BP 704T: NOVEL DRUG DELIVERY SYSTEMS (Theory)

Unit-II

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Microencapsulation

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 yielding microscopic particles (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.

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 (**Fig. 1**):

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.

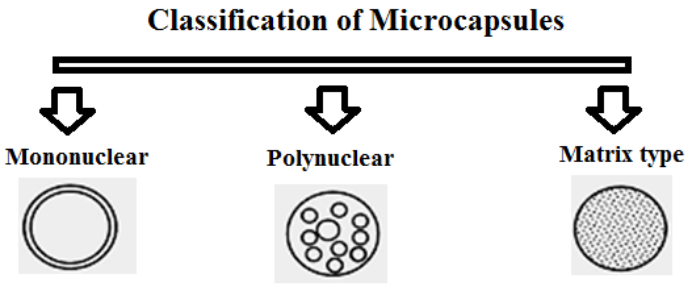

Fig. 1: Classification of microcapsules

***Advantages of microencapsulation*:**

i). Providing environmental protection to the encapsulated active agents or core materials.

ii). Liquids and gases can be changed into solid particles in the form of microcapsules.

iii). Surface as well as colloidal characteristics of various active agents can be changed.

iv). modify and delayed drug release form different pharmaceutical dosage forms

v). 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:

i). Expensive techniques.

ii). This causes reduction in shelf-life of hygroscopic agents.

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

Methods of microencapsulation:

(a) Air suspension:

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 (**Fig. 2**). 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, 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.

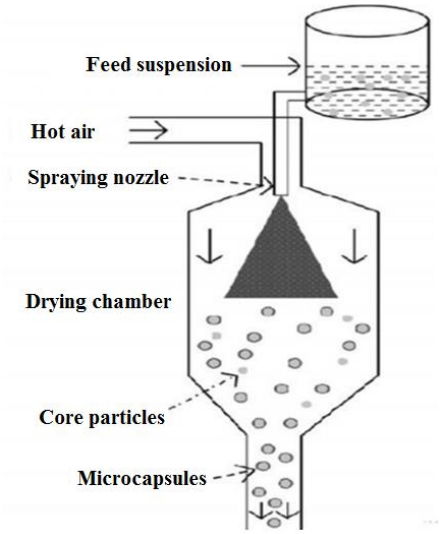

Fig. 2: Air suspension method for microencapsulation

(b) Coacervation phase separation:

Microencapsulation by coacervation phase separation method consists of 3 steps:

i). Formation of 3 immiscible phases: a liquid manufacturing phase, a core material phase and a coating material phase.

ii). Deposition of the liquid polymer coating on the core material.

iii). Rigidizing the coating usually by thermal, cross linking or desolvation techniques to form microcapsules.

The deposition of liquid polymer coating around the interface formed between the core material and the liquid vehicle phase (**Fig. 3**). 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. Also monomers can be dissolved in the liquid vehicle phase and subsequently polymerized at interface. Important equipments necessary for microencapsulation by coacervation phase separation method are jacketed tanks with variable speed agitators.

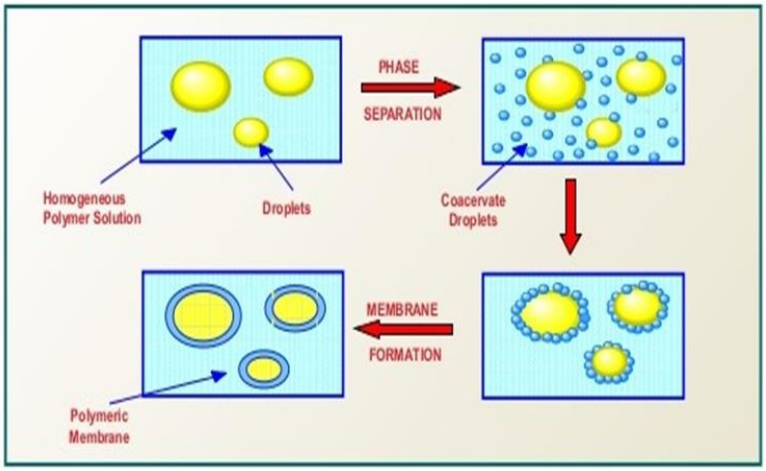

Fig. 3: Coacervation phase separation method for microencapsulation

(c) 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 (**Fig. 4**). In practice, the coating is applied as a solution or as an atomized spray to the desired solid core material in the coating pan. Generally, warm air is passed over the coated materials as the coatings are being applied in the coating pans to remove the coating solvent. In some cases, the process of final solvent removal is accomplished in the drying oven.

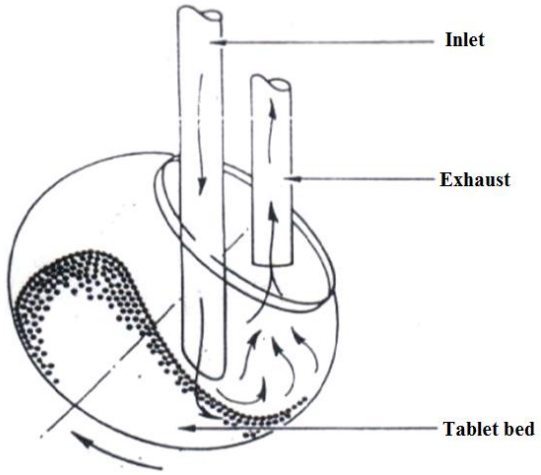

Fig. 4: Pan coating method for microencapsulation

(d) Fluidized-bed technology

Fluidized-bed technology method for microencapsulation is used for the encapsulation of solid core materials, including liquids absorbed into porous solids. This microencapsulation method is expansively employed to encapsulate pharmaceuticals. 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.

(e) Spray drying and spray congealing:

Spray drying and spray congealing methods of microencapsulation are almost similar in that 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 (**Fig. 5**). 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. Removal of non-solvent or solvent from the coated product is often done by sorption extraction or evaporation.

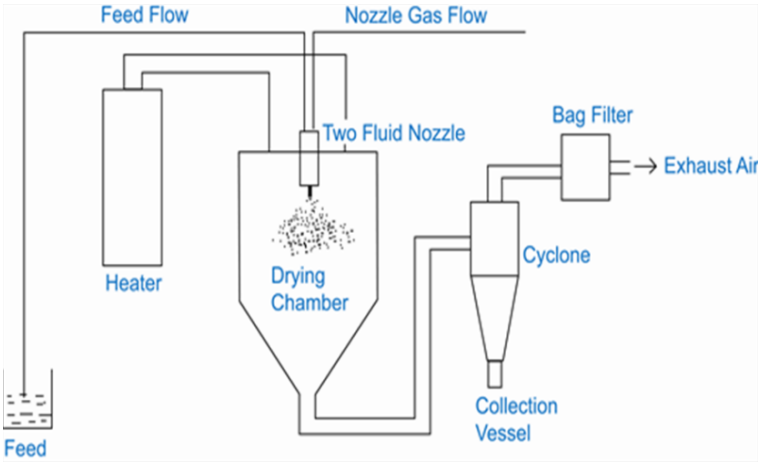

Fig. 5: Spray drying method for microencapsulation

(f) 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.

(g) 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.

(h) 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. The continuous or core material supporting phase is usually a liquid or gas, and therefore, the polymerization reaction occurs at the interfaces of liquid-liquid, liquid-gas, solid-liquid, or solid-gas.

(i) 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. The interfacial cross-linking method of microencapsulation is very versatile for pharmaceutical or cosmetic applications.

Applications:

Different applications of microencapsulation are:

1. Microencapsulation can be used to formulate various sustained controlled release dosage forms by modifying or delaying release of encapsulated active agents or core materials.
2. Microencapsulation 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.
3. Gastric irritant drugs are being microencapsulated to reduce the chances of gastric irritation.
4. The taste of bitter drug candidates can be masked by employing microencapsulation techniques.
5. Through microencapsulation, liquids and gases can be changed into solid particles in the form of microcapsules.
6. 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.
7. Microencapsulation can be used to decrease the volatility. A microencapsulated volatile substance can be stored for longer times without any substantial evaporation.

8. Microencapsulation provides environmental protection to the encapsulated active agents from various environmental issues, such as light, heat, humidity, oxidation, *etc*.
9. The hygroscopic characteristics of many core materials can be reduced by microencapsulation.
10. The separations of incompatible substances can be achieved by microencapsulation. For example, pharmaceutical eutectics can be separated by microencapsulation. This is a case where direct contact of materials brings about liquid formation. The stability enhancement of incompatible aspirin-chlorpheniramine maleate mixture is accomplished by microencapsulating both of them before mixing.
11. Microencapsulation is used to lessen the potential danger of toxic substance handling. The toxicity owing to handling of herbicides, insecticides, pesticides and fumigants, *etc*., can be usefully lessened after microencapsulation.

References:

[1]. Allen LV, Popovich NG, Ansel HC. *Pharmaceutical Dosage Forms and Drug Delivery Systems.* Delhi, India: BI Publication; 2005.
[2]. Lachman LA, Liberman HA, Kanig JL. *The Theory and Practice of Industrial Pharmacy.* Mumbai, India: Varghese Publishing House, 1976.
[3]. Benita S. Microencapsulation: Methods and Industrial applications, Marcel Dekker, Inc., New York, 1996.
[4]. Singh MN, Hemant KS, Ram M, Shivakumar HG. Microencapsulation: A promising technique for controlled drug delivery. Res Pharm Sci. 2010;5(2):65-77.
[5]. Sachan NK, Singh B, Rao KR. Controlled drug delivery through microencapsulation. Malaysian J Pharm Sci. 2006;4:65–81.
[6]. Kiyoyama S, Shiomori K, Kawano Y, Hatate Y. Preparation of microcapsules and control of their morphology. J Microencapsulation. 2003;20:497

Mucosal Drug Delivery system

Recent years, the drug delivery *via* mucosal drug delivery system has become highly popular. Certain drugs have lack of efficacy due to decreased bioavailability, gastrointestinal intolerance, unpredictable and erratic absorption or pre-systemic elimination of other potential route for administration. Various routes for mucosal drug delivery include oral, buccal, ocular, nasal and pulmonary routes, *etc*.

Typically, mucosal drug delivery systems can be classified as:

1. *Non-attached mucosal drug delivery systems:*

These systems are being formulated to be absorbed through the mucosa within the oral cavity. Examples: Sublingual tablets, Fast dissolving tablets (Melt-in-mouth or orally disintegrating tablets), *etc*.

2. *Attached or immobilized mucosal drug delivery systems:*

These systems are being formulated to be remained attached onto the mucosal surface by the adhesive properties. These systems are also known as mucoadhesive systems. Examples: Buccal drug delivery systems, rectal drug delivery systems, vaginal drug delivery, nasal drug delivery systems systems, *etc*.

Different strategies have been adopted for controlled mucosal delivery and are based on:

1. Prolonging solely the duration of absorption process.
2. Developing unidirectional delivery systems
3. Preparing user-friendly mucosal delivery systems.

Bioadhesion:

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 and being retained on them or holding them together for extended period of time. ‘Bioadhesion’ may occur *via* 3 ways:

i). Bioadhesion in-between biological layers without the involvement of artificial materials.

ii). Cell adhesion into the culture dishes or adhesion to a variety of substances, such as woods, metals, and other synthetic substances.

iii). Adhesion of artificial substances to the biological substrates like the adhesion of hydrophilic polymers to skin or other soft tissues.

Mucoadhesive drug delivery systems:

Mucoadhesive drug delivery systems utilizes the property of mucoadhesion/bioadhesion of certain polymers, which become adhesive on hydration and hence, can be used for targeting a drug to the particular region of the body for extended period of time. The ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability. Mucoadhesive drug delivery systems facilitate the possibility of avoiding either destruction by gastrointestinal contents or hepatic first-pass inactivation of drug.

Various mucoadhesive polymers are being used to formulate mucoadhesive drug delivery systems. These can be broadly categorized as:

(I) Synthetic polymers:

(a) Cellulose derivatives: Methylcellulose (MC), Hydroxy ethylcellulose (HEC), Hydroxyl propylcellulose (HPC), Hydroxy propyl methylcellulose (HPMC), Sodium carboxy methylcellulose (NaCMC), e*t*c.

(b) Poly (Acrylic acid) polymers: Carbomers, Polycarbophil.

(d) Poly vinyl alcohol (PVA).

(II) Natural polymers: Chitosan, gum tragacanth, sodium alginate, xanthan gum, locust bean gum, gellan gum, *etc*.

Principles of bioadhesion /mucoadhesion:

For bioadhesion /mucoadhesion, 3 stages are involved:

i). 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.

ii). Penetration of the bioadhesive/mucoadhesive into the tissue takes place.

iii). 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:

i). Wetting theory: Ability of bioadhesive/mucoadhesive polymers to spread and develop immediate attachment with the mucous membranes.

ii). Electronic theory: Attractive electrostatic forces in-between glycoprotein mucin network and the bioadhesive/mucoadhesive polymers.

iii). Adsoption theory: Surface forces (covalent bonds, ionic bonds, hydrogen bonds, and van der Waal's forces) resulting in chemical bonding.

iv). Diffusion theory: Physical entanglement of mucin strands and the flexible polymeric chain.

v). Fracture theory: Analyses the maximum tensile stress developed during detachment of mucoadhesive/bioadhesive drug delivery systems from the mucosal surfaces.

Advantages and disadvantages:

Advantages:

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

ii). High drug concentration can be maintained at the absorptive surface for a prolonged period.

iii). Dosage forms can be immobilized specifically at any part of the oral mucosa, buccal mucosa, sublingual or gingival mucosa, *etc*.

Disadvantages:

i). Small mucosal surface for contact

ii). Lack of flexibility of dosage forms

iii). Difficult to achieve high drug release rates required for some drugs.

iv). Extent and frequency and frequency of attachment may cause local irritation.

Transmucosal permeability:

The mucosal lining of the oral cavity is referred to as the oral mucosa. The oral mucosa comprises the buccal, sublingual, gingival, palatal and labial mucosa. The unique environment of the transmucosal route offers its potential as an effective route for the delivery of a variety of 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. In addition, oral mucosa facilitates an advantage of retaining drug delivery systems in contact with the absorptive mucosal surface for a longer period (*i.e.,* mucoadhesion) and thus, optimizing the drug concentration gradient across the mucosal membrane with the reduction of differential pathways. Thus, the delivery of drugs through the transmucosal route has attracted particular attention due to its potential for high patient compliance and unique physiological features.

The drugs to be administered through the transmucosal route need to be released from the dosage forms to the effective delivery site (*e.g.,* buccal or sublingual area) and pass through the mucosal layers to enter the systemic circulation. 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 secretion of saliva is also an important determinant for the performance of transmucosal drug delivery. The main mechanisms responsible for the penetration of various molecules include: Simple diffusion (paracellular or transcellular), carrier-mediated diffusion, active transport, pinocytosis or endocytosis. However, there is little research on to what extent this phenomenon affects the efficiency of oral transmucosal delivery from different drug delivery systems and thus, further research needs to be conducted to better understand this effect.

Drug delivery across the oral mucosal membranes is termed transmucosal drug delivery. It can be divided into three main categories of transmucosal drug delivery based on the characteristics of the oral cavity:

i). *Sublingual delivery:* Administration of drugs *via* the sublingual mucosa (the membrane of the ventral surface of the tongue and the floor of the mouth) to the systemic circulation.

ii). *Buccal delivery:* Administration of drugs *via* the buccal mucosa (the lining of the cheek) to the systemic circulation.

iii). *Local delivery:* For the treatment of conditions of the oral cavity, principally ulcers, fungal conditions and periodontal disease, gingival disease, bacterial and fungal infections, dental stomatitis, *etc*.

Formulation considerations of buccal delivery systems:

Transmucosal administration of drugs accross the buccal lining is defined as buccal drug delivery. The mucosa of the buccal area has a large, smooth and relatively immobile surface, which provides a large contact surface (**Fig. 6**). The large contact surface of the buccal mucosa contributes to rapid and extensive drug absorption. Buccal drug delivery was first introduced by Orabase in 1947, when gum tragacanth was mixed with dental adhesive powder to supply penicillin to the oral mucosa. Recent years, buccal drug delivery has proven particularly useful and offers several advantages over other drug delivery systems including: bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism; improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications; sustained drug delivery; increased ease of drug administration; and ready termination of delivery by detaching the dosage form.

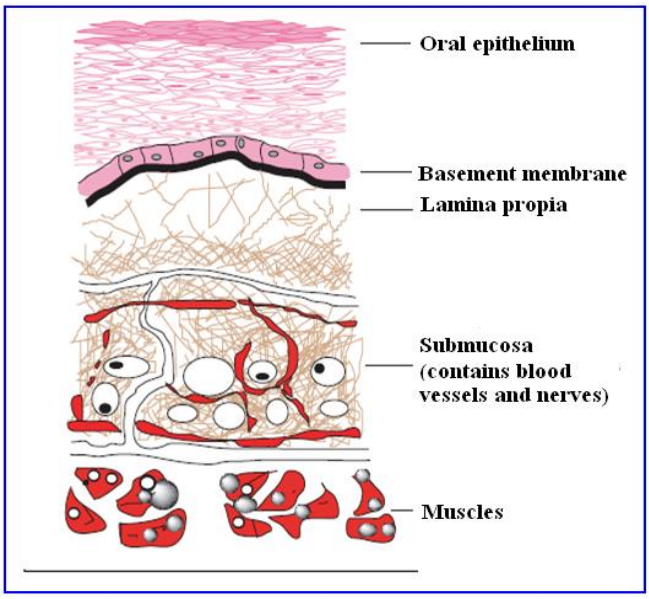

Fig. 6: Schematic diagram of buccal mucosa

Buccal drug delivery occurs in a tissue that is more permeable than skin and is less variable between patients, resulting in lower inter-subject variability. Because of greater mucosal permeability, buccal drug delivery can also be used to deliver larger molecules such as low molecular weight heparin. In addition, buccal drug delivery systems could potentially be used to deliver drugs that exhibit poor or variable bioavailability, and bioavailability will be enhanced for drugs that undergo significant first-pass metabolism. Because drug absorbed from the oral cavity avoids both first-pass metabolism and enzymatic/acid degradation in the gastrointestinal tract, buccal administration could be of value in delivering a growing number of potent peptide and protein drug molecules. In addition, buccal delivery of such drug molecules is a promising area for continued research with the aim of alternative non-invasive delivery.

The novel type buccal dosage forms include:

i). Buccal mucoadhesive tablets,

ii). Buccal patches and films,

iii). Semisolids (ointments and gels) and powders

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

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. These also offer advantages over creams and ointments in that they provide a measured dose of drug to the site. Recent years, puccal patches and films have received the greatest attention for buccal delivery of drugs. They present a greater patient compliance compared with tablets owing to their physical flexibility that causes only minor discomfort to the patient.

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.

Structure and design of buccal patches:

Buccal patches are of two types on the basis of their release characteristics:

i). Unidirectional buccal patches and

ii). Bidirectional buccal patches

Unidirectional patches release the drug only into the mucosa, while bidirectional patches release drug in both the mucosa and the mouth.

Buccal patches are structurally of two types:

i). **Matrix type:** The buccal patch is designed in a matrix configuration contains drug, adhesive, and additives mixed together (**Fig. 7**).

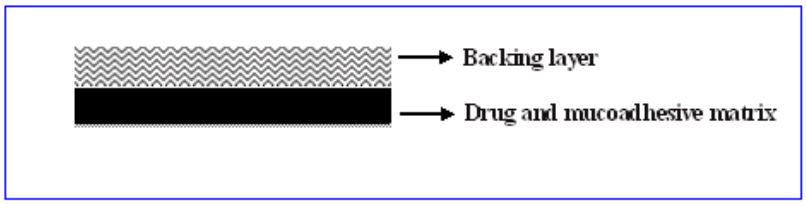

Fig 7: Schematic representation of the matrix-type buccal patch design

ii). **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.

Composition of buccal patches:

Drugs: The selection of suitable drug for the design of buccal drug delivery systems should be based on pharmacokinetic properties of the drugs to be administered. The drug should have following characteristics for the designing of effective buccal patches:

a) The conventional single dose of the drug should be small.
b) The drugs having biological half-life between 2-8 h are good candidates for controlled drug delivery.
c) T_{max} of the drug shows wider-fluctuations or higher values when given orally.
d) Through oral route drug may exhibit first pass effect or pre-systemic drug elimination.
e) The drug absorption should be passive when given orally.

f) Buccal adhesive drug delivery systems with the size 1–3 cm^2 and a daily dose of 25 mg or less are preferable.

Polymers (adhesive layer): Bioadhesive polymers play a major role in the designing of buccal patches. Bioadhesive polymers are from the most diverse class and they have considerable benefits upon patient health care and treatment. These polymers enable retention of dosage form at the buccal mucosal surface and thereby provide intimate contact between the dosage form and the absorbing tissue. Drug release from a polymeric material takes place either by the diffusion or by polymer degradation or by a combination of the both. Polymer degradation generally takes place by the enzymes or hydrolysis either in the form of bulk erosion or surface erosion.

An ideal bioadhesive polymer for buccal patches should have following characteristics:

a) The polymer should be inert and compatible with the buccal environment.
b) It should allow easy incorporation of drug in to the formulation.
c) The polymer and its degradation products should be non-toxic absorbable from the mucous layer.
d) It should adhere quickly to moist tissue surface and should possess the site specificity.
e) It should form a strong non covalent bond with the mucine or epithelial surface and should possess sufficient mechanical strength.
f) The polymer must not decompose on storage or during the shelf life of the dosage form.
g) It must have high molecular weight and narrow distribution.
h) The polymer should be easily available in the market and economical.
i) The polymer should have good spreadability, wetting, swelling and solubility and biodegradability properties.
j) The pH of the polymer should be biocompatible and should possess good viscoelastic properties.
k) It should demonstrate local enzyme inhibition and penetration enhancement properties.
l) It should demonstrate acceptable shelf life.

Backing layer: Backing layer plays a major role in the attachment of buccal patches to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. Such impermeable membrane on buccoadhesive patches prevents

the drug loss and offers better patient compliance. The commonly used materials in backing membrane include water insoluble polymers such as ethylcellulose, Eudrajit RL and RS, *etc*.

Penetration enhancer: Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Selection of the appropriate permeation enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. Permeation enhancers used for designing buccal patches must be nonirritant and have a reversible effect. The epithelium should recover its barrier properties after the drug has been absorbed. The most common classes of buccal penetration enhancers include fatty acids that act by disrupting intercellular lipid packing, surfactants, bile salts, and alcohols.

Plasticizers: To impart appropriate plasticity of the buccal patches, suitable plasticizers are required to add in the formulation of buccal patches. Typically, the plasticizers are used in the concentration of 0-20 % w/w of dry polymer. Plasticizer is an important ingredient of the film, which improves the flexibility of the film and reduces the bitterness of the film by reducing the glass transition temperature of the film. The selection of plasticizer depends upon the compatibility with the polymer and type of solvent employed in the casting of film. Plasticizers should be carefully selected because improper use of the plasticizers affects the mechanical properties of the film. Widely used plasticizers in buccal patches and films are PEG100, 400, propylene glycol, glycerol, castor oil *etc*.

Taste masking agents: Taste masking agents or taste masking methods should be used in the formulation if the drugs have bitter taste, as the bitter drugs makes the formulation unpalatable, especially for pediatric preparations. Thus, before incorporating the drugs in the buccal patches, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation, such as complexation technology, salting out technology, *etc*.

Mechanism of buccal absorption:

Buccal absorption leads systemic or local action *via* the buccal mucosa and it occurs by passive diffusion of the non ionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membrane and the more lipophillic the drug molecule, the more readily it is absorbed.

Factors affecting buccal absorption:

The oral cavity is a complex environment for drug delivery as there are many interdependent as well as independent factors which reduce the absorbable concentration at the site of absorption.

1. Membrane Factors: This involves degree of keratinization, surface area available for absorption, mucus layer of salivary pellicle, intercellular lipids of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/ lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation.
2. Environmental Factors:

(a) Saliva: The thin film of saliva coats throughout the lining of buccal mucosa and is called salivary pellicle or film. The thickness of salivary film is 0.07-0.10 mm. The thickness, composition and movement of this film affect the rate of buccal absorption.

(b) Salivary glands: The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucus on surface of buccal mucosa. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier to drug penetration.

Manufacturing methods of buccal patches

Manufacturing processes involved in making buccal patches, are namely solvent casting, hot melt extrusion and direct milling.

1. *Solvent casting:* In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin

layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry.

2. *Hot melt extrusion:* In hot melt extrusion blend of pharmaceutical ingredients is molten and then forced through an orifice to yield a more homogeneous material in different shapes such as granules, tablets, or films. Hot melt extrusion has been used for the manufacture of controlled release matrix tablets, pellets and granules, as well as oral disintegrating films. However, only a hand full article has reported the use of hot melt extrusion for manufacturing mucoadhesive buccal patches.
3. *Direct milling:* In this, patches are manufactured without the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described. While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.

Advantages of buccal drug delivery systems

(a) Sustained drug delivery.
(b) Increased ease of drug administration.
(c) Excellent accessibility.
(d) Drug absorption through the passive diffusion.
(e) 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.
(f) Versatility in designing as multidirectional or unidirectional release systems for local or systemic actions, *etc*.
(g) The drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
(h) Improved patient compliance.

(i) 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.

(j) Flexibility in physical state, shape, size and surface.

(k) 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.

(l) Transmucosal delivery occurs is fewer variables between patients, resulting in lower inter-subject variability as compared to transdermal patches.

Limitations of buccal drug delivery systems:

Depending on whether local or systemic action is required the challenges faced while delivering drug *via* buccal drug delivery can be enumerated as follows:

(a) For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.

(b) The non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.

(c) For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue.

References:

[1]. Chien YW. Novel Drug Delivery Systems, 2nd Ed, New York: Marcel Dekker Inc.: New York, 2007.

[2]. Jain NK. Controlled and Novel Drug Delivery, 1st edition, published by CBS Publishers and Distributors, New Delhi. 1997.

[3]. Gilles P, Ghazali FA, Rathbone J. Systemic oral mucosal drug delivery systems and delivery systems, in: Rathbone M.J. (ed.), Oral Mucosal Drug Delivery, Vol. 74, Marcel Dekker Inc, New York, 1996, pp. 241-285.

[4]. Kamath KR, Park K. Mucosal adhesive preparations, In: Swarbrick J, Boylan JC (eds)., Encyclopedia of Pharmaceutical Technology, vol. 10., Marcel Dekker, New York: 1994, pp. 133–163.

[5]. Mathiowitz E, Chickering D, Jacob JS, Santos C. Bioadhesive drug delivery systems. In: Mathiowitz E(ed), Encyclopedia of Controlled Drug Delivery, vol.1. Wiley, New York, 1999, pp. 9–44.

[6]. Boylan JC. Drug delivery buccal route. In: James Swarbrick, editor. Encyclopedia of Pharmaceutical Technology: Supplement 3, Marcel Dekker Inc 2001, pp. 800-811.

[7]. Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm, 1997; 23 (5): 489–515.

[8]. Hunt G, Kearney P, Kellaway IW. Mucoadhesive polymers in drug delivery systems. In: Johnson P, Lloyed-Jones JG (sds), Drug Delivery System: Fundamental and Techniqes. Elis Horwood, Chichester, 1987, pp. 180.
[9]. Woodley J. Bioadhesion: New Possibilities for Drug Administration. Clin Pharmacokinet, 2001; 40(2): 77-84.
[10]. Gandhi RB, Robinson JR. Oral cavity as a site for bioadhesive drug delivery, Adv. Drug Del. Rev. 1994; 13: 43-74.
[11]. Siegel IA. Permeability of the oral mucosa, In: Meyer J. The Structure and Function of Oral Mucosa, New York: Pergamon Press, 1984, pp. 95-108.

Implantable Drug Delivery Systems

Implantable drug delivery systems allow targeted and localized drug delivery and may achieve a therapeutic effect with lower concentrations of drugs. As a result, they may minimize potential side-effects of therapy, while offering the opportunity for increased patient compliance. This type of system also has the potential to deliver drugs which would normally be unsuitable orally, because it avoids first pass metabolism and chemical degradation in the stomach and intestine, thus, increasing bioavailability.

An ideal implantable parenteral system should possess following properties:

1. *Environmentally stable:* Implantable systems should not breakdown under the influence of light, air, moisture, heat, *etc*.
2. *Biostable:* Implantable systems should not undergo physicochemical degredation when in contact with biofluids (or drugs).
3. *Biocompatible:* Implantable systems should neither stimulate immune response (otherwise the implant will be rejected) nor thrombosis and fibrosis formation.
4. *Removal:* Implantable systems should be removability when required.
5. *Non-toxic or non-carcinogenic:* The degradation products or leached additives should be completely safe.
6. Implantable systems should have minimum surface area, smooth texture and structural characteristics similar to the tissue in which it is to be implanted to avoid irritation.
7. Implantable systems should release drugs at a constant predetermined rate for a predetermined period.

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. Invasive therapy
2. Chances of device failure

3. Limited to potent drugs
4. Biocompatibility issues

Concept of implants:

Implants for drug delivery are several types:

1. *In situ* forming implants (In situ depot forming systems):

(a) 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:

i). Requirement for the reconstitution before injection
ii). Inability to remove the dose one injected.
iii). Relatively complicated manufacturing procedures to produce a sterile, stable and reproducible product.

(b) In situ microparticle implants:

This type of implants is formed to overcome the disadvantages associated with *in situ* precipitating implants. These are:

i). High injection force.
ii). Local irritation at the injection site.
iii). Variability in the solidification rates.
iv). Irregular shape of the implants formed depending on the cavity into which the implants are introduced (implanted).
v). Undesirable high initial burst release of drugs.
vi). Potential solvent toxicity.

These *in situ* implantable systems consist of internal phase (drug-containing polymer solution or suspension) and a continuous phase (aqueous solution with a surfactant, oil phase with viscosity enhancer and emulsifier). The two phases are separately stored in dual-chambered syringes and mixed through a connector before administration.

2. 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*., whereas waxes include glyceryl monostearate. Drugs generally presented in such implantable systems are contraceptives, naltrexone, *etc*.

3. 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:

i). Osmotic pressure activated drug delivery systems
ii). Vapor pressure activated drug delivery systems
iii). Battery powered drug delivery systems.

Osmotic pumps:

Osmotic pumps are designed mainly by a semi-permeable membrane that surrounds a drug reservoir (**Fig. 8**). 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, 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.

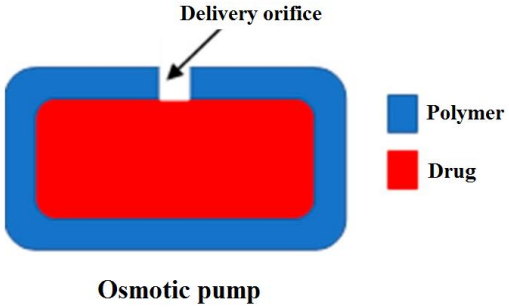

Fig. 8: Osmotic pump

Osmotic agents:

Osmotic agents are used for the fabrication of the osmotic device maintain a concentration gradient across the membrane by generating a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Osmotic agents usually are ionic compounds consisting of either inorganic salts such as sodium chloride, potassium chloride magnesium sulphate, sodium sulphate, potassium sulphate and sodium bicarbonate. Additionally, sugars such as glucose, sorbitol, sucrose and inorganic salts of carbohydrates can also act as effective osmotic agents.

References:

[1]. Chien YW. Novel Drug Delivery Systems, 2nd Ed, New York: Marcel Dekker Inc.: New York, 2007.
[2]. Jain NK. Controlled and Novel Drug Delivery, 1st edition, published by CBS Publishers and Distributors, New Delhi. 1997.
[3]. Stewart SA, Domínguez-Robles J, Donnelly RF, Larrañeta E. Implantable Polymeric Drug Delivery Devices: Classification, Manufacture, Materials, and Clinical Applications. Polymers (Basel). 2018;10(12):1379.
[4]. Verma RK, Mishra B, Garg S. Osmotically controlled oral drug delivery. Drug Dev Ind Pharm. 2000; 26 (7): 695-708.