquid polymer coating** on the core material.

• **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.



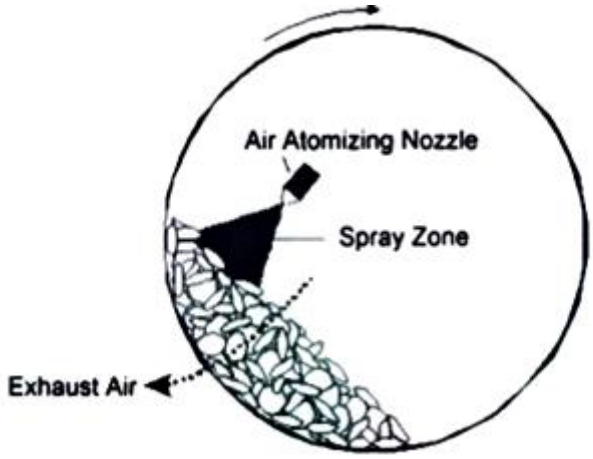
3. Pan coating

• For relatively large particles, which are **greater than 600 µm 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

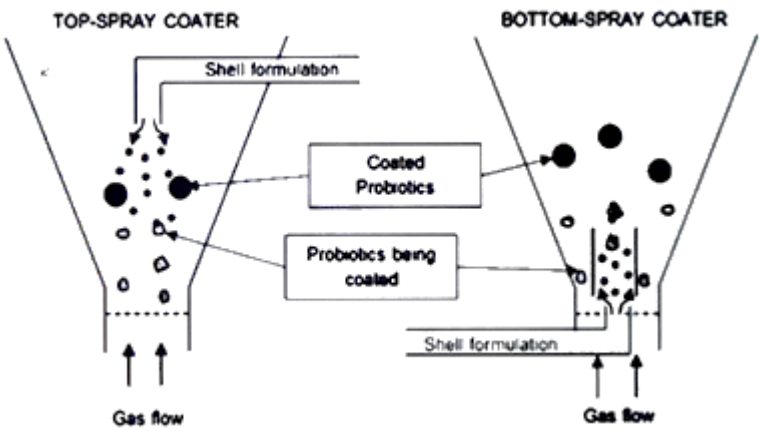
• Used for the encapsulation of **solid core materials**, including liquids absorbed into porous solids.

• 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**.

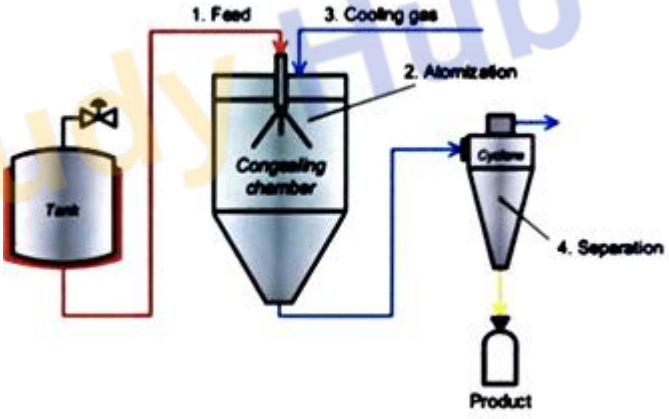
• Both the methods entail the **dispersion of core material in a liquefied coating agent** and **spraying or introducing the core-coating mixture** into some environmental condition.

• 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 through an **enveloping membrane**.

• Various processing variables of multiorific-centrifugation method include:

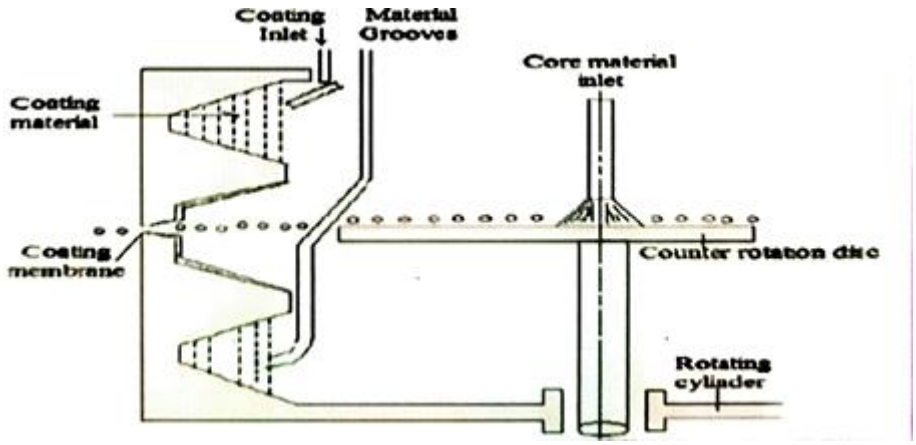
✓ Rotational speed of the cylinder

✓ Flow rate of the core and coating materials

✓ 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.

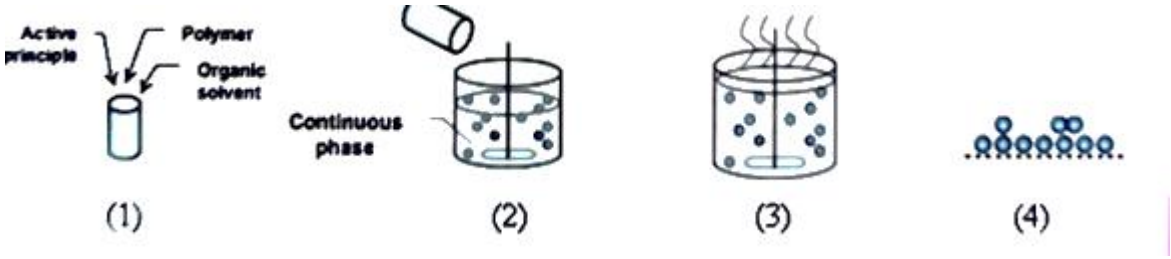
• A **core material (drug)** to be microencapsulated is **dissolved or dispersed** in the coating polymer solution with agitation.

• 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 **form 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 be 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 (PART - 2)

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:

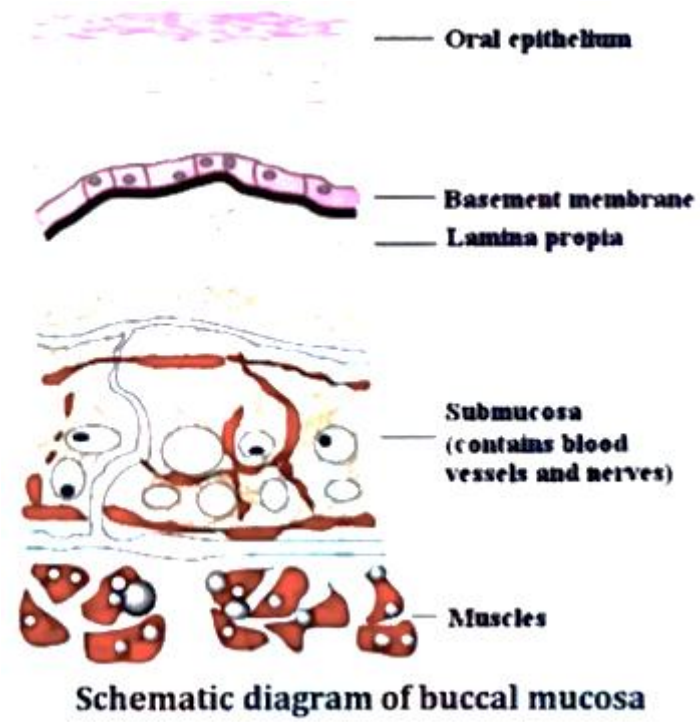
✓ Prolonging solely the duration of absorption process

✓ 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 mucus takes place and then, low chemical bonds can settle.

Theories explaining 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 van der 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

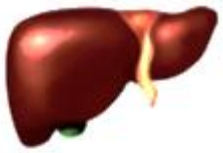
• Lack of flexibility of dosage forms

• Difficult to achieve high drug release rates required for some drugs

• Extent and frequency of attachment may cause **local irritation**

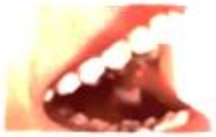
TRANSMUCOSAL PERMEABILITY

• 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.

Mechanisms involved in transmucosal penetration

• Certain physiological features of the transmucosal route play significant roles in this process, including **pH, enzyme activity, fluid volume and permeability of oral mucosa**.

• The main mechanisms responsible for penetration include:

✓ Simple diffusion (paracellular or transcellular)

✓ Carrier-mediated diffusion

✓ Active transport

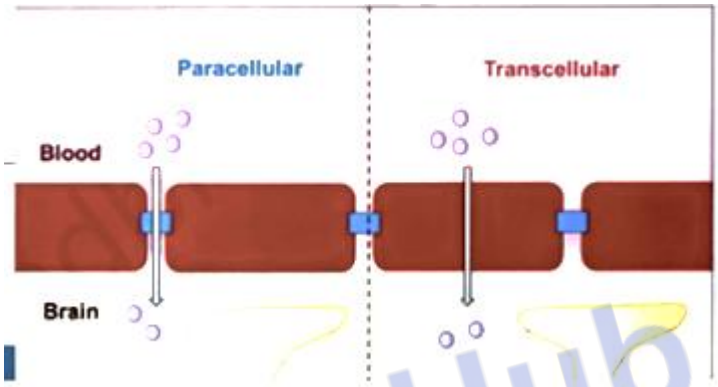
✓ Pinocytosis or endocytosis

• There are **two routes** potentially involved in drug permeation across epithelial membranes:

✓ **Transcellular route**

✓ **Paracellular route**

• Drug delivery across the oral mucosal membranes is termed **transmucosal drug delivery**, divided into **three main categories**:



✓ Sublingual delivery

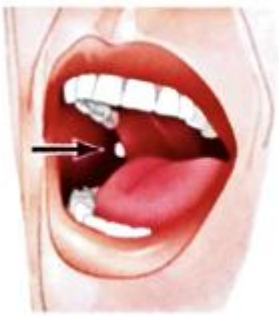
✓ Buccal delivery

✓ 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:**

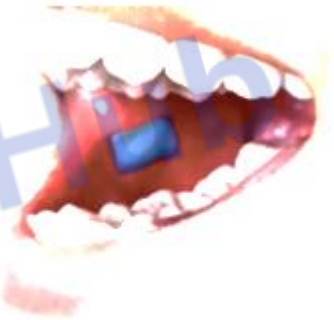
- Buccal mucoadhesive tablets are **dry dosage forms** that have to be **moistened** prior to placing in contact with **buccal mucosa**.

➤ **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 **buccoadhesive 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 **increase the** **permeation rate of the membrane**, co-administrated drug penetration enhancers 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 (PART - 3)

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.
2. Limited to potent drugs.
3. 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.

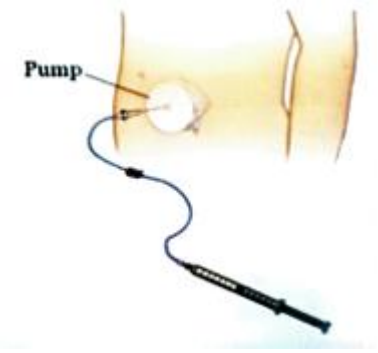
- In these implants, drugs may be **dissolved**, **dispersed** **or embedded in a matrix of polymers or waxes/lipids** that control the releasing via dissolution and/or diffusion, bioerosion, biodegradation, or an activation process, such as hydrolysis or osmosis.
- These systems are generally prepared 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 powered to release the drugs.

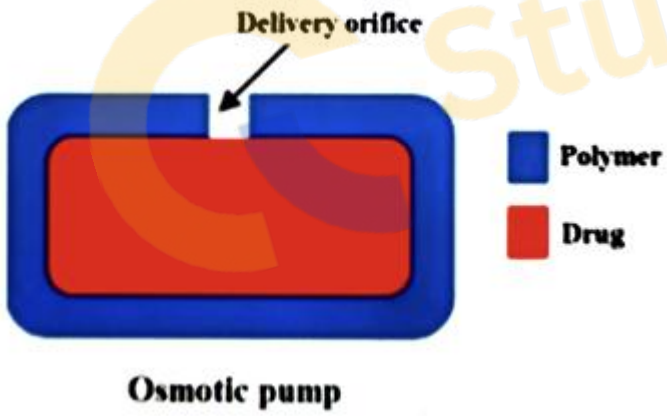
These are 3 types:

- 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 through 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