



Buccal Drug Delivery System: A Review

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ABSTRACT

Buccal 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, buccal dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity. In this regard, this review covers the overview of oral mucosa, factors affecting bioadhesion and also various buccal dosage forms.

Keywords: Buccal Delivery, Oral Mucosa, Mucoadhesion and Bio-adhesive Polymers.

INTRODUCTION

Buccal delivery of drugs is one of the alternatives to the oral route of drug administration, particularly to those drugs that undergo first-pass effect¹. The stratified squamous epithelium supported by a connective tissue lamina propria, which is present in buccal mucosa², was targeted as a site for drug delivery several years ago. Problems accompanied with oral route of administration such as extensive metabolism by liver, drug degradation in gastrointestinal tract due to harsh environment, and invasiveness of parenteral administration can be solved by administering the drug through the buccal route^{3, 4}. The buccal route appears to offer a number of advantages, like good accessibility, robustness of the epithelium, usage of the dosage form in accordance with need, and comparatively less susceptibility to enzymatic activity. Hence, adhesive mucosal dosage forms were prepared for oral delivery, in the form of adhesive tablets^{5, 6}, adhesive gels^{7, 8} and adhesive patches⁹. The permeation of hydrophilic drug through membrane is one of the major limiting factors for the development of bioadhesive buccal delivery devices. The epithelium that lines the buccal mucosa is a main barrier for the absorption of drugs¹⁰. In order to improve buccal absorption, several approaches have been introduced. Increased permeation of the drug through the buccal membrane and prevention of the drug degradation by enzymes was achieved by changing the physicochemical properties of the drug¹¹. Alternatively, improving the bioadhesion and release characteristics of buccal delivery devices increases the amount of drug available for absorption¹². The incorporation of absorption enhancers to the buccal formulation is one interesting approach. Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers¹³. Different types of potential permeation enhancers have been studied for buccal route to increase the penetration of drugs^{14, 15}. The

complexation of steroidal hormones with cyclodextrins was not effective in increasing the permeation through buccal route, whereas condensation products of cyclodextrin with propylene oxide or epichlorohydrins were able to form complexes with estradiol, testosterone, and progesterone, thereby enhancing absorption through the buccal membrane in humans¹⁶. The delivery of hydrophilic macromolecular drugs via buccal membrane was made possible by incorporation of absorption or permeation enhancers, which could reduce barrier properties of the buccal epithelium¹⁷. The aim of the present study was to discuss about oral mucosa and approaches for buccal drug delivery system.

Overview of the Oral Mucosa

Structure

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer^{18, 19} can be seen in figure 1. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The turnover time for the buccal epithelium has been estimated at 5-6 days²⁰, and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm , while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm . The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized²¹. The keratinized epithelia contain neutral



lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and

only have small amounts of ceramide²²⁻²⁴. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

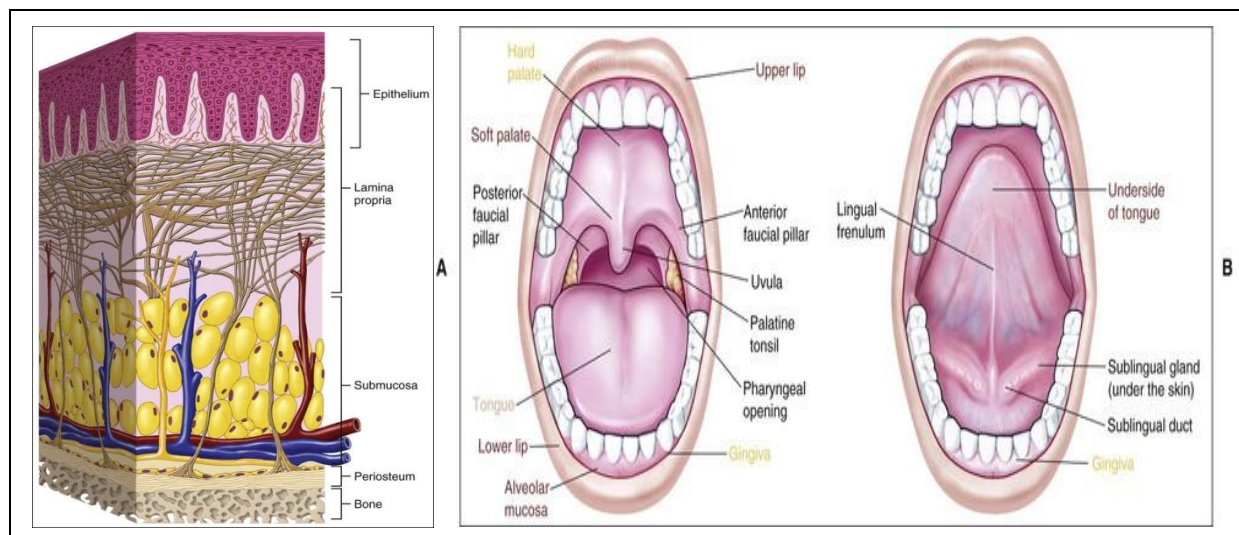


Figure 1: Anatomy of Oral Mucosa (<https://pocketdentistry.com/12-oral-mucosa/>)

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 skin²⁵. 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 mucosae. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal. This rank order is based on the relative thickness 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)²⁶. 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 200µm of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase²⁷ and lanthanum nitrate²⁸. When applied to the outer surface of the epithelium, these tracers penetrate only through outermost layer or two of cells. When applied to the submucosal 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 function²⁷. The components of the MCGs in keratinized and non-keratinized epithelia are different, however. 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 glycosphingolipids. 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 another²⁹. Along the same lines, the mucus is also believed to play a role in

bioadhesion of mucoadhesive drug delivery systems³⁰. 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. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands^{29, 31}. 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 layer. 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 mineralisation of the tooth enamel after eruption and helps in remineralisation of the enamel in the early stages of dental caries³². 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^{29, 31}. 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.

Ideal Characteristics of Buccal Drug Delivery System³²

- Should adhere to the site of attachment for a few hours.
- Should release the drug in a controlled fashion.
- Should provide drug release in a unidirectional way toward the mucosa.
- Should facilitate the rate and extent of drug absorption.
- Should not cause any irritation or inconvenience to the patient.
- Should not interfere with the normal functions such as talking and drinking.

Factors affecting Bioadhesion/ Mucoadhesion³³

1) Polymer-Related Factors

Polymer molecular weight

The optimum molecular weight for the maximum bioadhesion depends on the type of polymers. The bioadhesive forces increases with the molecular weight of bioadhesive polymer.

Molecular flexibility

It is important for interpenetration and enlargement. 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 chain which can penetrate into the mucus layer decreases even further and bioadhesion strength is reduced.

Concentration of active polymer

There is an optimum concentration of polymer corresponding to the best bioadhesion. In highly concentrated system, the adhesive strength drops significantly.

Polymer chain length

The polymer molecule must have an adequate length.

Environment Related Factors

pH

pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different charge density depending on pH because of differences in dissociation of functional groups on the carbohydrate moiety and amino acids of polypeptide backbone. Polycarbophil show the maximum adhesive strength at pH 3, the adhesive strength decreases gradually as the pH increases upto 5, polycarbophil does not show any mucoadhesive property above pH 5. This study, the first systematic investigation of the mechanism of mucoadhesion, clearly shows that the protonated carboxyl group rather than ionized carboxyl group react with mucin molecules presumably by numerous simultaneous hydrogen bonds³⁴.

Hydrogen bonding capacity

Hydrogen bonding is another important factor in mucoadhesion of a polymer. Park and Robinson found that in order for mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds. They have also confirmed that flexibility of the polymer is important to improve this hydrogen bonding potential.

Charge

Some generalizations about the charge of bioadhesive polymers have been made previously, where nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium. Additionally, some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties.

Hydration (swelling)

Hydration is required for a mucoadhesive polymer to expand and create a proper "macromolecular mesh" of sufficient size, and also to induce mobility in the polymer



chains in order to enhance the interpenetration process between polymer and mucin^{35,36}.

Basic Components of Buccal Drug Delivery System

The basic components of buccal drug delivery system are

Drug Substance

Before formulating buccal drug delivery systems, one has to decide whether the intended, action is for rapid release/prolonged release and for local/systemic effect. The selection of suitable drug for the design of buccoadhesive drug delivery systems should be based on pharmacokinetic properties. The drug should have following characteristics³⁷

- The conventional single dose of the drug should be small.
- The drugs having biological half-life between 2-8 hours are good candidates for controlled drug delivery.
- T_{max} of the drug shows wider-fluctuations or higher values when given orally^{38,39}.
- Through oral route drug may exhibit first pass effect or pre-systemic drug elimination.
- The drug absorption should be passive when given orally.

Bioadhesive Polymers

The first step in the development of buccal dosage forms is the selection and characterization of appropriate bioadhesive polymers in the formulation. Bioadhesive polymers play a major role in buccoadhesive drug delivery systems of drugs. 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. Bioadhesive polymers are by far the most diverse class and they have considerable benefits upon patient health care and treatment. The drug is released into the mucous membrane by means of rate controlling layer or core layer. A Bioadhesive polymer which adheres to the mucin/epithelial surface is effective and lead to significant improvement in the oral drug delivery⁴⁰.

An ideal polymer for buccal drug delivery systems should have following Characteristics⁴¹

- It should be inert and compatible with the environment.
- 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 some site specificity.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The polymer should be easily available in the market and economical.

- It should allow easy incorporation of drug in to the formulation.

Criteria followed in polymer selection⁴²

- It should form a strong non covalent bond with the mucin/epithelial surface.
- It must have high molecular weight and narrow distribution.
- It should be compatible with the biological membrane.
- The polymers that are commonly used as bioadhesive in pharmaceutical applications are:
 - Natural polymers, Ex: Gelatin, sodium alginate.
 - Synthetic and semi synthetic polymers, Ex: PVA, PEG, HPMC, PVP, Carbomers etc.

Backing Membrane

Backing membrane plays a major role in the attachment of bioadhesive devices 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 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, polycarbophil etc. (43).

Penetration Enhancers

Penetration enhancer's are used in buccal formulations to improve the release of the drug. They aid in the systemic delivery of the drug by allowing the drug to penetrate more readily into the viable tissues. The commonly used penetration enhancers are Sodium lauryl sulphate, CPC, Polysorbate 80, Laureth 9, Sodium Fusidate, Sodium glycocholate, Dimethyl formamide etc.

Bioadhesives

Bioadhesives are the substances that are capable of interacting with the biological material and being retained on them or holding them together for extended period of time. Bioadhesive can be used to apply to any mucous or non-mucous membranes and it also increases intimacy and duration of contact of the drug with the absorbing membrane^{44, 45}. The commonly used bioadhesives are sodium alginate, carbomers, polycarbophil, HPMC, HPC, gelatin etc.

The bioadhesive should have the following characters,

- It should not produce any residue on mucosa layer.
- It should be inert and compatible with biological environment.
- It should adhere to the mucus membrane aggressively.
- It should preferably form a strong non-covalent bond with mucin/ epithelial cell surface.



Approaches of Buccal Drug Delivery System

Non-attached drug delivery systems

This includes Fast dissolving tablet dosage forms, Chewing gum formulations and Micro-porous hollow fibers. The local physiological environment greatly affects the nonattached drug delivery system, e.g. the presence of saliva and the intake of foods and liquids.

Bio-adhesive drug delivery systems

a) Solid buccal adhesive dosage forms: Dry formulations achieve bio-adhesion via dehydration of the local mucosal surface.

b) Semi solid buccal adhesive dosage forms.

c) Liquid buccal adhesive dosage forms.

Solid buccal adhesive dosage forms

Buccal tablets

Buccal tablets are small, flat and oval in shape with a diameter of approximately 5–8 mm. The direct compression technique is most widely used for preparation of buccal tablets; other techniques like wet granulation can also be employed. These tablets stick to the buccal mucosa in presence of saliva. They are designed to release the drug either unidirectional, targeting buccal mucosa or multidirectional in to the saliva.

Microspheres, microcapsules, micro particles

The local irritation caused by microspheres or microcapsules or micro particles at the site of adhesion is less and provide comfortable sensation of a foreign object within the oral cavity.

Wafers

Wafer is a drug delivery system with surface layers possessing adhesive properties.

Lozenges

Bioadhesive lozenge offers prolonged drug release with improved patient compliance compared to Conventional lozenges, thus avoiding multiple daily dose.

Semi-solid buccal adhesive dosage forms.

Gels

Bioadhesive polymers forming gels which form cross linked polyacrylic acid used in which mucosal surfaces are fixed to provide the release in control manner for extensive period of time and drug at the absorption site. Bioadhesive polymers forming gels are of limited use for drugs with narrow therapeutic window due to their inability to deliver a measured dose of drug to the site.

Buccal patches

Patches are laminates consists of drug-containing reservoir layer and an impermeable backing layer. Drug is released in a controlled manner from the drug-containing

reservoir layer, and a bioadhesive surface for mucosal attachment. Buccal adhesive Patches can be prepared by two methods, Solvent casting technique and Direct milling method. In solvent casting technique, the solvent is evaporated by casting the solution of the drug and polymer onto a backing layer sheet and the patches were punched in intermediate sheet. In method like direct milling in which the constituents of formulation forms desire thickness by proper mixing, by which the desired shapes are cut and punched out in case of patches. Backing layer acts as protective layer which is impermeable and is applied to control the prevention of drug loss and direction of drug release during the administration.

Buccal films

These are the most recently developed dosage form which meant for buccal administration. Buccal films have more flexibility and comfort when compared with adhesive tablets. So, buccal films are preferred instead of adhesive tablets. In addition to these, they have saliva which removes and wash easy and short residence time on mucosa of oral gels. The wound surface is protected mainly by films, when the drugs are administered orally for local delivery and treat the disease more effectively by reducing the pain. An ideal film should be soft, elastic, flexible and posses adequate strength to withstand breakage due to stress from mouth movements. It should retain in the mouth to produce desired action with good bioadhesive strength. Swelling of film should not be too extensive in order to prevent discomfort. Solvent casting method is widely used for the preparation of buccal films. In solvent mixture, drug and polymer(s) are dissolved. The solution made in to film and dried, a liner or a backing layer are used to finally laminate. The salivary diffusion in to drug layer is avoided by the backing layer; there is a reduction in the drug loss and by enhancing adhesion time in oral cavity. The main disadvantage with solvent casting technique is time consuming, long processing and some concerns with the environment by the usage of different type of solvents. Hot-melt extrusion method is used to overcome the drawbacks.

c) Liquid buccal adhesive dosage forms

Liquids used to coat buccal surface are viscous and serve as either protective agents or as drug vehicles for delivery of drug on to the mucosal surface. Recently, pharmaceutically acceptable polymers were used to improve the viscosity of products to aid their maintenance in the oral cavity. Lubrication can be provided by treating dry mouth with artificial saliva solutions and to retain the drug on mucosal surfaces. This solution consists of SMC as bioadhesive polymer.

Advantages of Buccoadhesive Drug Delivery⁴⁶

Drug administration via the buccoadhesive drug delivery offers several advantages such as:



1. Drug is easily administered and extinction of therapy in emergency can be facilitated.
2. Drug release for prolonged period of time.
3. In unconscious and trauma patient's drug can be administered.
4. Drugs bypass first pass metabolism so increases bioavailability.
5. Some drugs that are unstable in acidic environment of stomach can be administered by buccal delivery.
6. Drug absorption by the passive diffusion.
7. Flexibility in physical state, shape, size and surface.
8. Maximized absorption rate due to close contact with the absorbing membrane.
9. Rapid onset of action.

Disadvantages of Buccoadhesive Drug Delivery ⁴⁷

There are some limitations of buccal drug delivery system such as

1. Drugs which are unstable at buccal pH cannot be administered.
2. Drugs which have a bitter taste or unpleasant taste or an obnoxious odor or irritate the mucosa cannot be administered by this route.
3. Drug required with small dose can only be administered.
4. Those drugs which are absorbed by passive diffusion can only be administered by this route.
5. Eating and drinking may become restricted.

CONCLUSION

The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. 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. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. However, the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery.

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