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REVIEW ON BUCCAL DRUG DELIVERY SYSTEM

Appala Mavya Sri* and V.Saikishore

Department of pharmaceutics, Bapatla college of Pharmacy, Bapatla - 522101, India.

Abstract:

The buccal area of the oral mucosa delivers an elegant channel of systemic medication distribution within the mouth mucosa. Drugs are delivered via oral mucosal layer, that has a higher first-pass metabolism and degrades in gastrointestinal tract. The medication is immediately transmitted via the systemic circulation via the buccal drug delivery mechanism, which allows for painless administration, quick enzymatic action, high bioavailability, and reduced liver metabolism. The drug delivery system helps the drug to remain at the same place of application longer for once or twice daily dosing. For some drugs, the alternate way of administration results in novel methods of action as opposed to the above-said procedure. The characteristics of the oral mucosa as well as physicochemical properties of the drug pose as a hindrance to the oral mucosal administration of some drugs. Commercial availability of drug is restricted, although most of the drugs are qualitatively assessed for oral transmucosal delivery. This review paper provides a comprehensive overview of the oral mucosa, mucoadhesion, variables influencing the whole process, assessment methodologies, and how to eliminate obstacles when formulating buccal drug delivery formulations.

Keywords: Buccal mucosa, Bucoadhesion, Transmucosal route, Diffusion

Corresponding author:

Appala Mavya Sri,

Department of pharmaceutics,

Bapatla college of Pharmacy, Bapatla - 522101, India.

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INTRODUCTION:

Among the various transmucosal routes, buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability [1].

Buccal mucosal structure

Buccal region is part of the mouth bounded anteriorly and laterally by the lips and the cheeks, posteriorly and medially by the teeth and/or gums, and above and below by the reflections of the mucosa from the lips and cheeks to the gums. Numerous racemose, mucous, or serous glands are present in the submucous tissue of the cheeks. The buccal glands are placed between the mucous membrane and buccinator muscle: they are similar in structure to the labial glands, but smaller. About five, of a larger size than the rest, are placed between the masseter and buccinators muscles around the distal extremity of the parotid duct; their ductsopen in the mouth opposite the last molar tooth. They are called molar glands. Maxillary artery supplies blood to buccal mucosa and blood flow is faster and richer (2.4ml/min/cm^2) than that in the sublingual, gingival and palatal regions, thus facilitates passive diffusion of drug molecules across the mucosa. The thickness of the buccal mucosa is measured to be 500–800 μm and is rough textured, hence suitable for retentive delivery systems. The turnover time for the buccal epithelium has been estimated at 5–6 days· Buccal mucosa composed of several layers of different cells as shown in Fig. 1. The epithelium is similar to stratified squamous epithelia found in rest of the body and is about 40–50 cell layers thick. Lining epithelium of buccal mucosa is the nonkeratinized stratified squamous epithelium that has thickness of approximately 500–600 μm and surface area of 50.2 cm^2. Basement membrane, lamina propria followed by the submucosa is present below the epithelial layer. Lamina propria is rich with blood vessels and capillaries that open to the internal jugular vein. The primary function of buccal epithelium is the protection of the underlying tissue. In nonkeratinized regions, lipid-based permeability barriers in the outer epithelial layers protect the underlying tissues against fluid loss and entry of potentially harmful environmental agents such as antigens, carcinogens, microbial toxins and enzymes from foods and beverages [2].

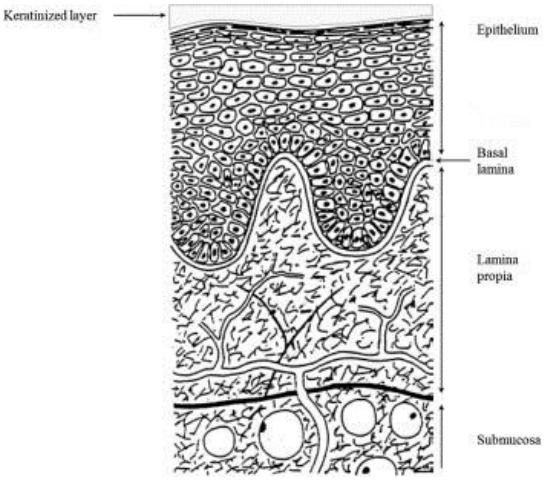

Figure 1: Structure of Buccal mucosa

Absorption pathways:

Studies with microscopically visible tracers such as small proteins and dextrans suggest that the major pathway across stratified epithelium of large molecules is via the intercellular spaces and that there is a barrier to penetration as a result of modifications to the intercellular substance in the superficial layers. However, rate of penetration varies depending on the physicochemical properties of the molecule and the type of tissue being traversed. This has led to the suggestion that materials uses one or more of the following routes simultaneously to cross the barrier region in the process of absorption, but one route is predominant over the other depending on the physicochemical properties of the diffusion[3].

➢ Passive diffusion

◦ Transcellular or intracellular route (crossing the cell membrane and entering the cell)

◦ Paracellular or intercellular route (passing between the cells)

➢ Carrier mediated transport

➢ Endocytosis

The flux of drug through the membrane under sink condition for paracellular route can be written as Eq. (1)

$$J_p = \frac{D_p \varepsilon}{h_p} C_d$$

Where, D_p is diffusion coefficient of the permeate in the intercellular spaces, h_p is the path length of the paracellular route, ε is thevarea fraction of the paracellular route and C_d is the donor drug concentration

Similarly, flux of drug through the membrane under sink condition for transcellular route can be written as Eq. (2).

$$J_c = \frac{(1-\varepsilon)D_c K_c}{h_c} C_d$$

Where, K_c is partition coefficient between lipophilic cell membrane and the aqueous phase, D_c is the diffusion coefficient of the drug in the transcellular spaces and h_c is the path length of the transcellular route.

In very few cases absorption also takes place by the process of endocytosis where the drug molecules were engulfed by the cells. It is unlikely that active transport processes operate within the oral mucosa; however, it is believed that acidic stimulation of the salivary glands, with the accompanying vasodilatation, facilitates absorption and uptake into the circulatory system. The absorption potential of the buccal mucosa is influenced by the lipid solubility and molecular weight of the diffusant. Absorption of some drugs via the buccal mucosa is found to increase when carrier pH is lowered and decreased with an increase of pH[9]. However, the pH dependency that is evident in absorption of ionizable compounds reflects their partitioning in to the epithelial cell membrane, so it is likely that such compounds will tend to penetrate transcellularly. Weak acids and weak bases are subjected to pH-dependent ionization. It is presumed that ionized species penetrate poorly through the oral mucosa compared with non-ionized species. An increase in the amount of non-ionized drug is likely to increase the permeability of the drug across an epithelial barrier, and this may be achieved by a change of pH of the drug delivery system. It has been reported that pH has effect on the buccal permeation of drug through oral mucosa. The diffusion of drugs across buccal mucosa was not related to their degree of ionization as calculated from the Henderson–Hasselbalch equation and thus it is not helpful in the prediction of membrane diffusion of weak acidic and basic drug. In general, for peptide drugs, permeation across the buccal epithelium is thought to be through paracellular route by passive diffusion. Recently, it was reported that drugs that have a monocarboxylic acid residue could be delivered into systemic circulation from the oral mucosa via its carrier. The permeability of oral mucosa and the efficacy of penetration enhancers have been investigated in numerous *in-vivo* and *in-vitro* models. Various kinds of diffusion cells, including continuous flow perfusion chambers, Using chambers, Franz cells and Grass–Sweetana, have been used to determine the permeability of oral mucosa. Cultured epithelial cell lines have also been developed as an *in- vitro* model for studying drug transport and metabolism at biological barriers as well as to elucidate the possible mechanisms of action of penetration enhancers. Recently, TR146 cell culture model was suggested as a valuable *in-vitro* model of human buccal mucosa for permeability and metabolism studies with enzymatically labile drugs, such as leu-enkefalin, intended for buccal drug delivery.

Barriers to penetration across buccal mucosa

The barriers such as saliva, mucus, membrane coating granules, basement membrane etc retard the rate and extent of drug absorption through the buccal mucosa. The main penetration barrier exists in the outermost quarter to one third of the epithelium [4].

Basement membrane

Although the superficial layers of the oral epithelium represent the primary barrier to the entry of substances from the exterior, it is evident that the basement membrane also plays a role in limiting the passage of materials across the junction between epithelium and connective tissue. A similar mechanism appears to operate in the opposite direction. The charge on the constituents of the basal lamina may limit the rate of penetration of lipophilic compounds that can traverse the superficial epithelial barrier relatively easily.

Mucus

The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness varies from 40 µm to 300 µm. Though the sublingual glands and minor salivary glands contribute only about 10% of all saliva, together they produce the majority of mucus and are critical in maintaining the mucin layer over the oral mucosa. It serves as an effective delivery vehicle by acting as a lubricant allowing cells to move relative to one another and is believed to play a major role in adhesion of mucoadhesive drug delivery systems. At buccal pH; mucus can form a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer. Mucus molecules are able to join together to make polymers or an extended three-dimensional network. Other substances such as ions, protein chains, and enzymes are also able to modify the interaction of the mucus molecules and, as a consequence, their biophysical properties. Mucus is composed chiefly of mains and inorganic salts suspended in water. Mucins contain approximately 70–80% carbohydrate, 12–25% protein and up to 5%

ester sulphate. The dense sugar coating of mucins gives them considerable water-holding capacity and also makes them resistant to proteolysis, which may be important in maintaining mucosal barriers [5].

Buccal adhesive polymers

Mucoadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, numerous hydrogen bond-forming groups, flexibility for interpenetration with mucus and epithelial tissue, and visco-elastic properties [6].

Ideal characteristics

- Polymer and its degradation products should be non-toxic, non-irritant, and free from leachable impurities.
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
- Should possess peel, tensile and shear strengths at the bioadhesive range.
- Polymer must be easily available and its cost should not be high.
- Should show bioadhesive properties in both dry and liquid state.
- Should demonstrate local enzyme inhibition and penetration enhancement properties.
- Should demonstrate acceptable shelf life.
- Should have optimum molecular weight.
- Should possess adhesively active groups.
- Should have required spatial conformation.
- Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- Should not aid in development of secondary infections such as dental caries.

Physiological considerations

Physiological considerations such as texture of buccal mucosa, thickness of the mucus layer, its turn over time, effect of saliva and other environmental factors are to be considered in designing the dosage forms. Saliva contains moderate levels of esterases, carbohydrases, and phosphatases that may degrade certain drugs. Although saliva secretion facilitates the dissolution of drug, involuntary swallowing of saliva also affects its bioavailability. Hence development of unidirectional release systems with backing layer results high drug bioavailability [7].

Pharmacological considerations

Drug absorption depends on the partition coefficient of the drugs. Generally lipophilic drugs absorb through the transcellular route, where as hydrophilic drugs absorb through the paracellular route. Chemical modification may increase drug penetration through buccal mucosa. Increasing nonionized fraction of ionizable drugs increases drug penetration through transcellular route. In weakly basic drugs, the decrease in pH increases the ionic fraction of drug but decreases its permeability through buccal mucosa. Residence time and local concentration of the drug in the mucosa, the amount of drug transported across the mucosa in to the blood are the responsible factors for local or systemic drug delivery. Optimization by a suitable formulation design hastens drug release from the dosage form and taken up by the oral mucosa[8].

Muco/bioadhesion

Bioadhesion is the phenomenon between two materials, which are held together for extended periods of time by interfacial forces. It is generally referred as bioadhesion when interaction occurs between polymer and epithelial surface; mucoadhesion when occurs with the mucus layer covering a tissue. Generally bioadhesion is deeper than the Mucoadhesion.

Bio/Mucoadhesive forces

The common nature of all adhesive events, interfacial phenomena and forces that are involved in bioadhesion are strongly related to those considered in classical colloid and surface science. Intermolecular forces are electromagnetic forces which act between molecules or between widely separated regions of a macromolecule. These are fundamentally electrostatic interactions or electrodynamic interactions. Such forces may be either attractive or repulsive in nature. They are conveniently divided into two classes: short-range forces, which operate when the centers of the molecules are separated by 3 angstroms or less and long-range forces, which operate at greater distances. Generally, if molecules do not tend to interact chemically, the short-range forces between them are repulsive. These forces arise from interactions of the electrons associated with the molecules and are also known as exchange forces. Molecules that interact chemically have attractive exchange forces; these are also known as valence forces.

Mechanical rigidity of molecules and effects such as limited compressibility of matter arise from repulsive exchange forces. Long-range forces, or van der Waal's forces as they are also called, are attractive and account for a wide range of physical phenomena, such as friction, surface tension, adhesion and cohesion of liquids and solids, viscosity, and the discrepancies between the actual behavior of gases and that predicted by the ideal gas law [8].

Many theories have been proposed to explain the forces that underpin bioadhesion[9]. They are;

Electronic theory
According to this theory, electron transfer occurs upon contact of an adhesive polymer with a mucus glycoprotein network because of differences in their electronic structures. This results in the formation of an electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

Adsorption theory
According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces are:

- Primary chemical bonds of covalent nature.
- Secondary chemical bonds having many different forces of attraction including electrostatic forces, Vander wall forces, and hydrogen and hydrophobic bonds.

Wetting theory
This theory describes the ability of mucus to spread and develop intimate contact with its corresponding substrate which is one important factor in bond formation. The wetting theory uses interfacial tensions to predict spreading and inturn adhesion.

Diffusion theory
According to this theory the polymer chains and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus depends on the diffusion coefficient and the time of contact. The diffusion coefficient, in turn, depends on the value of molecular weight between cross-links and decreases significantly as the linking density increases.

Fracture theory
This theory analyzes the forces required to separate two surfaces after adhesion. The maximum tensile stress produced during detachment can be determined by dividing the maximum force of detachment by the total surface area involved in the adhesive interaction. It does not require measuring entanglement, diffusion or interpretation of polymer chains.

However, there is yet to be a clear explanation. As bioadhesion occurs between inherently different mucosal surfaces and formulations that are solid, semisolid and liquid, it is unlikely that a single, universal theory will account for all types of adhesion observed. In biological systems it must be recognized that, owing to the amphiphilicity of many biological macromolecules, orientation effects can often occur at interfaces. These are crucially important and have infact been reported to be so dramatic as to change overall long-range interactions from being purely repulsive to their becoming attractive. For any type of charged surface, such as biosurfaces, it is common to distinguish between pure electrostatic repulsive forces, which oppose adhesion, and attractive forces, which, if the surfaces come close enough, will strive to bring the interacting bodies together. This balanced relationship between repulsive and attractive interactions is expressed in the Deryagin, Landau, Verwey and Overbeek (DLVO) theory. In biological systems, interactions can be more complex, as they often take place in high ionic strength aqueous media and in the presence of macromolecules. Therefore electrostatic contributions may be less important, at least at long range, in favor of force components such as steric forces, hydrophobic interactions, and hydration forces.

Factors affecting bio/Mucoadhesion
Numerous studies have indicated that there is certain molecular weight at which bioadhesion is optimum. The optimum molecular weight for the maximum bioadhesion depends on the type of polymers. It dictates the degree of swelling in water, which in turn determines interpenetration of polymer molecules within the mucus. It seems that the bioadhesive force increases with the molecular weight up to 100,000 and beyond this level there is not much effect. For the best bioadhesion to occur, the concentration of polymer must be at optimum. Flexibility of polymer chain is also important for interpenetration and entanglement. As water-soluble polymers become cross-linked, the mobility of the individual polymer chain decreases. As the cross linking density increases, the effective length of the chain, which can penetrate into the mucus layer, decreases even further and mucoadhesive strength is reduced.

Swelling is not only related to the polymer itself, and also to its environment. Interpenetration of chains is easier as polymer chains are disentangled and free of interactions. Swelling depends both on polymer

concentration and the presence of water. When swelling is too great, a decrease in bioadhesion occurs[10].

The duration of adhesion depends on the amount of water at the interface. Excessive water reduces the duration of adhesion. However the magnitude of this change is not the same for all the materials. It is believed that faster the rate of absorption of water, the shorter is the time required for the material to obtain initial adhesion and maximum adhesive strength. But rapid water absorbency may cause the shortening of the duration of adhesion .

Developments in buccal adhesive drug delivery

Retentive buccal mucoadhesive formulations may prove to be an alternative to the conventional oral medications as they can be readily attached to the buccal cavity retained for a longer period of time and removed at any time[11]. Buccal adhesive drug delivery systems using matrix tablets, films, layered systems, discs, microspheres, ointments and hydrogel systems has been studied and reported by several research groups. However, limited studies exist on novel devices that are superior to those of conventional buccal adhesive systems for the delivery of therapeutic agents through buccal mucosa. A number of formulation and processing factors can influence properties and release properties of the buccal adhesive system. There are numerous important considerations that include biocompatibility (both the drug/device and device/environment interfaces), reliability, durability; environmental stability, accuracy and permeability are to be considered while developing such formulations. While biocompatibility is always an important consideration, other considerations vary in importance depending on the device application. Bioadhesive formulations designed for buccal application should exhibit suitable rheological and mechanical properties, including pseudoplastic or plastic flow with thixotrophy, ease of application, good spreadability, appropriate hardness, and prolonged residence time in the oral cavity. These properties may affect the ultimate performance of the preparations and their acceptance by patients[12].

An ideal buccal adhesive system must have the following properties:

✓ Should adhere to the site of attachment for a few hours,

✓ Should release the drug in a controlled fashion,

✓ Should provide drug release in an unidirectional way toward the mucosa,

✓ Should facilitate the rate and extent of drug absorption.

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