MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM: A REVIEW
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ABSTRACT
Among the various routes of administration, oral route is the most suitable, convenient and widely accepted. Drug actions can be improved by developing new oral drug delivery systems such as the mucoadhesive buccal drug delivery system. Here the oral cavity is an attractive site for drug delivery due to ease of administration and avoids possible drug degradation in the gastrointestinal tract as well as first pass hepatic metabolism. Mucoadhesion is currently explained by six theories: electronic, adsorption, wettability, diffusion, fracture and mechanical. Several in vitro and in vivo methodologies are proposed for studying its mechanisms. The aim of present study was to review the mechanisms and theories involved in mucoadhesion, as well as to describe the most-used methodologies and polymers in mucoadhesive drug delivery systems.

KEYWORDS: Mucoadhesion, Bio-adhesion, Mucoadhesive systems, Mucoadhesive polymers, Drug delivery.

INTRODUCTION
Mucoadhesion has become an interesting topic for research over last two decades. This is due to its potential to optimize localized drug delivery by retaining the dosage form at its site of action or systemic delivery, by retaining the formulation in intimate contact with the absorption site. Mucoadhesive formulations are usually prepared with mucoadhesive polymers. These polymers are hydrophilic in nature, having limited solubility in other solvents forming high viscous liquid in water. These characteristics present challenges in the formulation development of mucoadhesive formulations. Also permeation enhancer enhances the absorption which has great appeal for systemic drug bioavailability. Among the various routes of drug delivery, oral drug delivery is most preferable route of drug administration due to ease of administration, patient compliance, flexibility in formulation. However in case of oral route there are several challenges such as first pass metabolism, enzymatic degradation within the gastrointestinal tract and poor pharmacological response. So there has been growing interest in the use of delivery of therapeutic agent through various transmucosal routes such as nasal, pulmonary, buccal, and
rectal and transdermal. These routes provide a therapeutic amount of drug to proper site in body to promptly achieve and then maintain the desired concentration. Consequently, other absorptive mucosa is considered as potential sire for drug administration. Transmucosal route offer distinct advantage over per oral route for systemic effect\textsuperscript{1,2}.

**Anatomy of oral cavity:**

![Fig.1: Schematic representation of the different linings of mucosa in mouth\textsuperscript{3}]

The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of mouth. The oral cavity is lined by relatively thick, dense and multilayered mucous membrane of highly vascularised nature. The mucous secreting region comprises soft palate, floor of mouth underside of tongue and labial and buccal mucosa which have normally non keratinized epithelium. The hard palate region is keratinized epidermis. Specialized zone consist of borders of lips and dorsal surface of tongue which is highly keratinized. The vascular drainage from oral mucosa is by lingual, facial and retromandibular veins. The veins open into the internal jugular vein and thus avoid first pass metabolism. As the stratum corneum may be potential barrier to mucosal penetration. The drugs are traditionally placed at the non keratinized sites like the buccal and sublingual regions\textsuperscript{3}.

**Overview of oral mucosa\textsuperscript{3,4,5}:**

![Fig.2: Structure of oral mucosa.]

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The oral mucosa consists of an outermost layer of stratified squamous epithelium, which is covered with mucous and consist of a stratum distendum, stratum filamentosum, and stratum suprabasale and stratum basale. The area below the basal lamina, covered with lamina propria and sub mucosa. The epithelium serves as the mechanical barrier that protects underlying tissues, where as the lamina propria provides a mechanical support and also carries the blood vessels and nerves. Some regions of oral mucosa are keratinized. The non keratinized region such as buccal mucosa is more permeable than the keratinized region\textsuperscript{3}.

The gingival and the hard palate are lined with a masticatory mucosa, where the epithelium has a cornified surface containing keratin. Keratin is found in the superficial cells of the epithelium, which become flattened and virtually devoid of organelles. Keratinized tissue may be subdivided into ortho-keratinized cells and Para-keratinized cells. In ortho-keratinized cells, a predominant granular layer is present, which is not present in Para-keratinized tissue cells. The labial buccal mucosa, floor of the mouth, soft palate and underside of tongue are lined with non-keratinized stratified squamous epithelium. The cells in these regions retain their nuclei and some cytoplasmic functions. The stratified squamous epithelia consist of a mitotically active basal cell layer, where the cells are shed from the surface of the epithelium. These regions represent the major absorption site in the oral cavity\textsuperscript{4}.

**Functions of mucus layer\textsuperscript{2}**

- The primary functions of mucus layer are
- They are protective in nature because of their hydrophobicity.
- It acts as barrier in tissue absorption of drug and other substrates.
- Mucus has strong adhesion properties and firmly binds to epithelial cell surface as continuous gel layer.
- Continuous secretion of mucus from goblet cells is necessary to compensate removal of mucus layer due to digestion, bacterial state.
- The mucus comprises of water (50%), glycolipid (0.5-5%), mineral salts (0.5-1%) and free proteins (0.5-1%)

**Mucin and Saliva\textsuperscript{6}:**
The mucosal tissues are further covered with mucus, which is negatively charged and contains large glycoprotein termed mucin. These contribute significantly to the viscoelastic nature of saliva and maintain a pH of 5.8-7.4. Mucin consists of protein core, rich in O-glycosylated serine and threonine, containing many helix-breaking proline residues. The salivary glands secreting
Mucus also synthesize saliva, which offer protection to the soft tissues from chemical and mechanical abrasions. The average thickness of salivary film in the mouth varies between 0.07 and 0.10 mm. Sustained adhesion of dosage form (tablet, patch) to the mucosa is an important first step to successful buccal delivery systems. The mean total surface area of the mouth has been calculated to be $214.7 \pm 12.98 \text{ cm}^2$. The teeth keratinized epithelium and nonkeratinized epithelium occupies about 20%, 50% and 30% of this surface area respectively.

**Table 1:** Oral epithelium characteristics

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Structure</th>
<th>Epithelial Thickness (µm)</th>
<th>Permeability</th>
<th>Residence Time</th>
<th>Blood (ml/min/cm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccal</td>
<td>Non keratinized</td>
<td>500-600</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>2.4</td>
</tr>
<tr>
<td>Sublingual</td>
<td>Non keratinized</td>
<td>100-200</td>
<td>Very good</td>
<td>Poor</td>
<td>0.97</td>
</tr>
<tr>
<td>Gingival</td>
<td>Keratinized</td>
<td>200</td>
<td>Poor</td>
<td>Intermediate</td>
<td>1.47</td>
</tr>
<tr>
<td>Palatal</td>
<td>Keratinized</td>
<td>250</td>
<td>Poor</td>
<td>Very good</td>
<td>0.89</td>
</tr>
</tbody>
</table>

**Mucoadhesion:**

Mucoadhesive drug delivery systems are the drug delivery systems which utilized the properties of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting the drug to particular region of the body for extended period of time. Bioadhesion is interfacial phenomenon in which two materials of which one is of biological nature are held together by interfacial forces. In case of polymer attached to the mucus layer of mucous membrane the term ‘mucoadhesion’ is used. Mucoadhesion can be defined as the ability of material (synthetic or biological) to adhere to a biological tissue for extended period of time. Oral route is the most commonly employed route for a lot number of drugs administered. Some drugs which are susceptible to highly acidic condition of stomach and posses high first pass metabolism, this route fails to attain bioavailability. To overcome these problems various mucoadhesive systems are designed which are given by other than oral route like buccal, nasal, vaginal.
Now days various newer researches are carried out on mucoadhesive drug delivery system. Various category of drugs like antihypertensive, antianginal, analgesic, anti-inflammatory, ophthalmic, hormonal in which mucoadhesive system are formulated.

**Mechanism of mucoadhesion:**

The mechanism of bioadhesion of number of macromolecules to the surface of mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promising diffusion of its chains within the mucus. Both attractive and repulsive forces arise, and for mucoadhesive to be successful, the attractive forces must dominate\(^8\). Thus the mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage (Fig.3).

![Fig.3: The two stages of mucoadhesion process.](image)

The first stage is contact stage which involves the contact between mucoadhesive and the mucous membrane with spreading and swelling of the formulation, results in deep contact with mucus layer. In case of vaginal or ocular formulations the delivery system is mechanically attached over the membrane. In case nasal route the deposition is promoted by aerodynamics of organ to which system is administered. While in gastrointestinal tract direct formulation attachment over the mucous membrane is not feasible. Peristaltic motion can contribute to this contact, as well as adhesion in esophagus can occur. There are some factors that may be responsible for the bioadhesion are peristaltic movement of gastrointestinal tract, Brownian movement, etc. if the particle approaches the mucous surface, it will come in contact with repulsive forces (osmotic pressure, electrostatic repulsion) and attractive forces (van der waals forces and electrostatic attraction). Therefore particle must overcome this repulsive barrier in order to make a good contact\(^9\)
The second stage is consolidation stage in which mucoadhesive materials are activated by moisture. Moisture plasticizes the system and allows the mucoadhesive molecule to break free and link up by weak van der Waals hydrogen bonds. The two theories explaining the stage are diffusion theory and dehydration theory. According to diffusion theory, mucoadhesive molecules and glycoprotein of mucus interact by interpretation of their chains and building of secondary bonds. Here both chemical and mechanical interactions are involved. For example, molecule with hydrogen bond building groups (-OH, -COOH) with anionic surface charge, high molecular weight, flexible chains and surface active properties, which results its spread throughout the mucus layer, can present mucoadhesive properties. According to dehydration theory, materials that are able to readily jellify in aqueous environment, when placed in contact with mucus can cause dehydration due to difference in osmotic pressure. The difference in concentration gradient draws the water into formulation till osmotic balance is reached. This process forms the mixture of formulation with mucus which results in increased contact time with mucous membrane. However, dehydration theory is not applicable for solid formulation or highly hydrated forms\textsuperscript{10}.

![Fig.4: Dehydration theory of mucoadhesion.](image)

**Mucoadhesion Theories\textsuperscript{11, 12,13,14}**

The various theories have been studied on the basis of physiochemical properties of bioadhesive material and polymer-polymer interaction. Although basis of mucoadhesion are still not understood.

**Electronic theory:**

This theory is based on fact that both mucoadhesive and biological materials possess opposite electrical charges. When these materials come into contact with each other, they transfer the
electrons leading to formation of double electronic layer at the interface, where attractive forces within this layer determines the mucoadhesive strength.

**Adsorption theory:**
In this theory primary and secondary chemical bonds of covalent and non covalent type are formed upon initial contact between the mucus and mucoadhesive polymer. The properties of polymer decide the formation of secondary chemical bond.

**Wetting theory:**
The wetting theory describes the ability of bioadhesive polymer to spread on biological surfaces. This theory applies to liquid system which present affinity to the surface in order to spread over it. This theory is based on measuring contact angle between two surfaces. Generally lower the contact angle grater is the affinity. To provide adequate spreadibility the contact angle should be zero or close to zero. Thus moderately wettable polymers have been shown to exhibit optimal adhesion to human endothelial cells.

![Fig.5: Schematic diagram showing influence of contact angle on bioadhesion.](image)

**Diffusion theory:**
According to this theory mucin and polymer chain penetrates each other to a sufficient depth to create a semi-permanent adhesive bond. The degree of penetration depends on diffusion coefficient, flexibility and nature of mucoadhesive chains, mobility and contact time of polymer chains. The depth of interpenetration required to produce an efficient bioadhesive bond lies in range 0.2-0.5 µm. in order diffusion to occur it is necessary that the components involved have good mutual solubility. Grater the structural similarity between bioadhesive and mucus better is the mucoadhesive bond.
Fracture theory:
This is the most accepted theory on the basis of mechanical measurement of mucoadhesion. It gives relation between the forces required for detachment of polymers from the mucus and strength of their adhesive bond. It is found that the work fracture is great when the network strands are longer or the degree of cross-linking is reduced.

Fig.7: Regions where the mucoadhesive bond ruptures can occur.

Mechanical theory:
According to this theory adhesion is due to the filling of irregularities on a rough surface by mucoadhesive liquid. This roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process. None of these theories alone could explain the phenomenon of mucoadhesion which can vary in different situations. However understanding of these mechanisms can help toward the development of new mucoadhesive products to certain extent.

Factors affecting mucoadhesion in the oral cavity:
Mucoadhesion depends on both bioadhesive polymer and medium in which the polymer will reside. The various factors affect mucoadhesive properties of polymers such as molecular weight, flexibility, hydrogen bonding capacity, cross linking density, charge, concentration and swelling of polymer.

**Polymer related factors:**

**Molecular weight:**

Generally at particular molecular weight there is maximum bioadhesion. Bioadhesive strength of polymer increases with molecular weight up to 100,000 and beyond this level there is no significant effect on bioadhesive strength. Size and configuration of polymer are important, as in case of polyethylene oxide adhesive strength increases even up to molecular weight 400,000 because of highly linear configuration of molecule.

**Concentration of active polymer:**

This factor is associated with development of strong adhesive bond with mucus and can be explained by polymer chain length available for penetration into mucus layer. When the concentration of polymer is too low, the interaction between polymer and mucus is unstable. So more concentrated polymer would result in longer penetrating chain length and better adhesion. However for each polymer there is critical concentration, above which the polymer produces an unperturbed state due to a significantly coiled structure. As a result chain penetration of polymer is reduced. Therefore higher concentration of polymer does not necessarily improve and in some cases actually diminish mucoadhesive properties. In case of solid dosage form such as tablets, higher the polymer concentration stronger is the bioadhesion.

**Flexibility of polymer chains:**

Bioadhesion starts with diffusion of the polymer chains in the interfacial region. Therefore polymer chains must have substantial degree of flexibility in order to achieve the desired entanglement with the mucus. The mobility and flexibility of polymer are related to their viscosity and diffusion coefficients. Cross-linking in water soluble polymer reduces the mobility of polymer chains. As polymer density increases due to cross-linking of molecule, the effective length of chain decreases and further mucoadhesive strength is decreased.

**Hydrogen bonding capacity:**

For mucoadhesion to occur desired polymer must have functional groups that are able to form hydrogen bonds. The flexibility of polymer is important to improve its hydrogen bonding
potential. Polymers such as poly (methacrylic acid), poly (vinyl alcohol) and their copolymers have good hydrogen bonding capacity.

**Cross linking density:**

The inverse relationship exists between degree of swelling at equilibrium and degree of cross-linking of polymer. Therefore as the density increases the diffusion of water in polymer network occurs at lower rate which in turn causes an insufficient swelling of polymer and decreases the rate of interpenetration between polymer and mucin.

**Charge:**

The nonionic polymers show smaller degree of adhesion as compare to anionic polymers. Some cationic polymers have superior mucoadhesive properties in neutral or slightly alkaline medium. In addition the high molecular weight polymers such as chitosan show good adhesive properties.

**Swelling:**

Hydration is necessary for mucoadhesive polymer to expand and create a proper macromolecular mesh of sufficient size and also induce mobility in polymer chains to enhance interpenetration process between polymer and mucin. Polymer swelling exposes the bioadhesive sites for hydrogen bonding, thus permits mechanical entanglement. However critical degree of hydration exist where optimum swelling and bioadhesion occurs.

**Environment related factors:**

**pH:**

pH was found to exert a significant effect on mucoadhesion as observed in studies of polyacrylic polymers cross linked with –COOH group. The pH of medium is determinant factor for degree of hydration of highly cross linked polyacrylic acid polymers and it will be increases between pH 4 and 5 and decreases more at alkaline pH.

**Applied strength:**

The solid bioadhesive system must need to apply a defined strength. The adhesion increases with applied strength or with duration of application. The pressure initially applied to mucoadhesive tissue contact site can affect the depth of interpenetration.

**Initial contact time:**

The extent of swelling and interpenetration of polymer chains is determined by initial contact time between mucoadhesive and mucus layer. The mucoadhesive strength increases with initial contact time. In case of mucoadhesive that used to be polymerized at the application sites the initial contact time is critical.
Swelling:
Swelling is related to both polymer and its environment. Interpenetration of chains is easier as polymer chains are disentangled and free of interaction. Swelling also depends on presence of water. When swelling is too great decrease in bioadhesion occur.

Physiological variables:
Mucin turnover:
The natural turnover of mucin molecules from mucus layer is important because of the two reasons. First, the mucin turnover is expected to limit the residence time of mucoadhesive on the mucus layer. Second the mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with mucoadhesive before they interact with mucus layer.

Disease states:
During the disease conditions such as common cold, ulcerative colitis, gastric ulcers, bacterial and fungal infections of female reproductive tract and inflammatory conditions of eye, the physiochemical properties of mucus changes. Mucoadhesive properties of delivery system should be checked under these conditions.

Different approaches of mucoadhesive drug delivery system:\(^{19}\):
Bioadhesion can be described as adhesion of artificial substances to biological substrates such as adhesion of polymer to skin or other soft tissue.
The mucosal layer lines number of regions of the body including gastrointestinal tract, urogenital tract, airway, ear, nose and eye. These represent potential sites for attachment of any bioadhesive system and hence, mucoadhesive drug delivery system include following.

- Buccal drug delivery system.
- Oral delivery system.
- Vaginal delivery system.
- Rectal delivery system.
- Nasal delivery system.
- Ocular delivery system.

Buccal drug delivery system:\(^{20}\):
Drug delivery via membranes of oral cavity can be subdivided as follows:

a) Sublingual delivery: The administration of drug is via sublingual mucosa to the systemic circulation.
b) **Buccal delivery**: The drug administered through the lining of cheek to the systemic circulation.

c) **Local delivery**: For treatment of conditions of oral cavity such as ulcer fungal conditions and periodontal diseases by application of bioadhesive system either to the palate, gingival or cheek. These sites differ for delivery in both structure and composition as well as in degree of permeability and therefore, also vary in their ability to retain a delivery system for a desired length of time.

**Advantages of buccal drug delivery**\(^{21}\):

- Ease of administration.
- Termination of therapy is easy.
- Permits localization of drug to the oral cavity for prolonged period of time.
- Can be administered to unconscious patient.
- Offers an excellent route to systemic delivery of drugs with high first pass metabolism thereby offering a great bioavailability.
- A significant reduction in dose can be achieved, therefore reduces dose dependant side effects.
- Drugs with poor bioavailability can be administered conveniently.
- Drugs which are unstable in acidic environment of the stomach or destroyed by enzymes or alkaline environment of the intestine can be administered by this route.
- This system does not require any activation for absorption.
- It allows for local modification of tissue permeability, inhibition of protease activity in immunogenic responses. Thus selective use of therapeutic agents like peptides, proteins and ionized species can be achieved.
- These can also administered to patients with nausea and vomiting or swallowing difficulty.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal or transdermal route.

**Limitations of buccal drug delivery**\(^{22}\):

- The drugs which irritate mucosa or have bitter or unpleasant taste or an obnoxious odour cannot be administered by this route.
- Drugs which are unstable at buccal pH cannot be administered by this route.
- Only drugs with small dose requirement can be administered.
Only drugs absorbed by passive diffusion can be administered by this route.

Eating or drinking may become restricted.

There is possibility of swallowing of the tablet.

Sometime they show unpredictable bioavailability. Relatively low permeability for most drugs.

**Basic components of buccal drug delivery system:**

The basic components of buccal drug delivery system are:

- Drug substance.
- Bioadhesive polymer.
- Backing membrane.
- Permeation enhancers.

**Drug substance:**

Before formulating buccoadhesive drug delivery system, one has to decide whether the intended action is for rapid/ prolonged release and for local/systemic effect. The selection of suitable drug for the design of buccoadhesive drug delivery system should be based on pharmacokinetic properties.

**Characteristics of drug substance:**

- The drug should have following characteristics.
- The conventional single dose of the drug should be small.
- The drug absorption should be passive when given orally.
- The drugs with biological half life of 2-8 hours are good candidates for controlled drug delivery.
- Tmax of the drug shows wider fluctuation or higher values when given orally.
- Through oral route drug may exhibit first pass effect or presystemic drug elimination.

**Buccoadhesive polymer:**

The important step in the formulation of buccoadhesive dosage form is the selection and characterization of appropriate bioadhesive polymer in the formulation. Polymers are also used in matrix devices in which the drug is embedded in the polymer matrix, which controls the duration of release of drugs. The drug is released in to the mucous membrane by means of rate controlling layer or core layer. Bioadhesive polymers which adhere to the mucin are effective and lead to significant improvement in the oral drug delivery.

**Characteristics of an ideal mucoadhesive polymer:**
- It should be inert and compatible with environment
- The polymer and its degradation products should be non-toxic.
- It should adhere quickly to moist tissue surface.
- The polymer must not decompose on storage or during the shelf life of dosage form.
- The polymer should be economic and easily available in the market.
- It should allow easy incorporation of drug in to the formulation.

Table 2: Some oral bioadhesive polymers

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Categories</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Natural</td>
<td>Agarose, Chitosan, Gelatin, Various gums (guar, xanthan, pectin, alginate).</td>
</tr>
<tr>
<td></td>
<td>Synthetic</td>
<td>Cellulose derivatives- CMC, HEC, HPC, HPMC, Polymethacrylate, Copolymer of acrylic acid, PEG.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Polyacrylic acid derivative</strong>- CP, PC, PAA, Polymethacrylate, Copolymer of acrylic acid, PEG.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Other</strong>- PVP, PVA, Polyoxyethylene, Thiolated polymer.</td>
</tr>
<tr>
<td>Aqueous solubility</td>
<td>Water soluble</td>
<td>CP, HEC, HPC, HPMC, PAA, Sodium CMC.</td>
</tr>
<tr>
<td></td>
<td>Water Insoluble</td>
<td>Chitosan, EC, PC.</td>
</tr>
<tr>
<td>Charge</td>
<td>Cationic</td>
<td>Aminodextran, Chitosan, Trimethylated Chitosan.</td>
</tr>
<tr>
<td></td>
<td>Anionic</td>
<td>Chitosan, EDTA, CP, CMC, PAA, Pectin.</td>
</tr>
<tr>
<td></td>
<td>Non-ionic</td>
<td>Hydroxyethyl starch, HPC, PVP, PVA.</td>
</tr>
<tr>
<td>Potential bioadhesive forces</td>
<td>Covalent</td>
<td>Cyanoacrylate.</td>
</tr>
<tr>
<td></td>
<td>Hydrogen</td>
<td>Acrylates, Methacrylic acid, CO, PC, PVA.</td>
</tr>
<tr>
<td></td>
<td>Electrostatic interaction</td>
<td>Chitosan.</td>
</tr>
</tbody>
</table>

**Backing membrane**:  
Backing membrane plays very vital role in attachment of bioadhesive devices to the mucus membrane. The material used as backing membrane should be inert, and impermeable to the
drug and penetration enhancer. Such a membrane on buccal bioadhesive patches prevents the drug loss and offers better patient compliance. The commonly used materials in backing membrane include carbopol, magnesium stearate, HPMC, HPC, CMC.

**Permeation enhancers**²⁵:

Substances that facilitate the permeation through buccal mucosa are called as permeation enhancers. Selection and efficiency of enhancer depends on physiochemical properties of the drug, site of administration, nature of vehicle and other excipients.

Though buccal administered drugs bypass hepatic first pass metabolism and degradation in stomach, their bioavailability is relatively small. Particularly for peptides the co-administration of permeation enhancer is essential. The different techniques can be applied to obtain enhanced absorption².

- Improvement of drug absorption via tissue by co-administration of permeation enhancer.
  These compounds may alter the drug properties (by complex formation) or reduce the barrier across the mucosa layer (By pretending the desmosomes fluidization of intracellular liquids).
- By minimizing the degradation of drug during transport across the tissue (enzyme inhibitors).

**Mechanism of action of permeation**⁶,⁹:

a) Changing mucus rheology:
   By reducing the viscosity of mucus and saliva overcome this barrier.

b) Increasing the fluidity of lipid bilayers membrane:
   Disturb the intracellular lipid packing by interaction with either lipid packing or protein components.

c) Acting on the components at tight junctions:
   By inhibiting various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier.

d) Increasing the thermodynamic activity of drug:
   Some enhancers increases the solubility of drug there by alters the partition coefficient.
**Table 3: Mucosal penetration enhancers**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surfactants</strong></td>
<td>Anionic: Sodium lauryl sulphate, Sodium laurate.</td>
</tr>
<tr>
<td></td>
<td>Cationic: Cetylpyridinium chloride.</td>
</tr>
<tr>
<td></td>
<td>Nonionic: Poloxamer, Span, Tween</td>
</tr>
<tr>
<td><strong>Bile salts</strong></td>
<td>sodium glycodeoxycholate, Sodium taurocholate.</td>
</tr>
<tr>
<td><strong>Fatty acids</strong></td>
<td>Oleic acid, Caprylic acid.</td>
</tr>
<tr>
<td><strong>Cyclodextrins</strong></td>
<td>a-, b-, g-cyclodextrins, methylated b- cyclodextrins.</td>
</tr>
<tr>
<td><strong>Chelators</strong></td>
<td>EDTA, Sodium citrate, Polyacrylates.</td>
</tr>
<tr>
<td><strong>Positively charged polymers</strong></td>
<td>Chitosan, Trimethyl chitosan</td>
</tr>
<tr>
<td><strong>Cationic compound</strong></td>
<td>Poly L-arginine, L- lysine</td>
</tr>
</tbody>
</table>

**Buccal formulation:**

- The size of the delivery system varies with the type of formulation, i.e. a buccal tablet may be approximately 5-8 mm in diameter, whereas a flexible buccal patch may be as large as 10-15 cm² in area.
- Mucoadhesive buccal patches with a surface area of 1-3 cm² are most acceptable.
- The shape of delivery system may also vary, although for buccal drug administration, an ellipsoidal shape is most accepted.
- The thickness of the delivery device is usually restricted to only a few mm.
- The location of delivery device is also important.
- The maximum duration of buccal drug retention and absorption is approximately 4-6 hr. because food and/or liquid intake may require removal of delivery device.
- The physiology of mucus membrane under disease condition needs to be considered.

**Types of buccal formulations:**

- Buccal tablets.
- Buccal patches and films.
- Buccal semisolids (ointments and gels).
- Buccal powder.
a) **Buccal tablets**\(^{27}\):

- Adhesive tablets are held between the gum and cheek.
- Tablets are generally flat and elliptical or capsule shaped.
- Lozenges and troches are other types of tablets used in oral cavity intended to exert a local effect in the mouth or throat.
- Buccoadhesive tablets may be monolithic or bilaminated. Monolithic is multidirectional release while bilayerd contain core layer and backing layer.
- Backing layer may be of water insoluble material like Ethyl cellulose or hydrogenated castor oil or may be polymeric coating layer.
- Backing layer avoids sticking of the tablet to the finger during application.

**Limitations of buccal tablets:**

- The small surface of contact with mucosa.
- The lack of physical flexibility. In case of certain drugs it is difficult to get high release rate.
- The extent and frequency of contact may cause irritation.

**Evaluation of buccal tablet**\(^{28}\):

- In vitro swelling rate and bioadhesion studies.
- In vitro surface pH studies.
- In vitro drug release studies.
- In vitro permeation studies.
- In vitro mucoadhesion strength.
- In vitro residence time.
- In vivo release studies.
- Stability studies in human saliva.
- Ex vivo mucoadhesion time.
- Ex vivo mucoadhesion force.
- Ex vivo transmucosal permeation studies.

b) **Buccal patches and films**\(^{4}\):

Buccal patch consist of two poly laminates or multilayered thin film round or oval as consisting of bioadhesive polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bioadhesive films are formulated by incorporating drug in alcohol solution of bioadhesive polymer.
Example:

- Isosorbide dinitrate in the form of unidirectional erodible buccal film are developed and characterized for improving bioavailability.
- Buccal film of salbutamol sulphate and terbutalin sulphate for the treatment of asthma.

**c) Buccal semisolid dosage forms**

A buccal semisolid dosage form consists of finely powdered natural or synthetic polymer dispersed in a polyethylene or in aqueous solution.

**Example:** Gels, Ointments.

- Gels are usually clear, transparent, semisolids containing solubilised active substances.
- Vehicle containing therapeutic agents are especially useful for application to mucus membrane and ulcerated or burned tissues, as their high water content reduces irritancy.
- Due to plastic rheological property they remain to the site of application for sufficient duration before they washed out.
- In comparison to solutions, gels can significantly prolong residence time and hence improve bioavailability.
- Orabase is one of the important original oral mucosal adhesive delivery system consists of finely ground pectin, gelatin and sodium carboxy methyl cellulose dispersed in a poly(ethylene) and a mineral oil gel base, which can maintain at its site of application for 15-150 minutes.

**d) Buccal powder dosage forms**

Buccal bioadhesive powder dosage forms are a mixture of bioadhesive polymers and drug which are sprayed onto the buccal mucosa. A significance increase in residence time relative to oral solutions was observed.

**CONCLUSION**

Mucoadhesive buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drug as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. However, the need of safe and effective buccal permeation and absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery. The safety and efficacy of current treatments may be improved if their delivery rates, biodegradation, and site specific targeting can be predicted, monitored and controlled. The buccal mucosa is a promising delivery route for drugs that need to avoid the gastrointestinal tract due to degradation by the gastric pH, intestinal enzymes or due to
a substantial hepatic first pass effect. With the great influx of new molecules stemming from
drug research, mucoadhesive systems may play an increasing role in the development of new
pharmaceuticals.

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