

Available online at <http://jddtonline.info>**BUCCAL ADHESIVE DRUG DELIVERY SYSTEM: SAFER DELIVERY OF BIOTHERAPEUTICS**Garg SK¹, Danodia A², Dangi V³, *Dhakar RC⁴¹National Institute of Pharmaceutical Education and Research (NIPER), Export Promotion Industrial Park, Hajipur, INDIA, 844101²Delhi University, New Delhi, INDIA³IPCA Laboratories Ltd, Industrial Estate Ltd, Kandivli (West), Mumbai, INDIA- 400067⁴Dept of Pharmaceutics, JJT University, Chudela, Jhunjhunu, INDIACorresponding Author's Email: dhakar_rc@yahoo.co.in

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ABSTRACT

The route of administration is critical for any medicine. For decades, the most common dosage forms were either oral or injection. Patients generally preferred oral therapies over injected medications because oral delivery is non-invasive and convenient. Drug delivery by buccal route presents unique advantages that are not available with other modes of administration. Buccal drug delivery is a promising option where common drug administrations (e.g., intravenous, intramuscular) are inapplicable. Recently, it has been shown that many drugs have better bioavailability by buccal route than by oral route. This has been attributed to rich vasculature and a highly permeable structure of the buccal mucosa coupled with avoidance of hepatic first-pass elimination, gut wall metabolism and/or destruction in the gastrointestinal tract. The physiology of the buccal mucosa offers a promising route for non-invasive systemic delivery of biotherapeutics. The present article highlights the advantages, physicochemical factors and formulation related parameters affecting the buccal drug delivery. It also includes a note on polymer used in buccal drug delivery and buccal drug absorption pathways.

Key Words: Buccal route, bioavailability, non-invasive, Biotherapeutics

INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike because oral mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage¹⁻⁴, and the virtual lack of Langerhans cells⁵ makes the oral mucosa tolerant to potential allergens. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery of potent peptide and perhaps protein drug molecules. The mucosa has a rich blood supply and it is relatively permeable.

Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption. Additionally, buccal drug delivery has a high patient acceptability compared to other non-oral routes of drug administration. Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal delivery. Avoiding acid hydrolysis in the gastrointestinal (GI) tract and bypassing the first-pass effect are some of the advantages of this route of drug delivery. Moreover, rapid cellular recovery and achievement of a localized site on the smooth surface of the buccal mucosa are among the other advantages of this route of drug delivery.

The disadvantages associated with this route of drug delivery are the low permeability of the buccal membrane⁶, specifically when compared to the sublingual membrane^{7,8},

and a smaller surface area. The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm²⁵, of which ~50 cm² represents non-keratinized tissues, including the buccal membrane⁹. The continuous secretion of saliva (0.5–2 l/day) leads to subsequent dilution of the drug⁸. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form. These are some of the problems that are associated with buccal drug delivery. Success of buccal drug delivery system based on the selection of proper excipients and taking consideration of factors affecting buccal drug delivery i.e. physiological properties of drug, pathological state of patient and the polymer related factors etc. Thus present focuses on the various perspectives of buccal drug delivery which are necessary to consider before designing any dosage form. The review also assesses the polymers used in buccal drug delivery as well as various factors affecting buccal adhesive drug delivery systems.

STRUCTURE OF THE ORAL MUCOSA

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. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium¹⁰. 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.

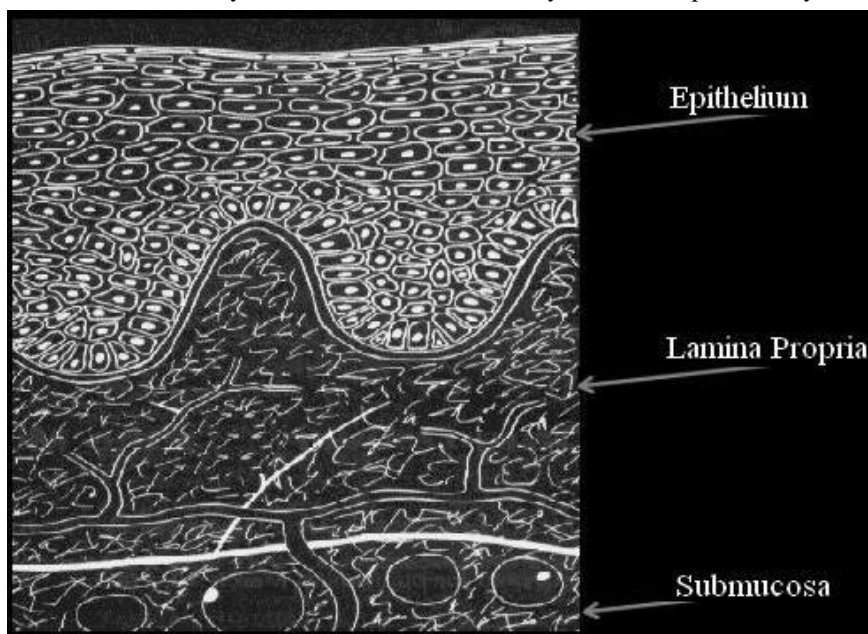


Figure 1: Structure of buccal mucosa

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 keratinized. 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 ceramide¹¹⁻¹³. 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 epithelia¹⁰⁻¹².

DRUG DELIVERY PATHWAY THROUGH BUCCAL MUCOSA:

The main mechanisms responsible for the penetration of various substances include simple diffusion (paracellular, transcellular), carrier-mediated diffusion, active transport, and pinocytosis or endocytosis. Recent evidence has shown that passive diffusion is the primary mechanism for the transport of drugs across the buccal mucosa, although carrier-mediated transport has been reported to have a small role. Two routes of passive transport are available in the buccal epithelium; one involves the transport of compounds through the intercellular spaces between the cells (paracellular), and the other involves passage into and across the cells (transcellular). Depending on the nature of the permeant, i.e. the overall molecular geometry, lipophilicity, and charge, either of the transport pathways across buccal epithelium can be selected.

While considerable evidence has been presented to document that most compounds diffuse through the buccal mucosa by passive diffusion or simple Fickian diffusion¹⁴, some are transported by a carrier mediated process across the buccal mucosa. Glucose¹⁵, monocarboxylic acids and salicylic acid^{16,17}, and nicotinic acid^{18,19}, are examples of substances which utilize a carrier-mediated diffusion mechanism for permeation across buccal epithelium.

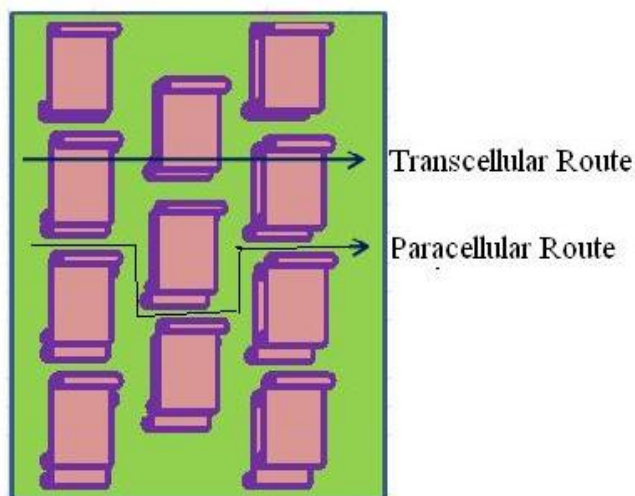


Figure 2: Drug delivery pathway through buccal mucosa

LOCAL AND SYSTEMIC DRUG DELIVERY VIA THE ORAL MUCOSA

Absorption of drug via the mucous membranes of the oral cavity can occur in either the sublingual, buccal, or local regions. The local region includes all areas other than the former two regions. The oral mucosa is classified as a somewhat leaky epithelium with a permeability rank order of sublingual, buccal, palatal, based on the thickness and degree of keratinization of the tissues⁷. Different regions of the oral cavity vary greatly in terms of their composition and their potential utility in drug delivery. The thin and

highly permeable membrane of the sublingual tissue is a perfect target if a prompt onset is desired. Considerable surface area and high blood flow to this region provide a means for rapid access to the systemic circulation. However, if a retentive, sustained-release system is desired, the sublingual membrane fails to be an appropriate target tissue.

Sustained-release systems, which are able to provide sustained drug concentrations in the systemic circulation due to delayed release of the drug from the formulation, are suitable dosage forms for the buccal region of the oral cavity. The lower permeability of this region compared to the sublingual site is ideal for controlled-release systems. Additionally, drug delivery via this site avoids extensive enzyme degradation and first-pass metabolism seen with oral administrations, which are desired outcomes for the delivery of therapeutic proteins and peptides. However, the low permeability of this site is not always an attractive feature and, depending on the choice of drug, can be a major limitation. Use of sub-toxic levels of penetration enhancers and targeted delivery may potentially overcome this problem in the buccal region of the oral cavity.

Local delivery in the oral cavity has had particular applications in the treatment of toothache, periodontal diseases, and bacterial infections. However, because of its specificity, local delivery does not have the broad range of applications that sublingual and buccal drug administration provides.

MECHANISM OF MUCOADHESION²⁰:

1. Hydration mediated adhesion:
Certain hydrophilic polymers have the tendency to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.
2. Bonding mediated adhesion:

For adhesion to occur, molecules must bond across the interface. These bonds can arise in the following way.

- Ionic bonds
- Covalent bonds
- Hydrogen bonds
- Vander-Waals bonds
- Hydrophobic bonds

POLYMERS IN BUCCAL ADHESIVE DRUG DELIVERY

Mucoadhesive delivery systems are being explored for the localization of the active agents to a particular location/site. Polymers have played an important role in designing such systems so as to increase the residence time of the active agent at the desired location. Polymers used in mucosal delivery system may be of natural or synthetic origin.

Hydrophilic polymers

The polymers within this category are soluble in water. Matrices developed with these polymers swell when put into an aqueous media with subsequent dissolution of the matrix. The polyelectrolyte extends greater mucoadhesive property when compared with neutral polymers²¹. Anionic polyelectrolytes, e.g. poly (acrylic acid) and

carboxymethyl cellulose, have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer^{22, 23}. Chitosan provides an excellent example of cationic polyelectrolyte, which has been extensively used for developing mucoadhesive polymer due to its good biocompatibility and biodegradable properties²⁴. Chitosan undergoes electrostatic interactions with the negatively charged mucin chains thereby exhibiting mucoadhesive property²¹. The ionic polymers may be used to develop ionic complex with the counter-ionic drug molecules so as to have a drug delivery matrix exhibiting mucoadhesive property. Mucoadhesive microcapsules can be designed with same principle by using orifice-ionic gelation method. Non-ionic polymers, e.g. polyoxamer, hydroxypropyl methyl cellulose, methyl cellulose, poly (vinyl alcohol) and poly (vinyl pyrrolidone), have also been used for mucoadhesive properties²¹. Cellulose and its derivatives have been reported to have surface active property in addition to its film forming capability^{24, 25}. Cationic cellulose derivatives (e.g. cationic hydroxyethyl celluloses) have been used in conjunction with various anionic polymers for the development of mucoadhesive sustained delivery systems^{21, 26}.

Hydrogels

Hydrogels can be defined as three-dimensionally cross linked polymer chains which have the ability to hold water within its porous structure due to the presence of hydrophilic functional groups like hydroxyl, amino and carboxyl groups. In general, with the increase in the cross linking density there is an associated decrease in the mucoadhesion²⁷. Thielmann et al. reported the thermal cross linking of poly (acrylic acid) and methyl cellulose. They reported that with the increase in the cross linking density, there was a reduction in the solubility parameters and swelling which resulted in a reduction of mucoadhesion²⁷.

Thiolated polymers:

The presence of free thiol groups in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin which can substantially improve the mucoadhesive properties of the polymers (e.g. poly (acrylic acid) and chitosan) in addition to the paracellular uptake of the bioactive agents²⁸⁻³². Various thiolated polymers include chitosan–iminothiolane, poly (acrylic acid)–cysteine, poly (acrylic acid)–homocysteine, chitosan–thioglycolic acid, chitosan–thioethylamine, alginate–cysteine, poly (methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine²².

Lectin-based polymers:

Lectins are proteins which have the ability to reversibly bind with specific sugar / carbohydrate residues and are found in both animal and plant kingdom in addition to various microorganisms³³⁻³⁵. Many lectins have been found to be toxic and immunogenic which may lead to systemic anaphylaxis in susceptible individuals on subsequent exposure²². The specific affinity of lectins towards sugar or carbohydrate residues provides them with

specific cytoadhesive property and is being explored to develop targeted delivery systems. The various lectins which have shown specific binding to the mucosa include lectins extracted from *Ulex europaeus* I, soybean, peanut and *Lens culinaris*³⁶.

FACTORS AFFECTING MUCOADHESION IN THE BUCCAL CAVITY

A variety of factors affect the mucoadhesion in the buccal cavity are discussed below:

1. Polymer-related factors

1.1. Molecular weight

In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above 100,000⁸. As one example, the direct correlation between the bioadhesive strength of polyoxyethylene polymers and their molecular weights, in the range of 200,000 to 7,000,000, has been shown by Tiwari et al.³⁷

1.2. Flexibility

Bioadhesion starts with the diffusion of the polymer chains in the interfacial region. Therefore, it is important that the polymer chains contain a substantial degree of flexibility in order to achieve the desired entanglement with the mucus. In general, mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients, where higher flexibility of a polymer causes greater diffusion into the mucus network³⁸.

1.3. 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 bonds³⁹. They have also confirmed that flexibility of the polymer is important to improve this hydrogen bonding potential. Polymers such as poly(vinyl alcohol), hydroxylated methacrylate, and poly(methacrylic acid), as well as all their copolymers, are polymers with good hydrogen bonding capacity¹⁰.

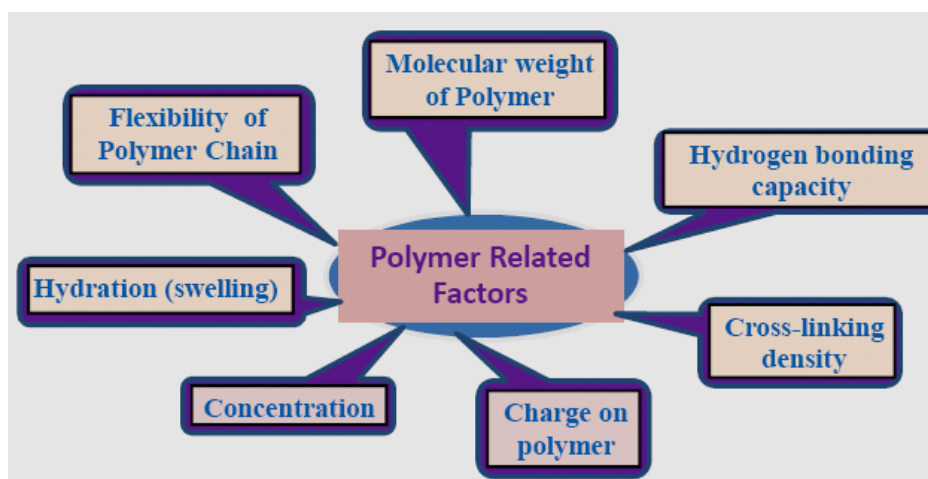


Figure 3: effect of polymer properties on mucoadhesion

1.4. Cross-linking density

The average pore size, the number average molecular weight of the cross-linked polymers, and the density of cross-linking are three important and interrelated structural parameters of a polymer network⁵⁹. Therefore, it seems reasonable that with increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin³⁸. Flory has reported this general property of polymers, in which the degree of swelling at equilibrium has an inverse relationship with the degree of cross-linking of a polymer⁴⁰.

1.5. Charge on polymer

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. Peppas and Buri have demonstrated that strong anionic charge on

the polymer is one of the required characteristics for mucoadhesion¹⁰. It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium⁴¹. Additionally, some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties.

1.6. Concentration

The importance of this factor lies in the development of a strong adhesive bond with the mucus, and can be explained by the polymer chain length available for penetration into the mucus layer. When the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is small, and the interaction between polymer and mucus is unstable⁹. In general, the more concentrated polymer would result in a longer penetrating chain length and better adhesion. However, for each polymer, there is a critical concentration, above which the polymer produces an

“unperturbed” state due to a significantly coiled structure. As a result, the accessibility of the solvent to the polymer decreases, and chain penetration of the polymer is drastically reduced. Therefore, higher concentrations of polymers do not necessarily improve and, in some cases, actually diminish mucoadhesive properties. One of the studies addressing this factor demonstrated that high concentrations of flexible polymeric films based on polyvinylpyrrolidone or poly (vinyl alcohol) as film-forming polymers did not further enhance the mucoadhesive properties of the polymer⁴².

1.7. 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 mucin³⁸. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network³⁸.

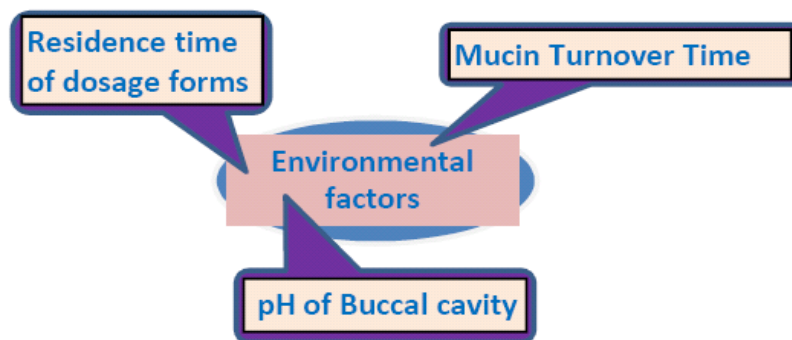


Figure 4: effect of mucosal environment on mucoadhesion

Movement of the buccal tissues while eating, drinking, and talking, is another concern which should be considered when designing a dosage form for the oral cavity. Movements within the oral cavity continue even during sleep, and can potentially lead to the detachment of the dosage form. Therefore, an optimum time span for the administration of the dosage form is necessary in order to avoid many of these interfering factors⁴⁶.

3. Physiological Variables

3.1 Applied strength:

To place a solid bioadhesive system, it is necessary to apply a defined strength. The adhesive strength increases with the applied strength or with the density of its application up to an optimum. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a satisfactory longer period of time polymers become mucoadhesive even though they do not have attractive interaction with mucins^{43,47}.

3.2 Secretion of the model substrate surface:

Since physical and biological changes may occur in the mucus gels on tissues under experimental conditions, the variability of biological substrate should be confirmed by examining properties like permeability, electro physiology,

However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bioadhesion occurs¹⁰.

1.8 Initial contact time:

The initial contact time between mucoadhesive and the mucus layer determines the extent of swelling and the interpenetration of polymer chains. Although with the initial pressure the initial contact time can dramatically affect the performance of a system the mucoadhesive strength increases as the initial contact time increases.⁴³

2. Environmental factors

The mucoadhesion of a polymer not only depends on its molecular properties, but also on the environmental factors adjacent to the polymer. Saliva, as a dissolution medium, affects the behavior of the polymer. Depending on the saliva flow rate and method of determination, the pH of this medium has been estimated to be between 6.5 and 7.5. The residence time of dosage forms is limited by the mucin turnover time, which has been calculated to range 1 and 270 min in rats⁴⁴ and 12–24 h in humans⁴⁵.

or histology etc. Such studies may be necessary before and after preparing the in vitro tests using tissues for the better in vitro / in vivo correlation.^{48,49}

3.3 Disease state:

The physicochemical properties of the mucus are known to change during disease conditions such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract and inflammatory conditions of the eye. The exact structural changes taking place in mucus under these conditions are not clearly understood. If mucoadhesive are to be used in the diseased state, the mucoadhesive property needs to be evaluated under it.^{43,48}

ADVANTAGES OF BUCCAL ADHESIVE DRUG DELIVERY SYSTEM^{50,51}

1. Ease of administration.
2. Systemic absorption is rapid.
3. The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.
4. Permits localization of drug to the oral cavity for a prolonged period of time.
5. Can be administered to unconscious patients.

6. Offers an excellent route, for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
7. Reduction in dose results reducing dose related side effects.
8. Drugs which destroyed by enzymatic, alkaline or acidic environment can be administered by this route.
9. Drugs with poor bioavailability via the oral route can be administered conveniently.
10. It offers a passive system of drug absorption and does not require any activation.
11. The presence of saliva ensures relatively large amount of water for drug dissolution.
12. This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents etc.
13. Termination of therapy is easy.

LIMITATIONS OF BUCCAL ADHESIVE DRUG ADMINISTRATION^{50,51}

Drugs, which irritate the oral mucosa, has unpleasant taste/odor, cannot be administered by this route.

1. Drugs which are unstable at buccal pH cannot be administered by this route.
2. Only drugs with small dose requirements can be administered.
3. Drugs may swallow with saliva and loses the advantages of buccal route.
4. Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
5. Swallowing of the formulation by the patient may be possible.

GENERAL CONSIDERATIONS IN DESIGNING OF BUCCAL DOSAGE FORMS

1. *Physiological aspects/Role of Saliva and Mucus:*

Constant flow of saliva and mobility of the involved tissues challenge drug delivery to the oral cavity. The residence time of drugs delivered to the oral cavity is typically short, in the range of 5–10 min⁹. Buccal mucoadhesive formulations are expected to overcome this problem. Bioadhesive polymers offer a means by which a delivery system is attached to the buccal mucosa, and hence, provide substantially longer retention times at the absorption site. They also provide a means to confine and

maintain high local concentrations of the drug and/or excipient(s) to a defined, relatively small region of the mucosa in order to minimize loss to other regions and limit potential side effects.

The buccal mucosa is a very suitable region for bioadhesive system application because of its smooth and relatively immobile surface, as well as direct accessibility. However, there are some inherent limitations associated with buccal drug delivery, including short residence time, small absorption area, and barrier properties of the buccal mucosa. The size of a buccal dosage form is restricted by the very limited area available for application of the delivery system.

This size restriction, in turn, limits the amount of drug that can be incorporated in the dosage forms. In general, a buccal delivery device that is 1–3 cm² in size⁵² and a drug with a daily dose requirement of 25 mg or less⁷ would be preferred. In addition, an ellipsoid shape appears to be most acceptable⁵², and the thickness of buccal delivery devices is usually limited to a few millimeters⁵³.

The mucus layer covering the buccal mucosa is necessary for bioadhesive systems. Unfortunately, it not only forms a physical barrier to drug permeation, but also prevents long-term bioadhesion and sustained drug release by its short turnover time. Interestingly, the presence of bioadhesive polymers on a mucous membrane might alter the turnover of mucin, since the residence time of mucoadhesives are usually longer than the reported mucin turnover time⁹. Nevertheless, the maximum duration for buccal drug delivery is usually limited to approximately 4–6 h, since meal intake and/or drinking may require dosage form removal⁵⁴.

2. *Pathological aspects:*

Many diseases can affect the thickness of the epithelium, resulting in alteration of the barrier property of the mucosa. Some diseases or treatments may also influence the secretion and properties of the mucus⁵⁵, as well as the saliva. Changes at the mucosal surface due to these pathological conditions may complicate the application and retention of a bioadhesive delivery device. Therefore, understanding the nature of the mucosa under relevant disease conditions is necessary for designing an effective buccal delivery system. In addition, drugs with the potential of changing the physiological conditions of the oral cavity may not be suitable for buccal delivery.

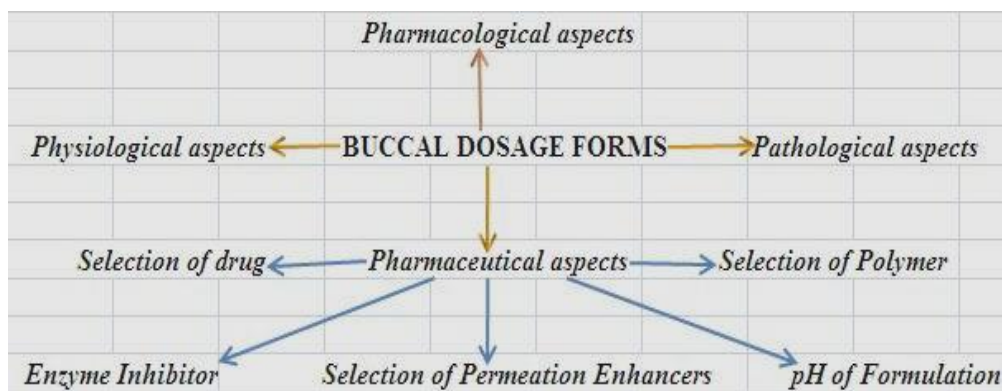


Figure 5: Basic considerations in Design of Buccal Adhesive Dosage forms

3. Pharmacological aspects:

A buccal dosage form may be designed to deliver a drug to the systemic circulation, or merely indicated for local therapy of the oral mucosa. Selection of dosage forms is affected by the intended application, target site of action, drug characteristics, and the site to be treated (periodontal pockets, gingival, teeth, buccal mucosa, or systemic).

4. Pharmaceutical aspects:

Factors affecting both drug release and penetration through buccal mucosa must also be considered in the formulation design. In addition to the physicochemical characteristics required for desirable drug release and absorption, organoleptic properties of the drug or the delivery device should also be considered, since the buccal delivery systems are to be exposed to a highly developed sensory organ.

A. Selection of drug:

Poor drug solubility in saliva could significantly retard drug release from the dosage form. Various solubilizers have been used to solubilized and increase the absorption of poorly water-soluble drugs delivered via the buccal mucosa.

Criteria for selection of drug for buccal adhesive delivery:

1. Drugs those are primarily absorbed in buccal cavity;
2. Drugs those are easily permeate through buccal mucosa
3. Drugs those degrade in the G.I.T.
4. Drugs acting locally in the buccal cavity;
5. Drugs which are absorbed by passive diffusion
6. Drug those have small dose are suitable.

Table 1: Mucosal penetration enhancers and mechanisms of action

CLASSIFICATION	EXAMPLES	MECHANISM
Surfactants	Anionic: sodium lauryl sulphate Cationic: cetylpyridinium chloride Nonionic: poloxamer, span, tween	Perturbation of intercellular lipid, protein domain integrity, Distrusts membrane,
Bile salts	Sodium glycodeoxycholate, Sodium glycocholate, Sodium taurodeoxycholate,	Distrusts membrane, Open tight junctions, Mucolytic activity
Cyclodextrins	α , β , γ -cyclodextrin, Methylated β -cyclodextrins	Inclusion of membrane Compounds, Open Tight junctions
Fatty acids	Oleic Acid, Lauric Acid, Caprylic Acid, Phosphotidylcholine	Increase fluidity of phospholipid domains, Distrusts membrane
Cationic compounds	Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface
Chelators	EDTA, Citric Acid, Na-citrate	Interfere with Ca Polyacrylates
Cationic polymers	Chitosan, Trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface
Mucoadhesive Polymers	Carbopol, Starch, Chitosan	Reduce nasal clearance, Open tight junctions

D. Enzyme Inhibition:

Even though the enzyme activity in the buccal mucosa is relatively low and, as a result, drug inactivation is slower and less extensive than in other mucosal routes⁵⁷, susceptible drugs, especially peptides and proteins, can still be degraded by the enzymes in saliva and buccal mucosa. Therefore, enzyme inhibitors may be incorporated in the dosage forms to increase drug bioavailability. some bioadhesive polymers, such as poly(acrylic acid), polycarbophil, and carbopol, can also inhibit certain

B. Selection of formulation excipients

Selection of formulation excipients is yet another important consideration, since acidic compounds can stimulate the secretion of saliva, which enhances not only drug dissolution, but also drug loss by involuntary swallowing. Besides, addition of a separate additive for each function could complicate and enlarge the dosage form, which might be problematic for buccal applications. Therefore, as mentioned previously, polymers with multiple functions seem promising.

C. Permeation Enhancers:

Permeability characteristics of the buccal mucosa may be continually changed by the rapid turnover of the buccal epithelium (3–8 days compared to about 30 days for the skin⁸). Generally, the buccal mucosa is considerably less permeable, and hence, does not provide rapid absorption and good bioavailability seen with sublingual administration. Permeability of the buccal mucosa can be increased by various penetration enhancers capable of increasing cell membrane fluidity, extracting the structural intercellular and/or intracellular lipids, altering cellular proteins, or altering mucus structure and rheology⁵⁶.

Incorporation of unsaturated fatty acids into the mucoadhesive polymers has been shown to be effective in buccal delivery of drugs. The mechanism for the permeability enhancement by unsaturated fatty acids is through increasing the fluidity of the membrane phospholipids. This class of permeation enhancers reversibly alters the physical structure of the membrane by incorporating themselves into the phospholipid membrane.

proteolytic enzymes (trypsin, α -chymotrypsin, carboxypeptidases A and B, and leucine aminopeptidase)⁵⁸. However, cysteine protease

(pyroglutamyl aminopeptidase) may not be inhibited by polycarbophil and carbopol⁵⁸.

E. pH of Formulation

Maximal permeation occurs at the pH at which these drugs are predominantly in the unionized form. Control of pH is critical for successful buccal delivery of ionizable drugs.

Saliva has a weak buffering capacity to maintain pH value within local regions. It might be desirable to include some pH modifiers in the formulation in order to temporarily modulate the microenvironment at the application site for better drug absorption.

It is worth noting that pH can also influence the charge on the surface of the mucus, as well as certain ionizable groups of the polymers, which might affect the strength of mucoadhesion. In addition, it has been shown that the pH of the medium influences the degree of hydration of cross-linked poly(acrylic acid), e.g. polycarbophil⁵⁹⁻⁶⁰. Therefore, the pH needs to be carefully chosen to optimize both drug permeation and mucoadhesion.

ORAL MUCOSA AS A BARRIER TO DRUG PERMEABILITY

A. *Oral Mucosal epithelium as a barrier to permeability:*

Oral mucosa containing epithelium acts as a protective layer for the tissues beneath and as a barrier to the entry of foreign material and microorganisms. However, oral mucosa is 4–4000 times more permeable than that of skin⁶¹.

The permeability barrier property of the oral mucosa is predominantly due to intercellular materials derived from the so-called membrane coating granules (MCGs)⁸. MCGs are spherical or oval organelles that are 100–300 nm in diameter and found in both keratinized and non-keratinized epithelia. MCGs were first named as such because it was believed that they were subject to exocytosis from the cytoplasm of the stratum spinosum of keratinized epithelia following thickening of these cells. Nonetheless, it is actually the contents of MCGs that are subject to exocytosis prior to the onset of membrane thickening.

MCGs are found near the upper, distal, or superficial border of the cells, and a few occur near the opposite border⁶² and references therein). Several hypotheses have been suggested to describe the functions of MCGs, including a membrane thickening effect, cell adhesion, production of a cell surface coat, cell desquamation, and permeability barrier. Hayward has reviewed the literature related to these functions, and it appears that the permeability barrier is most often attributed to MCGs⁶². They discharge their contents into the intercellular space to ensure epithelial cohesion in the superficial layers, and this discharge forms a barrier to the permeability of various compounds. Cultured oral epithelium devoid of MCGs has been shown to be permeable to compounds that do not typically penetrate oral epithelium⁶³. This same pattern is observed in both keratinized and nonkeratinized epithelia⁸, which indicates that keratinization of the epithelia, in and of itself is not expected to play a major role as a barrier to permeation⁶⁴.

B. *Enzymes as a barrier to permeability*

Another barrier to drug permeability across buccal epithelium is enzymatic degradation. Saliva contains no proteases, but does contain moderate levels of esterases, carbohydrases, and phosphatases⁶⁵.

However, several proteolytic enzymes have been found in the buccal epithelium¹⁶. Walker et al.⁶⁶ reported that

endopeptidases and carboxypeptidases were not present on the surface of porcine buccal mucosa, whereas aminopeptidases appeared to be the major enzymatic barrier to the buccal delivery of peptide drugs. Aminopeptidase N and A (plasma membrane-bound peptidases) and aminopeptidase B (cytosolic enzyme) have been found in the buccal tissue⁶⁷. The use of mucoadhesive polymers as enzyme inhibitor agents has been developed to overcome this obstacle in peptide and protein delivery.

MUCOADHESIVE POLYMERS AS ENZYME INHIBITORS AND PERMEATION ENHANCERS

It has been shown that some mucoadhesive polymers can act as an enzyme inhibitor. The particular importance of this finding lies in delivering therapeutic compounds that are specifically prone to extensive enzymatic degradation, such as protein and polypeptide drugs. Investigations have demonstrated that polymers, such as poly(acrylic acid), operate through a competitive mechanism with proteolytic enzymes.

This stems from their strong affinity to divalent cations (Ca²⁺, Zn²⁺)⁶⁸⁻⁶⁹. These cations are essential cofactors for the metalloproteinases, such as trypsin.

Circular dichroism studies suggest that Ca²⁺ depletion, mediated by the presence of some mucoadhesive polymers, causes the secondary structure of trypsin to change, and initiates a further autodegradation of the enzyme⁶⁸⁻⁶⁹.

The increased intestinal permeability of various drugs in the presence of numerous mucoadhesive polymers has also been attributed to their ability to open up the tight junctions by absorbing the water from the epithelial cells. The result of water absorption by a dry and swellable polymer is dehydration of the cells and their subsequent shrinking. This potentially results in an expansion of the spaces between the cells (increased radius of the paracellular pathway)⁷⁰⁻⁷¹.

The use of multifunctional matrices, such as polyacrylates, cellulose derivatives, and chitosan, that display mucoadhesive properties, permeation-enhancing effects, enzyme-inhibiting properties, and/or a high buffer capacity have proven successful strategies in oral drug delivery⁷². The inhibition of the major proteolytic enzymes by these polymers is remarkable and represents yet another possible approach for the delivery of therapeutic compounds, particularly protein and peptide drugs, through the buccal mucosa.

Any newly developed excipients are likely to be subject to safety and toxicity testing to ensure the safety of these new-generation bioadhesive polymers.

Since lectins are found in many species in the plant kingdom (e.g. tomato, wheat germ, mistletoe), they are not likely to be toxic. The fact that the source plants can be consumed raw, e.g. tomato fruit, would seem to suggest the safety of lectins. As mentioned previously, tomato lectin has been shown to bind to the surface of several cell monolayers, as well as rat intestinal epithelium without causing any harmful effects to the membranes. Another example is the clinical application of mistletoe lectin

(*Viscum album*) for antitumor therapy in rabbits and cancer patients⁷³. To achieve the desired level of cytoadhesion, genetically engineered lectins or lectinomimetics with reduced toxicity/immunogenicity could also be used. In contrast, haemagglutinin from red kidney beans (*Phaseolus vulgaris*) and bacterial adhesive proteins might require more extensive testing.

Interestingly, thiolated compounds exhibited a significantly lower membrane-damaging effect than the unmodified compounds after a 1-h incubation of rat red blood cells with a 0.025% solution of each compound. The lower membrane-damaging effect of

thiolated chitosan was attributed to the increased rigidity of the molecule due to intra- and intermolecular disulfide bonds, leading to reduced attachment to the cell membrane.

An enhanced cytotoxicity of thiolated chitosan at concentrations of 0.25% and 0.5% was attributed to the increase in molecular weight and viscosity due to crosslinking via disulfide bond formation. It was concluded that these thiolated compounds displayed a low cytotoxicity profile comparable to that of the unmodified controls, which should not compromise their potential use in drug delivery.

Table 2: Research carried out on various buccal adhesive polymers

BUCCAL ADHESIVE MATERIAL(S)	AIM OF THE RESEARCH
HPC & CP	Preferred mucoadhesive strength on CP, HPC, HPC-CP combination ⁷⁴
HPC and CP	Measured bioadhesive property using mouse peritoneal membrane ⁷⁵
CP, HPC, PVP, CMC	Studied interpolymer complexation and its effects on bioadhesive strength ⁷⁶
CP & HPMC	Controlled-release delivery ⁷⁷
HPC, HEC, PVP, PVA	Tested mucosal adhesion on patches with two-ply laminates with an impermeable backing layer and hydrocolloid polymer layer ⁷⁸
CP, PIP & PIB	bioadhesive buccal patch formulation ⁷⁹
Xanthum & locust bean gum	Hydrogel formation by combination of natural gums ⁸⁰
Chitosan, HPC, CMC, pectin, PC	Evaluate mucoadhesive properties by routinely measuring the detachment force from pig intestinal mucosa ⁴¹
HEC	synthesis of a bilayer patch for thyroid gland diagnosis ⁸¹
PC	Design of unidirectional buccal patch for delivery of peptide drugs ⁸²
HEMA with Poly tetramethylene glycol	Bioadhesive buccal hydrogel for controlled-release delivery of buprenorphine ⁸³
Polymer blend of CP, PIB	Patch system for buccal mucoadhesive drug delivery ⁸⁴
PVP, CP, CPC	Device for oramucosal delivery of LHRH-device containing a fast release and a slow release layer ⁸⁵
CMC, CP-974P, CP-EX55 pectin, CC	Mucoadhesive gels for intraoral delivery ⁸⁶
HPMC, PC	Buccal mucoadhesive tablets yielding the highest force of adhesion ³⁵
PVP, PAA	Transmucosal controlled delivery of isosorbide dinitrate ^{87,88}
Maize starch, CP 974P, SSF	Bioadhesive erodible buccal tablet for progesterone delivery ⁸⁹
Natural oligosaccharide gum,	Mucoadhesive buccal tablets for sustained release of salmon calcitonin ⁹⁰
P(AA-co-EHA)	Evaluation of P(AA-co-EHA) films for buccal mucoadhesive drug delivery ⁹¹
HPC & CP	Used HPC-CP powder mixture as peripheral base for strong adhesion and HPC-CP freeze-dried mixture as core base ⁹²
Cetylpyridinium chloride=CPC, SSF= Sodium Stearyl fumarate, P(AA-co-EHA)= Poly(acrylic acid-co-ethylhexyl acrylate), CP=Carbopol, PC=Polycarbophil, CC= Chitosan chloride	

CONCLUSION:

During the last few years research on buccal drug delivery has revealed considerable growth and advances. Among the various transepithelial sites available, the oral mucosa is the most convenient and accessible. If low drug concentrations are required to gain access to the blood, the transbuccal route may be very satisfactory, provided the physicochemical properties of a given drug allow permeation through the mucosa. Buccal mucosa allows drug delivery for both local and systemic therapies.

Despite the advantages of delivering drugs through buccal mucosa, the formulative approach alone is not sufficient for an effective delivery control. The intrinsic physicochemical properties of the drug, such as solubility, partitioning, stability, crystallinity, thermodynamic activity, molecular size, pKa and half-life, can constitute limiting factors to drug absorption. Therefore deep understanding of the various variables which affecting the delivery of drug through buccal mucosa is the most important considerations before designing of such drug delivery system.

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