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A REVIEW ARTICLE ON MUCOSAL DRUG DELIVERY SYSTEM

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Abstract:

Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption. The drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Thus, mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity. In this regard, this review covers the areas of mechanisms and theories of mucoadhesion, factors influencing the mucoadhesive devices and also various mucoadhesive dosage forms.

Keywords: *Mucoadhesion, theories, mucoadhesive dosage forms*

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INTRODUCTION:

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.,

Mucosal drug delivery involves administration to moist cavities, such as the lining of the mouth, vagina, and bladder. This allows for high drug concentration in local treatment of disease with reduced systemic side-effects.

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 etc.

Bio adhesion

The term 'bio-adhesive' describes materials that bind or adhere to the biological substrates. 'Bio-adhesive' 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. 'Bio-adhesion' may occur via 3 ways:

i) Bio-adhesion 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.

Structural Features of Oral Mucosa

Buccal mucosa Structure:

The total area of the oral cavity is about 100cm. Out of this about one third is the buccal surface, which is lined with an epithelium of about 0.5mm thickness. The keratinized and non-keratinized regions of the oral epithelium differ from each other in terms of lipid composition of the cells. The keratinized epithelium has predominantly neutral lipids (e.g., ceramides) while the non-keratinized epithelium has few but polar lipids, particularly cholesterol sulphate and glucosylceramide. Buccal membrane has numerous elastic fibres in the dermis, which is another barrier for diffusion of drug across the buccal membrane.

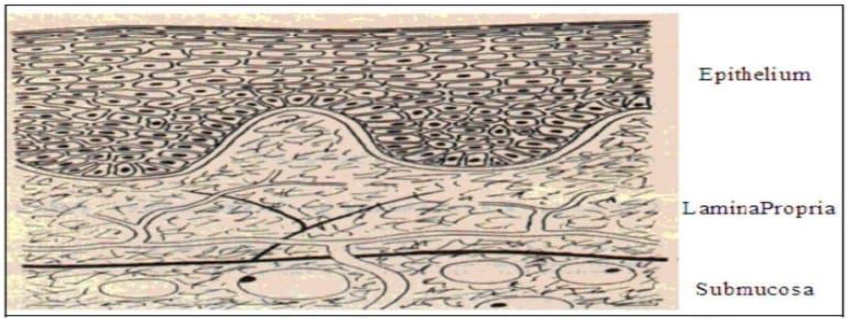
Drug that penetrates this membrane enters the systemic circulation via network of capillaries and arteries. The lymphatic drainage almost runs parallel to the venous vascularization and ends up in the jugulary ducts .

The oral mucosal surface is constantly washed by the saliva (daily turn out is about 0.5 to 2 litres). The drug absorption across the oral mucosa occurs in the non-keratinized sections for protein/peptide delivery buccal route offers distinct benefits over other mucosal routes like nasal, vaginal, rectal, etc.

STRUCTURE OF ORAL MUCOSA

Environment:

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some maybe attached to certain regions on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another.

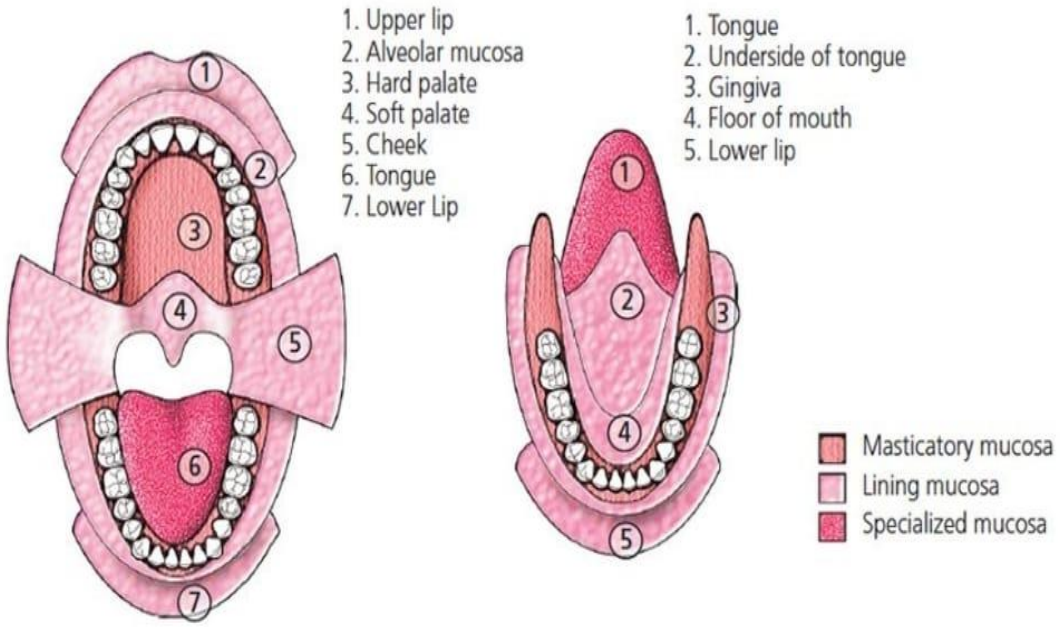


At physiological pH the mucus network carries a negative charge (due to the sialic acid and sulphate residues) which may play a role in mucoadhesive. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer .The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the pH. The daily salivary volume is between 0.5 to 2 litres and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

Absorption via buccal mucosa:

There are two permeation pathways for passive drug transport across the oral mucosa: Para cellular and Tran cellular routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment.

The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier topermeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.

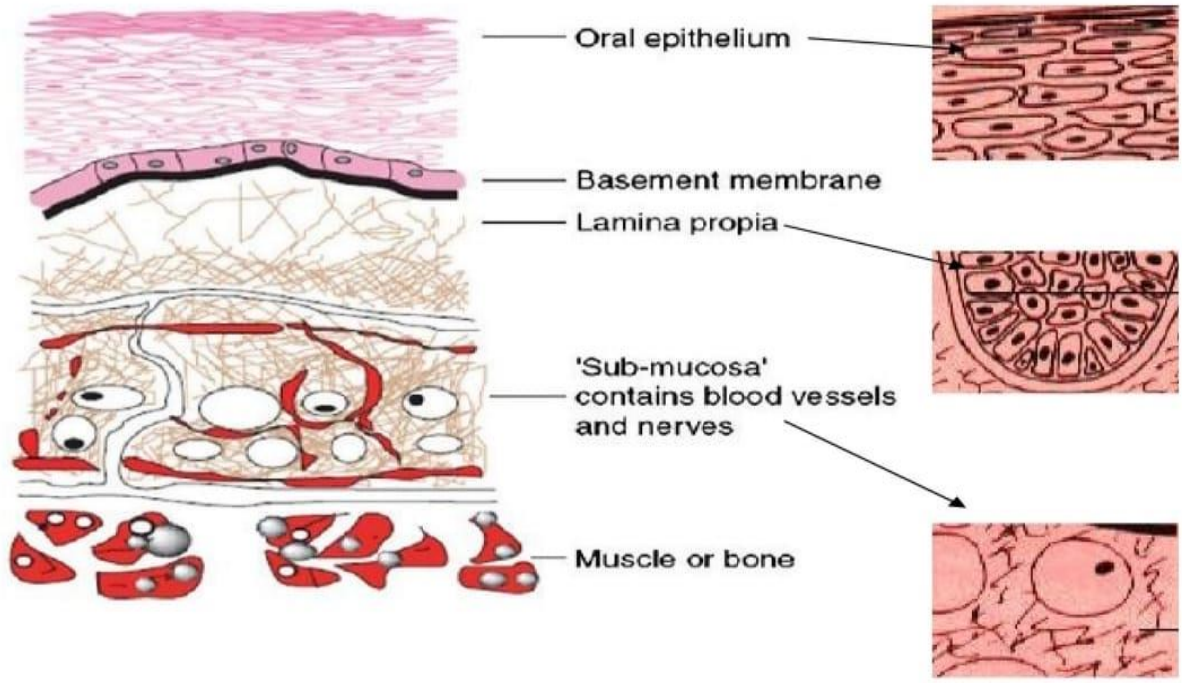


Factors Affecting Buccal Absorption:

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

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.



Environmental Factors:

Saliva:

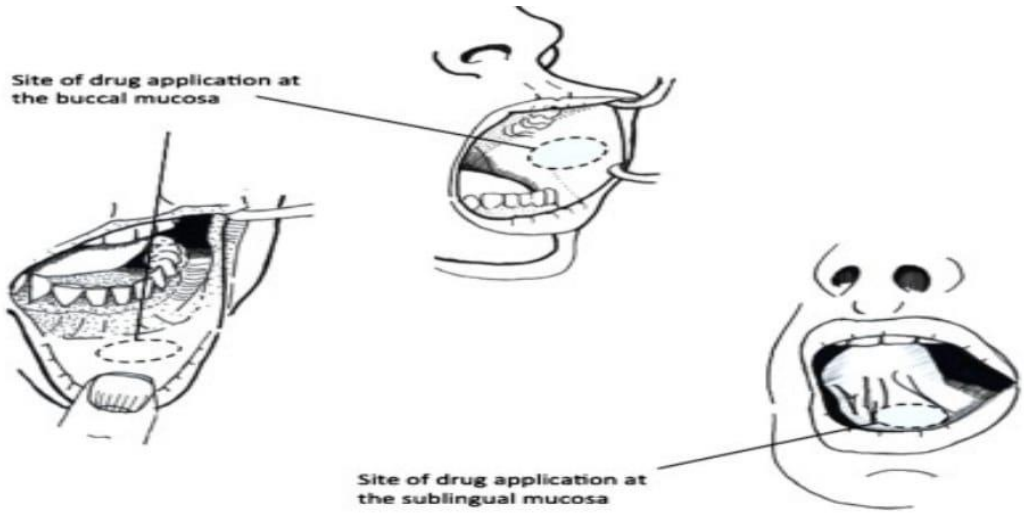
The thin film of saliva coats throughout the lining of buccal mucosa and is called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10 mm. The thickness, composition and movement of this film effects buccal absorption.

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.

Movement of oral tissues:

Buccal region of oral cavity shows less active movements. The mucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods while withstanding tissue movements during talking and if possible during eating food or swallowing.



Advantage and Limitation:

The administration of drugs by the buccal route has several advantages over per oral administration such as;

- The drug is not subjected to destructive acidic environment of the stomach.
- Therapeutic serum concentration of the drug can be achieved more rapidly.
- The drug enters the general circulation without first passing through the liver.
- With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation.
- Delivery can also be terminated relatively easily if required.

Oral Mucosal Dosage Forms:

Various drug delivery systems are their which uses the oral mucosa as a drug delivery site such as – fast dissolving tablets, oral dissolving films, fast caps, buccal adhesive film and tablets, chewing gums etc.

a) Fast Dissolving Tablet (FDT):

Recently fast dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery system, because they are easy to administer and lead to better patient compliance. They also impart unique product differentiation thus enabling use as line extension for existing commercial products. FDTs can be prepared by various techniques like direct compression, sublimation, melt granulation, moulding, volatilization and freeze drying.

Some of patented technologies are zydis, orasolve, durasolv, flash dose, wowtab, flash tab etc. some drugs which are poorly water soluble and have a variable bioavailability and bio-in equivalence related to its poor water solubility. The solubility of drug was increased by various methods to make a fast dissolving tablet like solid dispersion technique, by co-granulation with beta – cyclodextrin. Because fast dissolving systems dissolves or disintegrate in patient's mouth, thus the active constitute come in contest with the taste buds and hence taste masking of the drugs become critical to patient compliance.

Taste masking can be done by various methods like addition of sweeteners, or by mass extrusion technique using eudragit E100. Recently various comparative studies were done between fast dissolving and conventional formulations. In an acceptance survey of FDT in allergic patients it is observed that if given the choice 93 % would choose FDT formulations.

b)Fast Dissolving Films:

However, the fear of taking solid tablets and the risk of choking for certain patient population still exist despite their short dissolution/disintegration time. Recent development in novel drug delivery system aims to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration. One such approach is rapidly dissolving film. It consists of a very thin oral strip, which releases the active ingredient immediately after uptake into the oral cavity. Rapid film combines all the advantages of tablets (precise dosage, easy application) with those of liquid dosage forms (easy swallowing, rapid bioavailability).

c)Fast Caps:

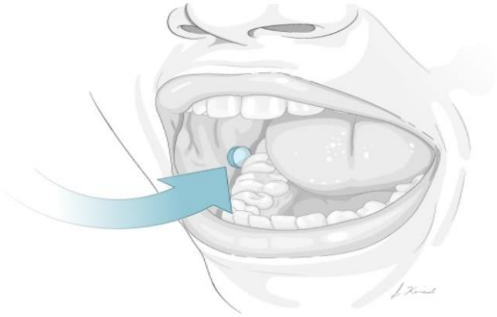
A new type of fast dissolving drug delivery system based on gelatine capsules was developed. In contrast to conventional hard capsules, the fast caps consist of gelation of low bloom strength and various additives to improve the mechanical and dissolution properties of the capsule shell. The advantage of these fast disintegrating capsules are high drug loading, possible solid and liquid filling, no compression of coated taste-masked or extended release drug particles/pellets, good mechanical properties, simple manufacturing, mechanical stability and requirement of special packaging.

d)Bucco adhesive Film and Tablets:

Recent years have seen an increasing interest in the development of novel muco- adhesive buccal dosage forms. These are useful for the systemic delivery of drugs as well as for local targeting of drug to a particular region of the body. Water soluble drugs are considered difficult to deliver in the form of sustained or controlled release preparations due to their susceptibility to "dose dumping phenomena ". Attempts have been made to regulate their release process by use of mucoadhesive polymers in order to achieve a once- a- day dose treatment.

e)Medicated Chewing Gums:

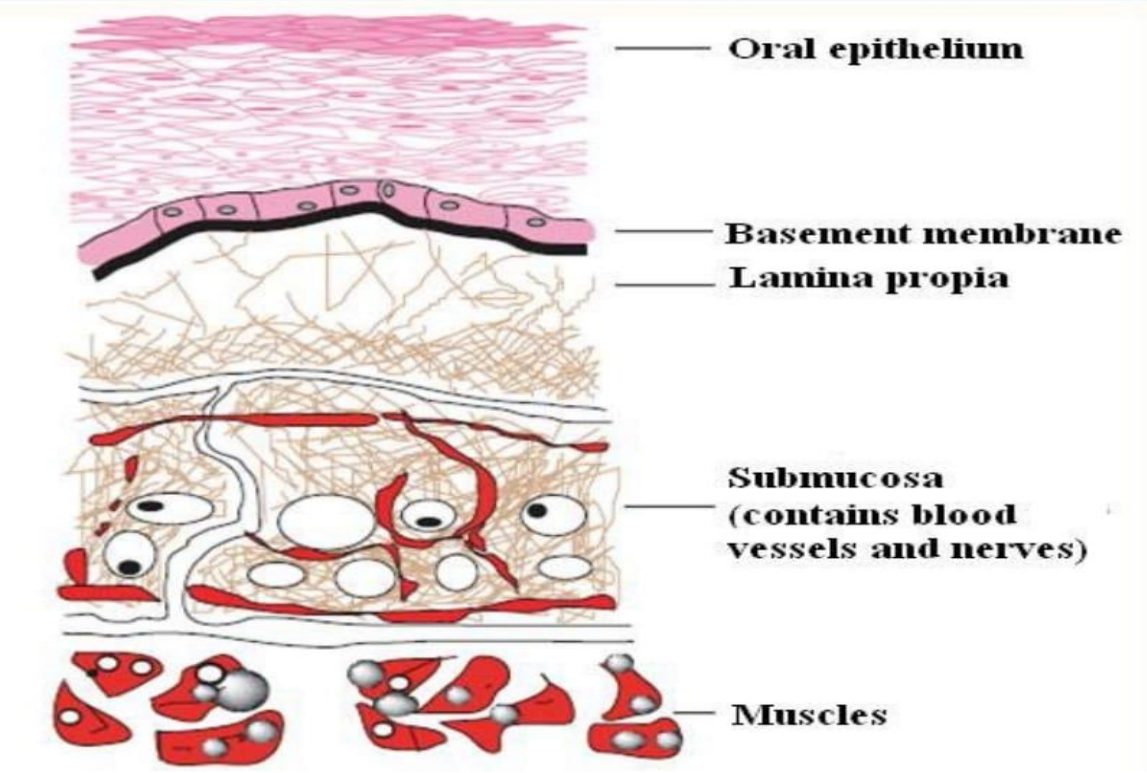
Medicated chewing gum is an attractive alternative for drug delivery system with several advantages including convenience for administration, individually controlled release of active substance and effective buccal drug administration for the treatment of local oral disease and systemic action. Mainly chewing gum is used to promising controlled release drug delivery. Medicated chewing gums are currently available for pain relief, smoking cessation, travel illness and freshening of breath. A hydrophobic gum was used for the formulation of chewing gum. A new chewing gum device in the form of a three layer tablet has been also developed. In vitro release study of chewing gum requires special apparatus and instrumental setting.



Formulation considerations of buccal delivery systems:

Transmucosal administration of drugs across 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. 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.



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:

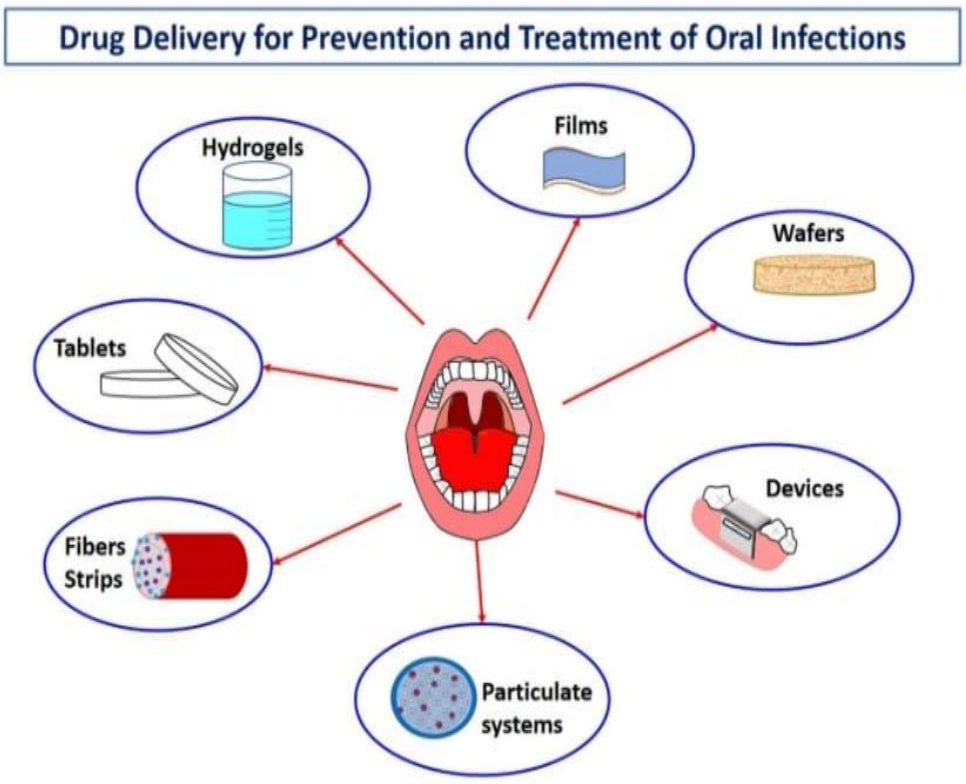
Buccal mucoadhesive tablets are dry dosage forms that have to be moistened prior to placing in contact with buccal mucosa.

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, buccal 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):

Bio adhesive gels or ointments have less patient acceptability than solid. bio adhesive 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

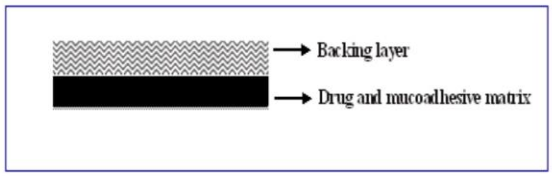
ii). Bidirectional buccal patches

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:

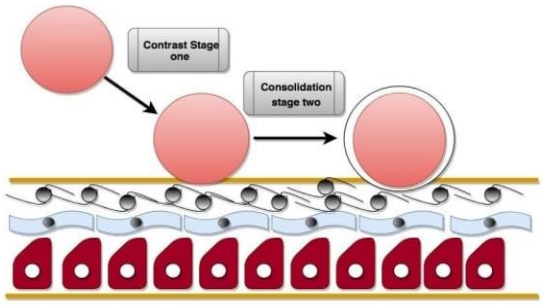
The buccal patch is designed in a matrix configuration contains drug, adhesive, and additives mixed together.



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) Tmax 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 cm2 and a daily dose of 25 mg or less are preferable.

Polymers (adhesive layer): Bio adhesive polymers play a major role in the designing of buccal patches. Bio adhesive 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 bio adhesive polymer for buccal patches should have following characteristics:

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

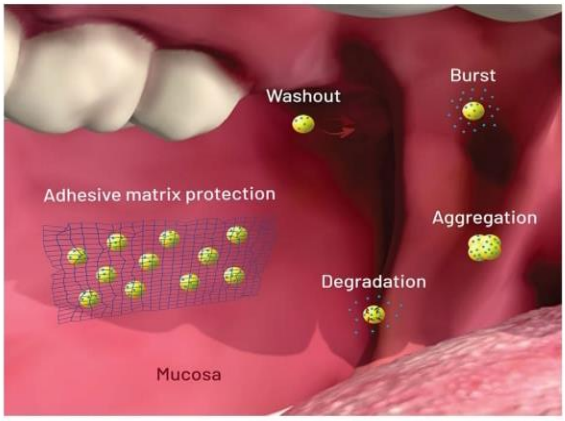
Penetration enhancer: Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Selection of the appropriate permeation enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. Permeation enhancers used for designing buccal patches must be non-irritant 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.



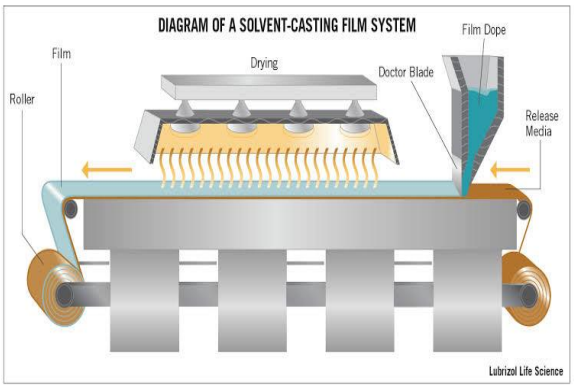
Manufacturing methods of buccal patches

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 for a laminate that is die-cut to form patches of the desired size and geometry.

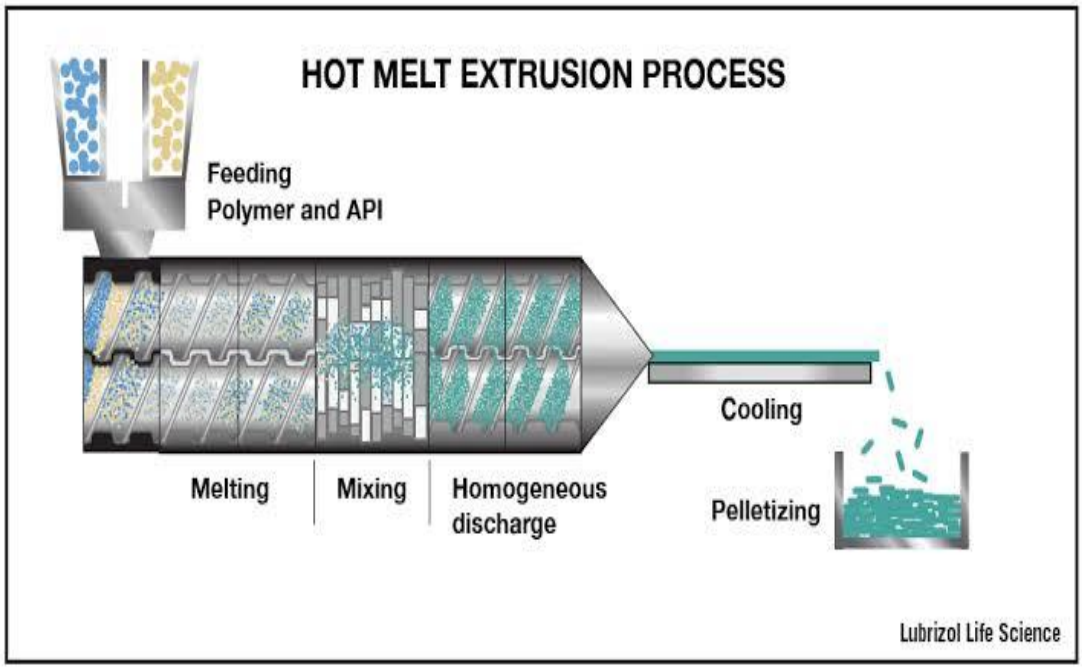
Figure 1



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.

Figure 1



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.

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.

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