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Mucoadhesive Buccal Drug Delivery System- A Promising Alternative for Orally Poor Efficient Drugs

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ABSTRACT

The current review article describe on the principles of mucoadhesive buccal drug delivery systems based on adhesion to biological surfaces that are covered by mucus. The delivery of drugs through the buccal mucosa has attracted and numerous approaches, both conventional and complex, have been developed in an attempt to deliver a variety of pharmaceutical compounds via the buccal route. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Buccal transmucosal delivery helps to bypass first- pass metabolism by allowing direct access to the systemic circulation, maintaining the drug concentration between the effective and toxic levels, inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site. It is a complex phenomenon which involves wetting or swelling and interpenetration of polymer chains, it can be of Matrix or Reservoir types. This article aims at reviewing the numerous techniques that has been designed till date for optimizing novel transmucosal buccal drug delivery system.

Keywords: transmucosal delivery, buccal delivery, complexation, first-pass effect

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INTRODUCTION

Oral drug delivery is well accepted because it has been the most extensively utilized route of administration for the systemic delivery of drugs. The lack of effectiveness of certain drugs due to decreased bioavailability, unpredictable and erratic absorption, GI intolerance, or pre-systemic elimination has prompted the examination of other potential route for administration. This limitation leads to the development of alternative routes of administration. Buccal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods[1]. Buccal mucosa has absorptive function and offers many benefits like noninvasive administration, rapid onset of action, good bioavailability, avoiding of hepatic first pass metabolism and reduce side effects[2, 3]. Buccal, sublingual, palatal and gingival[4] regions in the oral cavity have effective drug delivery. Buccal and sublingual route of drug delivery are most widely used for the treatment of local or systemic diseases. The oral mucosal permeability is related to the physical nature of the tissues. The sublingual mucosa is more permeable and thinner than the buccal mucosa and because of the considerable surface area and high blood flow; it is a feasible site when a rapid onset of action is desired. The buccal mucosa is very useful route for the treatment of either local or systemic therapies overcoming the drawbacks of conventional administration routes. These characteristics present significant challenges in the formulation development of novel transmucosal buccal drug delivery system.

Mucoadhesive polymers have been used to formulate tablets, patches, microparticles, ointments, pastes gels, vaginal rods, pessaries and suppositories, with the adhesive polymer forming the matrix into which the drug is dispersed, or the barrier through which the drug must diffuse.

Need of Mucoadhesive Drug Delivery System

To compare to the oral controlled release systems, mucoadhesive delivery system comprises to target local disorders at the mucosal surface to reduce dose and to minimize the side effects. Mucoadhesive formulations use polymers as the adhesive component. These polymers are often water soluble and when used in a dry form, they attract water from the mucosal surface and this water convey leads to a strong interaction further increasing the retention time over the mucosal surfaces and leads to adhesive interactions. Extended contact time of a drug with a body tissue through the use of a bioadhesive polymer can considerably improve the performance of many drugs[5]. Bioadhesion' is well defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces.

Advantages:

1. It is richly vascularised and more accessible for administration and removal of dosage forms.
2. Patient accessibility is high.
3. Retentive dosage forms are suitable for administration.
4. Improves bioavailability by eliminating first-pass metabolism[6-9].
5. More rapid cellular recovery and achievement of a localized site on smooth surface of buccal mucosa.
6. Low enzyme activity.
7. Non-invasive method of drug administration.
8. Ability to incorporate permeation enhancer in the formulation.

Disadvantages:

1. Buccal membrane has low permeability.
2. Small surface area (170 cm^2).
3. Continuous secretion of saliva results in subsequent dilution of the drug.
4. Inconvenience route of drug administration when the patient is eating or drinking.

Limitations:

1. Effect of salivary scavenging and accidental swallowing of delivery system.
2. Barrier property of buccal mucosa.
3. Relatively small absorption area.

Table-1 Comparison of buccal, nasal and transdermal drug delivery

	Buccal	**Nasal**	**Transdermal**
Tissue permeability/ bioavailability	Intermediate	very good	Not so good
Onset	Intermediate	very good	Not so good
Robustness	Intermediate	Not so good	very good
Duration	very good	Not so good	Intermediate
Ease of use	Intermediate	Not so good	very good
Avoiding metabolism and degradation	very good	Not so good	Intermediate
Available tissue area	Not so good	Intermediate	very good

Anatomy of Oral Mucosa

Buccal cavity is a component 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. The buccal glands are positioned between the mucous membrane and buccinator muscle. The thickness of buccal mucosa is 500–800 μm[10] and has rough texture, hence suitable for retentive delivery systems.

The return time for the buccal epithelium has been anticipated at 5–6 days[11]. Lining epithelium of buccal mucosa is the non-keratinized stratified squamous epithelium that has thickness of approximately 500–600 µ and surface area of 50.2 cm^2.

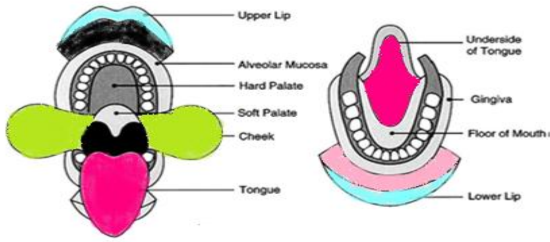


Figure 1: Schematic representation of oral mucosa

Structure

The oral mucosa consists of three distinctive layers. They are epithelium, basement membrane and connective tissues.

Buccal cavity is lined with epithelium; supported by basement membrane which intern supported by connective tissues (Fig. 1). The epithelium acts as a protective layer for the underlying tissues and it is divided into[12]

(a) Non-keratinized[13] surface in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth, alveolar mucosa, vestibule, lips, and cheeks.

(b) Keratinized[13] epithelium which is found in the hard palate and non-flexible regions of the oral cavity.

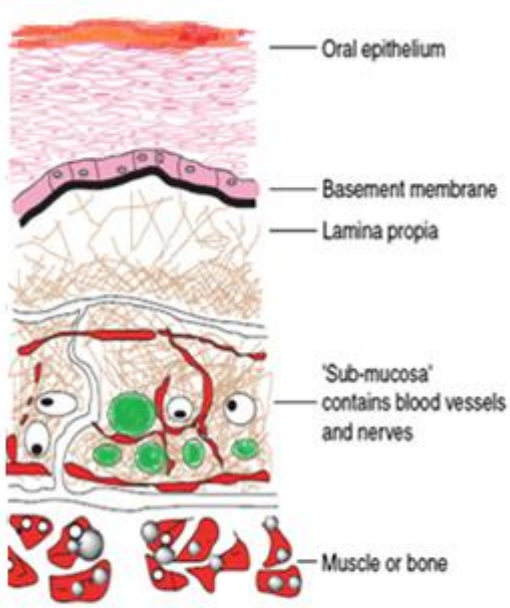


Figure 2: Cross-section of buccal mucosa

The epithelial cells originating from the basal cells mature, change their shape, and increase in size while moving towards the surface. The basement membrane acts as mechanical support for the epithelium and forms a distinctive layer between the connective tissues and the epithelium. The underlying connective tissues provide many of the mechanical properties of oral mucosa. The non keratinized tissue is a part of buccal epithelium which is penetrated by connective tissues that are tall and conical in form. These tissues, which are also referred to as the lamina propria, consists of collagen fibers, smooth muscles, blood vessels and a supporting layer of connective tissues. Lamina propria is followed by the sub mucosa.

Permeability

The oral mucosal epithelium is somewhat leaky and intermediate between that of the epidermis and intestinal mucosa. Buccal mucosal permeability is 4–4000 times greater than that of the skin[14]. There are considerable differences in permeability between different regions of the oral cavity because of its diverse structures and functions of the oral mucosa[15, 16]. The relative thickness and degree of keratinization of the tissues precedes the ranking. Both the sublingual mucosa and buccal mucosa are non-keratinized, however they differ in thickness. The permeability of the oral mucosa is in the decreasing order[17] sublingual >buccal > palatal.

Environment

The intercellular ground substance surrounds the oral epithelium known as mucus which covers the entire oral cavity. Mucus acts as a protective layer to the cells below by bounding to the apical cell surface[18]. Mucus primarily consists of about 95–99% water, 0.5–5% of water insoluble glycoproteins and several other components in small quantities, such as free proteins (1%), enzymes, electrolytes, and nucleic acids[19]. Mucus looks like a visco-elastic hydrogel. Mucus composition can vary based on the origin of the mucus secretion in the body[20].

At physiological pH, the mucus network carries a negative charge due to the presence of sialic acid and sulfate residues. Mucus plays a major role in mucoadhesion by forming a strong cohesive gel structure which attached to the epithelial cell surface as a gelatinous layer [21]. Depending on the flow rate the pH of saliva ranges from 5.5 to 7. At high flow rates, the pH is proportional to the concentration of sodium and bicarbonate. The daily salivary volume of secretion is between 0.5 to 2 liters and plays a major role to hydrate oral mucosal dosage forms[22].

Barriers to penetration across buccal mucosa

The barriers which retard the rate and extent of drug absorption through the buccal mucosa are,

- Membrane coating granules
- Basement membrane

- Mucus
- Saliva

Membrane coating granules or cored granules

Membrane-coating granules[23] become evident at the superficial aspect of the cells and appear to fuse with the plasma membrane so as to extrude their contents into the intercellular space. The membrane-coating granules found in non-keratinizing epithelia are spherical in shape, membrane-bounded and measure about 0.2 μm in diameter. Such granules have been observed in a variety of other human non-keratinized epithelia, including uterine cervix[24, 25] and esophagus.

Basement membrane

The superficial layers of the oral epithelium represent the primary barrier to the entry of substances from the exterior; the basement membrane also plays a role in limiting the passage of materials across the junction between epithelium and connective tissue. 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[26].

Mucus

Mucus is composed mainly of mucins and inorganic salts that are suspended in water[27].Mucins are of large family, heavily glycosylated proteins composed of oligosaccharide chains attached to a protein core[28]. Three quarters of the protein core are heavily glycosylated and impart a gel like characteristic to mucus. Mucins contain approximately 70–80% carbohydrate, 12–25% protein and up to 5% ester sulphate[29].

Table-2 Regional variation in the composition of oral mucos

Tissue	Structure	Epithelial Thickness (μ m)	Residence Time	Blood flow (ml/min/cm^2)
Buccal	Non-keratinized	500-600	+	2.40
Sublingual	Non-keratinized	100-200	--	0.97
Gingival	keratinized	200	+	1.47
palatal	Keratinized	250	--	0.89

Saliva

The mucosal surface has a salivary coating estimated to be 70 μm thick, which act as unstirred layer. Saliva consists of high molecular weight mucin named MG1 which maintains hydration, provides lubrication, concentrate protective molecules such as secretory immunoglobulin's and limit the attachment of microorganisms by binding to the surface of oral cavity[31]. The intercellular spaces act as a major source for permeation of hydroophilic compounds, and major transport barrier for lipophilic compounds is the cell membrane which is lipophilic in nature. Due to a low partition coefficient it is difficult to permeate through the cell membrane[30, 31].

Mechanisms of Action

1. Changing mucus rheology

The drug absorption is affected by forming viscoelastic layer by the mucus of varying thickness[32]. Further, the absorption is hindered by saliva covering the mucus layers. So permeation enhancers are used to increase the absorption, they act by reducing the viscosity of the mucus and saliva which overcomes this barrier.

2. Increasing the fluidity of lipid bilayer membrane

The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid or protein components[33].

3. Acting on the components at tight junctions

Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption[34].

4. By overcoming the enzymatic barrier

Some of the substances overcome the enzymatic barrier by inhibiting the various peptidases and proteases present within buccal mucosa. In addition, enzymatic activity is indirectly affected by the changes in membrane fluidity.

5. Increasing the thermodynamic activity of drugs

Some enhancers may alter the partition coefficient by increase the solubility of drug. This leads to increased thermodynamic activity resulting better absorption. Surfactants like anionic, cationic, non-ionic and bile salts increases permeability of drugs.

DRUG TRANSPORT MECHANISMS

The main mechanisms involved for the penetration of various substances include simple diffusion (paracellular and transcellular), carrier mediated transport and endocytosis[35]. Depending on the physicochemical properties of the molecule and the type of tissue being traversed rate of penetration may vary and leads to the suggestion that materials uses one or more of the following routes simultaneously to cross the barrier region in the process of absorption which depends on the physicochemical properties of the diffusant[36], but one route is predominant over the other.

i. Passive diffusion

   a. Transcellular or intracellular route
      (crossing the cell membrane and entering in to the cell)

   b. Paracellular or intercellular route

(passing between the cells)

ii. Carrier mediated transport

iii. Endocytosis

The transport of drugs across buccal epithelium may follow different pathways but their selection depends upon the nature of the permeant, i.e. the overall molecular geometry, lipophilicity and charge. Most of the compounds diffuse through the buccal mucosa by passive diffusion or simple Fickian diffusion.

Under sink condition, the flux of drug passing through the membrane for paracellular route can be written equation as follows [37]

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

Where, Dp is diffusion coefficient of the permeate in the intercellular spaces, hp is the path length of the paracellular route, ε is the area fraction of the paracellular route and Cd is the donor drug concentration.

Similarly, flux of drug through the membrane under sink condition for transcellular route can be written equation as follows[38, 39]

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

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 hc is the path length of the transcellular route.

Substances like Glucose, monocarboxylic acids and salicylic acid[40] and nicotinic acid are examples of substances which utilize a carrier-mediated diffusion mechanism for permeation across buccal epithelium. Mucoadhesive substances have been developed as enzyme inhibitor agents to overcome this obstacle in peptide and protein delivery.

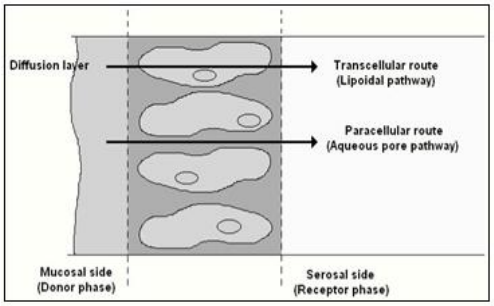


Figure 3: Drug absorption pathway across buccal mucosa

Enhancement of buccal transport

The buccal mucosa exhibits insufficient permeability depending on physicochemical properties of the drug and represents a major limitation in the development of a transmucosal drug delivery system[41]. Also, the limited absorptive area and the short exposure time, due to the washing effect of saliva can decrease absorption efficiency even more. 'Permeation enhancers' are used to permeate the drugs across epithelial barriers. However, proper penetration enhancers are used to improve the drug permeability[42].

Classification of permeation enhancers[43]

a) Chelators: sodium salicylate, methoxy salicylates, EDTA, citric acid.
b) Surfactants: polyoxyethylene, sodium lauryl sulphate, Polyoxyethylene-9-laurylether, cetyltrimethyl ammonium bromide, Polyoxythylene-20-cetylether, Benzalkonium chloride, cetylpyridinium chloride.
c) Bile salts: sodium glycocholate, sodium tauro cholate, sodium deoxy cholate, sodium tauro deoxycholate.
d) Fatty acids: phosphatidylcholine, oleic acid, capric acid, lauric acid, propylene glycol, methyl oleate.
e) Inclusion complexes: cyclodextrins.
f) Others: polysorbate 80, sulfoxides, aprotinin, azone, cyclodextrin, dextran sulfate, menthol, and various alkyl glycosides.
g) Thiolated polymers : chitosan - 4 - thiobutylamide, chitosan - 4 - thiobutylamide, chitosan - cysteine, chitosan -4- thioglycholic acid.

THEORIES OF MUCO/BIOADHESION POLYMER ATTACHMENT

Theories of mucoadhesion are a complex process and it has been presented to explain the mechanism involved. These theories include mechanical-interlocking, electrostatic, diffusion-interpenetration[44], absorption and fracture process. These numerous theories should be considered as the different stages of the mucus, substrate interaction, rather than individual and alternative theories[45].

(a) The Electronic Theory

This theory relies on the assumption that the two materials to be bonded have different electronic structures. When the two materials come together, electron transfer occurs in an attempt to balance Fermi charge levels. This electron transfer causes the formation of an electronic double layer of charges at the interface of the two materials.

(b) The Adsorption Theory

In this model, the adhesive bond between the two materials is due to Vander Waals interactions, hydrogen bonds and related forces. These forces are weak, but the large number of interactions produces the adhesive bond.

(c) The Wetting Theory

The ability of a bioadhesive polymer to spread on biological surfaces is wettability; this theory is predominantly applicable to liquid bioadhesive systems moderately wettable polymers have been shown to exhibit optimal adhesion to human endothelial cells.

(d) The Diffusion Theory

Interpenetration and entanglement of the polymer chains with the mucous chains is predicted by the diffusion theory. The bond strength should increase as the degree of interpenetration increases. To aid diffusion, the two materials should be soluble in the other. Therefore, bioadhesive polymers should have similar properties as the mucus glycoproteins.

(e) The Fracture Theory

It relates the force required for the detachment of polymer s from mucus to the strength of their adhesive bond. It has been found that work fracture is greater when the network strands are longer or the degree of cross-linking is reduced.

MUCOADHESIVE POLYMERS

Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units of monomers connected by covalent chemical bonds. Polymers act as adhesive component bioadhesive formulations. These formulations are often water soluble and forms strong interaction by attracting water from the biological surface. When hydrated with water these polymers form viscous liquids and allow long retention time on the mucosal surfaces leading to the formation of adhesive interactions. Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, viscoelastic properties, numerous hydrogen bond-forming groups, flexibility for interpenetration with mucus and epithelial tissue[46].

Ideal characteristics

The degraded products of the polymer should be non-toxic, non-irritant and free from leachable impurities.

1. Should have better spreadability, wetting, swelling, solubility and biodegradability properties.
2. Should have biocompatible pH and possess good visco-elastic properties.
3. Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
4. Should possess bioadhesive ranges of peel, tensile and shear strengths.
5. Should posse’s penetration enhancement properties by inhibiting local enzyme.

6. Should demonstrate acceptable shelf life, optimum molecular weight.

Classification mucoadhesive polymers[12]

a) Based on source

Natural: e.g. Agarose, chitosan, gelatin, Hyaluronic acid, various gums like guar, hakea, xanthan, gellan, carragenan, Pectin and sodium alginate.

Synthetic: e.g. Cellulose derivatives like CMC, SCMC, HEC, HPC, MC, Thiolated CMC and HPMC.

Based on aqueous solubility

Water soluble: e.g. CP, HEC, HPC, HPMC, SCMC, sodium alginate.

Water insoluble: e.g. Chitosan (soluble in dilute aqueous acids), EC.

b) Based on charge

Cationic: e.g. Chitosan, Dimethylaminoethyl (DEAE), Dextran,

Anionic: e.g. CP, CMC, pectin, sodium alginate, SCMC, xanthan gum.

Non-ionic: e.g. HPC, Poly(ethylene oxide), PVA, PVP.

c) Based on potential bioadhesive forces

Covalent bond: e.g. Cyanoacrylate.

Hydrogen bond: e.g. Acrylates, CP, PVA.

Electro-static interaction: e.g.Chitosan

BASIC COMPONENTS OF BUCCAL DRUG DELIVERY SYSTEM

- Drug substance
- Bioadhesive polymers
- Backing membrane
- Penetration enhancers
- Adhesives

Drug substance

Before formulating buccoadhcsive drug delivery systems, one has to decide whether the intended of therapeutic action is for rapid release/prolonged release and for local/systemic effect the drug should have following characteristics[47].

1. The conventional single dose of the drug should be small; and having biological half-life between 2-8 hours are good candidates for controlled drug delivery.
2. T_{max} of the drug shows wider-fluctuations or higher values when given orally[48].
3. The drug absorption should be passive when given orally

Bioadhesive Polymers

Bioadhesive polymers play a major role in buccoadhcsive drug delivery systems of drugs. Polymers arc also used in matrix devices in which the drug is embedded in the polymer matrix, which controls the duration of release of drugs

Backing Membrane

It is also one component which provides unidirectional drug flow to buccal mucosa. It prevents the drug to be dissolved in saliva and hence swallowed avoiding the contact between drug and saliva. The thickness of backing membrane must be around 75-100 μ. The material used for backing membrane must be inert and impermeable to drugs and penetration enhancers Ex: ethyl cellulose, Cellophane-325, Polyglassine paper.

Penetration Enhancers

Penetration enhancers are used in buccoadhcsive 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[49].

Bioadhesive Substances

Bioadhesive 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 no mucous membranes and it also increases intimacy and duration of contact of the drug with the absorbing membrane. The commonly used bioadhesive are sodium alginate, carbomers, polycarbophil, HPMC, HPC, gelatin etc.

The bioadhesive should have the following characters,

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

FORMULATION DESIGN

Buccal adhesive drug delivery systems with the size 1–3 cm^2 and a daily dose of 25 mg or less are preferable. The maximal duration of buccal delivery is approximately 4–6 h[19]. The general considerations in buccal dosage form design includes

- Pharmaceutical considerations.
- Physiological considerations.
- Pathological considerations.
- Pharmacological considerations.

Pharmaceutical considerations

The drug release from the dosage form can be retarded by its solubility in saliva. The absorption of poorly water-soluble drugs can be increased by solubilizing the drug in Cyclodextrin and administered via buccal route. The physicochemical characteristics, organoleptic properties of the drug al influence the desirable drug release and absorption[50]. Some excipients may be incorporated to enhance the effectiveness and acceptability of the dosage forms. Permeability of the buccal mucosa can be increased by various penetration enhancers. Enzyme inhibitors may be included in the dosage forms to prevent enzyme degradation and pH modifiers may be included in order to temporarily modulate the microenvironment at the application site for better drug absorption.

Physiological considerations

Challenges of drug delivery to the oral cavity are Constant flow of saliva and mobility of tissues. The residence time of drugs in the oral cavity is typically short, in the range of <5–10 min[51]. Buccal mucoadhesive formulations overcome this problem. In general, a buccal delivery device that is 1–3 cm^2 in size and a drug with a daily dose requirement of 25 mg or less would be preferred[52]. In addition, an ellipsoid shape appears to be most acceptable and the thickness of buccal delivery devices is usually limited to a few millimeters.

Pathological considerations

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 mucus [20], 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.

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[9].

STRUCTURE AND DESIGN OF BUCCAL DOSAGE FORM

1. **Matrix type:** The buccal formulation designed in a matrix configuration contains drug, adhesive, and additives mixed together.

2. **Reservoir type:** The buccal formulation designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce formulation deformation and disintegration while in the mouth; and to prevent drug loss. Additionally, the formulation can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately[53].

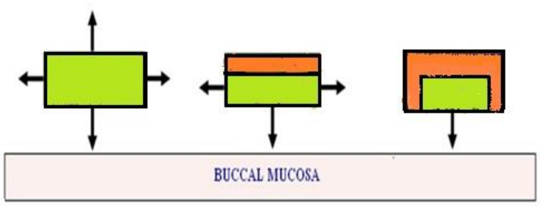
Buccal mucoadhesive dosage forms

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry[54].

Stage I: A single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

Stage II: An impermeable backing layer is superimposed on top of the drug-loaded bioadhesive layer, creating a double-layered device and preventing drug loss from the top surface of the dosage form into the oral cavity.

Stage III: A unidirectional release device, since the drug is released only from the side adjacent to the buccal mucosa from which drug loss is minimal. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa.



Stage1 Stage II Stage III

Figure 4: Design of buccal mucoadhesive dosage forms

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.

- Bio-adhesive drug delivery systems
  a) Solid buccal adhesive dosage forms.
  b) Semi-solid buccal adhesive dosage forms.
  c) Liquid buccal adhesive dosage forms.
- Liposome
- Delivery of proteins and peptides

Non-attached drug delivery systems

The local physiological environment greatly affects the non-attached drug delivery system, e.g. the presence of saliva and the intake of foods and liquids[55].

Bio-adhesive drug delivery systems

a) Solid buccal adhesive dosage forms

Dry formulations achieve bio-adhesion via dehydration of the local mucosal surface.

Buccal tablets

Buccal tablets are small, flat and oval in shape with a diameter of approximately 5–8 mm [56]. 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[57]or microcapsules[58] 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, while the bulk layer consists of antimicrobial agents, biodegradable polymers and matrix polymers[59].

Lozenges

Bioadhesive lozenge offers prolonged drug release with improved patient compliance compared to Conventional lozenges, thus avoiding multiple daily dose[60].

b) Semi-solid buccal adhesive dosage forms.

Gels

Bioadhesive polymers forming gels include cross linked poly-acrylic acid that has been used to stick to mucosal surfaces for extended periods of time and provide controlled release of 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[61].

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[62]. 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 direct milling method, the constituents of formulation are mixed evenly and compressed to the desired thickness; patches of predetermined size and shape are then cut or punched out.

Buccal films

Buccal films[63] have more flexibility and comfort when compared with adhesive tablets. buccal films are relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. Moreover the films also helps to protect the wound surface, 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.

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 enhance the viscosity of products to aid their retention 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 SCMC as bioadhesive polymer.

Liposomes

Drugs which are encapsulated in liposome formulations have been investigated for buccal administration. Applications of liposome formulation in buccal delivery resulted in a decrease of systemic and an increase of local, drug concentration. Peptides can be entrapped within the liposome[64]. The transport of hydrophilic substances to the layer of the epithelium through liposome formulations can be limited. Poly methyl methacrylate is a hydrophilic polymer and found to be the most appropriate mucoadhesive ointment for local application in the oral cavity since the liposomes were shown to be more stable in this polymer.

Table-3 commercially available buccal adhesive formulations[66]

Brand Name	Bioadhesive Polymer	Company	Dosage forms
Buccastem	PVP, Xanthum gum, Locust bean gum	Rickitt Benckiser	Tablet
Suscard	HPMC	Forest	Tablet
Gaviscon Liquid	Sodium alginate	RickittBenckiser	Oral liquid
Orabase	Pectin,gelatin	Orabase	Pectin,gelatin
Corcodyl gel	HPMC	Glaxosmithkline	Oromucosal Gel
Corlan pellets	Acacia	Celltech	Oromucosal Pellets
Luborant	Sodium CMC	Antigen	Artificial Saliva
Saliveze	Sodium CMC	Wyvem	Artificial Saliva
Buccastem buccal	Xanthan gum	Reckitt	Tablet

Delivery of proteins and peptides

The buccal drug delivery systems avoids pre systemic (or) hepatic first-pass metabolism, acidity and protease activity come across in the gastrointestinal tract hence provide as potential important site for controlled delivery of macromolecular therapeutic agents, such as peptides and protein drugs[65].

CONCLUSION

The recent improvement in the area of targeted drug delivery system extends beyond ways to administer new pharmaceutical therapies. The safety and efficacy of current treatments may be improved if their delivery rates, biodegradation, and site specific targeting can be predicted, monitored and controlled. Oral mucosal drug delivery is one such route designed to deliver a therapeutically effective amount of drug across the mucosal surface of a patient and having to produce better bioavailability, bypassing first-pass hepatic metabolism, avoidance of pre-systemic elimination of the drug within the gastrointestinal tract, localization of drug to oral cavity for prolonged period of time, reduction in dose-dependent side effects and an ideal route of administration of drug for geriatric and pediatric patients. Buccal drug delivery is a promising area for systemic delivery of orally inefficient drugs as well as an attractive alternative for wide variety of drugs.

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