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A Review on Oral Mucosal Drug Delivery System

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Buccal controlled drug delivery system has been developed since the environment of the oral cavity provides potential sites for drug delivery. The acid hydrolysis and first pass effects can be avoided. The release of drug can be affected by continuous secretion of saliva. The mucin film exists in oral mucosa offers an opportunity to develop mucoadhesive system, which retain at absorption site for prolonged time by mucoadhesive binding. The administration of drugs by the buccal route has several advantages over per oral administration such as QUICK ACTION, improved patient compliance particularly with pediatric & geriatric patient. It is the objective of this article to review the oral mucosal drug delivery by discussing briefly the structural feature of mucosa as drug delivery such as buccoadhesive film & tablet, medicated chew gum, fast dissolving tablet, film & capsule etc.

Keyword: Buccal Drug Delivery, NDDS, Quick Action, Absorption via buccal mucosa

INTRODUCTION:

A drug can be administered via a many different routes to produce a systemic pharmacological effect. The most common method of drug administration is via per oral route in which the drug is swallowed and enters the systemic circulation primarily through the membrane of the small intestine. The oral route of drug administration is the most important method of administering drugs for systemic effect. The parenteral route is not routinely used for self-administration of medication. It is probable that at least 90 % of all drugs used to produce systemic effects are administered by the oral route.

Absorption of drugs after oral administration may occur at the various body sites between the mouth

and rectum. In general, the higher up a drug is absorbed along the alimentary tract, the more rapid will be its action, a desirable feature in most instances. A drug taken orally must withstand large fluctuation in pH as it travels along the gastrointestinal tract, as well as resist the onslaught of the enzymes that digest food and metabolism by micro flora that live there. It is estimated that 25% of the population finds it difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by their doctor resulting in high incidence of non-compliance and ineffective therapy. Difficulty is experienced in particular by pediatrics and geriatric patients, but it also applies to people who are ill bedridden and to those active working patient who are busy or travelling, especially those who have no access to water. In these cases oral mucosal drug delivery is most preferred.

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It has been known for centuries that buccal and sublingual administration drug solutes are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa and transported through the facial veins, internal jugular vein, and braciocephalic vein and are then drained into the systemic circulation. Therefore the buccal and sublingual routes of administration can be utilized to bypass the hepatic first-pass elimination of drugs. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable. The oral cavity is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply and the virtual lack of langerhans cells makes the oral mucosa tolerant to potential allergens.

Structural Features of Oral Mucosa:

Buccal mucosa Structure: The total area of the oral cavity is about 100cm^2 ¹. Out of this about one third is the buccal surface, which is lined with an epithelium of about 0.5mm thickness (**Fig. 1**). 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 glucosylceramides². Buccal membrane has numerous elastic fibers 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 jugular ducts. The oral mucosal surface is constantly washed by the saliva (daily turn out is about 0.5 to 2 liters). 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.

Permeability: The oral mucosa in general is somewhat leaky epithelia intermediate between

that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin³. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa. In general, the permeability's of the oral mucosa decrease in the order of sublingual greater than buccal and buccal greater than palatal⁴. This rank order is based on the relative thickness

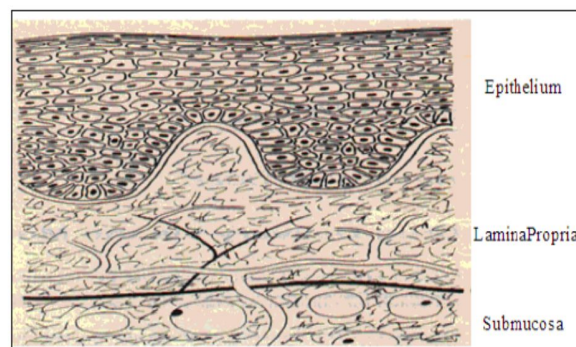


FIG 1: STRUCTURE OF THE ORAL MUCOSA

and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized. It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called 'membrane coating granules' (MCG)⁵. When cells go through differentiation, MCGs start forming and at the apical cell surfaces they fuse with the plasma membrane and their contents are discharged into the intercellular spaces at the upper one third of the epithelium. This barrier exists in the outermost $200\mu\text{m}$ of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase⁶ and lanthanum nitrate⁷. When applied to the outer surface of the epithelium, these tracers penetrate only through outermost layer or two of cells. When applied to the sub mucosal surface, they permeate up to, but not into, the outermost cell layers of the epithelium. According to these results, it seems

apparent that flattened surface cell layers present the main barrier to permeation, while the more isodiametric cell layers are relatively permeable. In both keratinized and non-keratinized epithelia, the limit of penetration coincided with the level where the MCGs could be seen adjacent to the superficial plasma membranes of the epithelial cells. Since the same result was obtained in both keratinized and non-keratinized epithelia, keratinization by itself is not expected to play a significant role in the barrier function⁶. The components of the MCGs in keratinized and non-keratinized epithelia are different, however⁸. The MCGs of keratinized epithelium are composed of lamellar lipid stacks, whereas the non-keratinized epithelium contains MCGs that are non-lamellar. The MCG lipids of keratinized epithelia include sphingomyelin, glucosylceramides, ceramides, and other nonpolar lipids, however for non-keratinized epithelia, the major MCG lipid components are cholesterol esters, cholesterol, and glycosphingolipids⁸. Aside from the MCGs, the basement membrane may present some resistance to permeation as well, however the outer epithelium is still considered to be the rate limiting step to mucosal penetration. The structure of the basement membrane is not dense enough to exclude even relatively large molecules.

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 another⁹. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems¹⁰. In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized mucus secreting cells like the goblet cells, however in the oral mucosa; mucus is secreted by the major and minor salivary glands as part of saliva^{9,11}. Up to 70% of the total mucin

found in saliva is contributed by the minor salivary gland^{9, 11}. At physiological pH the mucus network carries a negative charge (due to the sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer¹². Another feature of the environment of the oral cavity is the presence of saliva produced by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals. It allows for the continuous mineralization of the tooth enamel after eruption and helps in re-mineralization of the enamel in the early stages of dental caries¹³. Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus, and the degree of stimulation^{9, 11}. 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 liters 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 to

permeation 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.

Promoting buccal absorption: Absorption enhancers:

Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates. These may act by a number of mechanisms, such as increasing the fluidity of the cell membrane, extracting inter/intracellular lipids, altering cellular proteins or altering surface mucin. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labeled dextrans across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism.

Prodrugs: Hussain *et al.*, delivered opioid agonists and antagonists in bitter less prodrug forms and found that the drug exhibited low bioavailability as prodrug. Nalbuphine and naloxone bitter drugs, when administered to dogs via the buccal mucosa, causes excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in prodrug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds, which is generally 5% or less¹².

pH: Shojaei *et al.*, evaluated permeability of acyclovir at pH ranges of 3.3 to 8.8, and in the presence of the absorption enhancer, sodium glycocholate. The in vitro permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at

both pH extremes (pH 3.3 and 8.8), as compared to the mid-range values (pH 4.1, 5.8, and 7.0)¹².

Buccal mucosa-site for drug delivery:

Controlled drug delivery systems specifically designed for buccal cavity, where the drug releases in a controlled manner. The drug can be administered for local or systemic action. These systems are generally based on the polymers including bioadhesive polymers.

TABLE 1: LIST OF PERMEATION ENHANCERS^{12, 13}

Sr. no	Permeation Enhancers	Sr. no	Permeation Enhancers
I	2, 3-Lauryl ether	XIV	Phosphatidylcholine
II	Aprotinin	XV	Polyoxyethylene
III	Azone	XVI	Polysorbate 80
IV	Benzalkonium chloride	XVII	Polyoxyethylene
V	Cetylpyridinium chloride	XVIII	Phosphatidylcholine
VI	Cetyltrimethyl ammonium bromide	XIX	Sodium EDTA
VII	Cyclodextrin	XX	Sodium glycocholate
VIII	Dextran sulfate	XXI	Sodium glycodeoxycholate
IX	Glycol	XXII	Sodium lauryl sulfate
X	Lauric acid	XXIII	Sodium salicylate
XI	Lauric acid/Propylene	XXIV	Sodium taurocholate
XII	Lysophosphatidylcholine	XXV	Sodium taurodeoxycholate
XIII	Menthol	XXVI	Sulfoxides

The various dosage forms including buccal bioadhesive tablets, laminated film, hydrogels, buccal patches, chewing gums and hollow fibers have been designed to extend the time of drug release from buccal cavity.

The absorption of drug through buccal mucosa can be increased using some absorption enhancers. Different peptides including insulin can be delivered to or through buccal cavity using control drug delivery systems. Particulate systems such as microspheres and nanoparticles have also been tried for the buccal control drug delivery. Buccal control drug delivery can be achieved in three ways; delivery through buccal mucosa, delivery through sublingual mucosa and local delivery to mouth. Local delivery includes the systems designed mainly to deliver drugs to periodontal pocket. Bioadhesion is a major approach involved in the designing of buccal controlled drug delivery systems. Theoretically,

maximum buccal residence time can be in the order of several days. But it has been observed that usually it does not exceed several hours, possibly due interference with drinking, eating and talking.

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;^{13, 14}

- 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.

For some drugs a considerable barrier contribution arises as a result of presystemic metabolism. The enzymatic activity of the buccal mucosa is relatively low, and drug inactivation is neither rapid nor extensive. Nevertheless, enzymes existing in the oral cavity could degrade some drugs, particularly peptide or protein drugs. Co- administration of enzyme inhibitors such as aprotinin, bestatin, puromycin and bile salts reduces the activity of proteolytic enzymes, altering the conformation of the peptide drug or forming micelles, and/or rendering the drug less accessible to enzymatic degradation. The main obstacles that drugs meet when administered via the buccal route derive from the limited absorption area and the barrier properties of the mucosa. The mucin film may act as a barrier, although unless the drug binds specifically with the mucin or are large molecules, the diffusion through the mucus is not a rate limiting step. Rapid removals of conventional delivery system, primarily through copious salivary flow are also clear impediments to successful use of this route. Bioadhesive polymer can overcome the removal issue.

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, orodissolving films, fast caps,

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