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Review Article

BUCCAL DRUG DELIVERY SYSTEM: THE CURRENT INTEREST

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ABSTRACT
This review highlights the several advantages of buccal drug delivery system (BDDS) over the conventional and systemic formulation majorly. It helps to enhance bioavailability through bypassing the first pass metabolism. On this drug delivery system the formulation keeps in contact with the mucosal surface resulting in better absorption and prolonged resident time. Though all drugs are not suitable for this drug delivery system yet is useful for most of the drugs. Bioadhesive polymers roles a major part in this drug delivery system because the extent of Mucoadhesion is a very important phenomena for the buccal drug delivery system. This review covers merits and demerits of buccal drug delivery system, anatomy of oral mucosa, mechanism of drug permeation, polymers and permeation enhancer used in buccal drug delivery system. This review also covers available marketed product as buccal drug delivery system and future aspects of buccal drug delivery system.

KEY WORDS: buccal drug delivery system, bioadhesion, Mucoadhesion, residence time.

INTRODUCTION

In recent years, there has been increasing interest on the use of bioadhesive polymers to control the delivery of biologically active agents systemically or locally. These bioadhesive systems are useful for the administration of drugs, which are susceptible to extensive gastrointestinal degradation and first pass metabolism. Buccal bioadhesive system appears to be attractive because it avoids significant limitations of traditional routes and first pass metabolism. Buccal delivery necessitates the use of mucoadhesive polymer as these dosage forms should ideally adhere to the mucosa and withstand salivation, tongue movement and swallowing for a significant period of time[1].

Traditionally, per-oral delivery has been the primary route of administration for therapeutic agents targeting systemic delivery. Technologic advances in biomaterials and techniques have resulted in the formulation of novel designs more pertinent to the oral cavity, meeting the challenges of the physicochemical properties of the drug entity itself and achieving the therapeutic aims of the drug delivery system. Issues of patient compliance and convenience have recently resulted in a trend toward once-a-day administration regimens, requiring drugs with high potency and sustained effect. Such drugs usually have a short biologic half-life, exhibit poor permeability and solubility, and are susceptible to enzymatic degradation. However, because of the advantages of delivering a drug through the oral mucosa, these drugs are viable candidates for delivery via this route. Many investigators have studied the potential of transmucosal delivery through the oral cavity, and the oral mucosa is increasingly being considered as an effective route for many drug classes[2].

A bioadhesive system plays a major role, due to its potential. Besides acting as platforms for sustained release dosage forms, bioadhesive polymers can themselves exert some control over the rate and amount of drug release and thus contribute to the therapeutic efficacy of bioadhesive drug delivery systems. Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as the adhesion between polymer and /or copolymer and a biological membrane. In the case of polymer attached to the mucin layer of mucosal tissue, the term "mucoadhesion" is employed[3].

Administration of the drug via the mucosal layer is a novel method that can render treatment more effective and safe, not only for the topical diseases but also for systemic ones. These unique dosage forms, which can be applied on a thick gel like structure known as mucin, therefore all bio-adhesives must interact with the mucin layer during the process of attachment, these represent the potential sites for attachment of any bioadhesive system[1] wet tissue, are formulated by utilizing the adhesive properties of some water - soluble polymers. The mucosal layer lines a number of regions of the body including the gastrointestinal tract, buccal cavity, airways, ear, nose, eye, urogenital tract, vagina and rectum are covered[4].

Transmucosal routes of drug delivery involve the delivery of the drug through the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity. Amongst these oral cavities is a novel site for drug delivery. The oral mucosa has been investigated in several studies as a means to give both local and systemic amounts of drug. Drug delivery across the oral mucosa, can be divided into three different types[5,6].

1. Sublingual delivery, consisting of administration through the membrane of the ventra surface of the tongue and the floor of the mouth.

2. Buccal delivery, consisting of administration through the buccal mucosa, mainly composed of the lining of the cheeks and

3. Local delivery, consisting of administration through all areas other than former two regions.

These sites differ anatomically in their permeability to drugs, rate of drug delivery, and ability to maintain a delivery system for the time required for drug release out of the delivery apparatus and into the mucosa[7].

Alternative routes of administration to Bypass the Presystemic metabolism

The hepatic first pass effect can be avoided to a great extent by use of buccal tablets, transdermal preparations, and inhalations and to a lesser extent by use of rectal suppositories. Buccal absorption provides direct access to systemic not portal veins. The transdermal route and inhalation offers the same advantages.

The disadvantage with transdermal route is less penetration rate of the drug through the skin. Galey ES at al, estimated the permeability of the skin to be 4 to 4000 times lesser than that of the buccal mucosa[8].

Drugs absorbed fro suppositories in the lower rectum enter vessels that drain into the inferior venacava, thus bypassing the liver. However suppositories tend to move upwards in the rectum that leads to the liver, such as superior hemorrhoid vein, predominate. In addition, there are extensive anastomoses between the superior and middle hemorrhoid veins; thus only about 50% of a rectal dose can be assumed to bypass the liver.

Although drugs administered by inhalation bypass the hepatic first pass effect, the lungs may also serve as a site of first pass loss by excretion and possibly metabolism for drugs administered by non-gastrointestinal (parenteral) routes. The lungs also provide a filtering function for particulate matter that may be given by i.v. injection[9].

Buccal administration as a method of preventing Presystemic metabolism

The buccal cavity provides a highly vascular mucous membrane site for the administration of drug. The epithelial lining of the oral cavity differs both in type (keratinised and non-keratinised) and in thickness in different areas and the differences give rise to regional variation in permeability to drugs.

Although some macromolecules have been shown to the absorption barrier (lipid membrane), the absorption of smaller drug molecules occurs more reproducibly and rapidly. The main absorption mechanism is passive diffusion of unionized (lipid soluble) form of drug. Facilitated diffusion has also been shown to take nutrients. The blood drainage from the mouth enters the general circulation directly without first passing through the liver. This feature enhances the bioavailability of certain drugs, compared with per oral administration, because first pass metabolism is avoided. The major drugs currently available for buccal administration fall within the vasodilators and strong analgesics pharmacological classes[10].

Buccal Drug Delivery

The buccal mucosa lines the inner cheek, and buccal formulations are placed in the mouth between the upper gingivae (gums) and cheek to treat local and systemic conditions. The buccal route provides one of the potential routes for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides, as well as conventional small drug molecules. The oral cavity has been used as a site for local and systemic drug delivery[6].

Advantages of Drug Delivery via the Buccal Lining

Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. In addition the drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.

- Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.
- Sustained drug delivery.
- A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- Increased ease of drug administration
- Though less permeable than the sublingual area, the buccal mucosa is well vascularized, and drugs can be rapidly absorbed into the venous system underneath the oral mucosa.
- In comparison to TDDS, mucosal surfaces do not have a stratum corneum. Thus, the major barrier layer to transdermal drug delivery is not a factor in transmucosal routes of administration. Hence transmucosal systems exhibit a faster initiation and decline of delivery than do transdermal patches.
- Transmucosal delivery occurs is fewer variables between patients, resulting in lower intersubject variability as compared to transdermal patches.
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.[11]

Limitations of Buccal Drug Delivery

Depending on whether local or systemic action is required the challenges faced while delivering drug via buccal drug delivery can be enumerated as follows.

- For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.
- The non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.
- For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue.
- Once placed at the absorption site the patch should not be disturbed.
- Eating and drinking are restricted until complete absorption has taken place[12].



Fig 1: Structure of the human oral mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (Fig.1). Below this lies a basement membrane, lamina propria followed by the submucosa as the innermost layer (Fig.3)[13]. The epithelium is similar to stratified squamous epithelia found in 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 epithelium[14]. 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 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 (Fig.2), the floor of the mouth, the ventral tongue and the gingivae measure at about 100-200 μm. The mucosae of the gingivae and hard plate are keratinized and the mucosae of the soft palate, the sublingual and the buccal regions, are not keratinized[15]. The non keratinized epithelia are more permeable to water than the keratinized epithelia (Fig.3)[16].

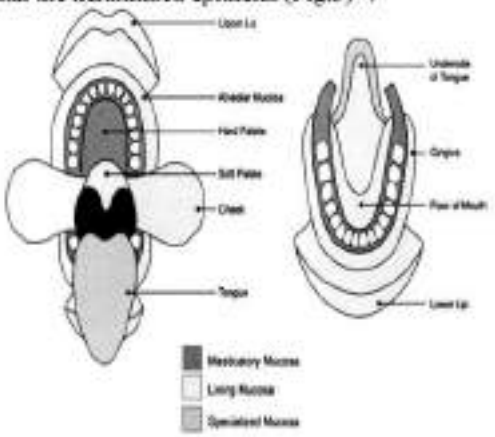


Fig 2: Diagram to show the anatomic location and extent of masticatory, lining, and specialized mucosa in the oral cavity

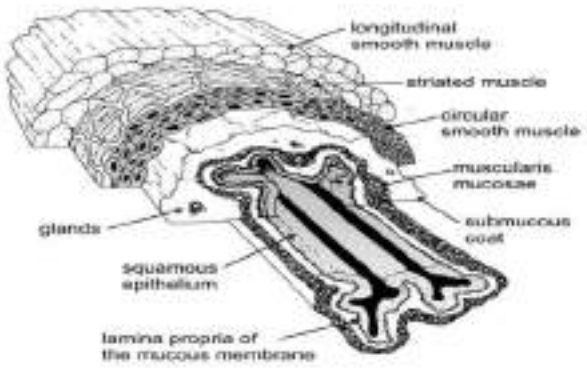


Fig 3: General Structure of oral mucosae

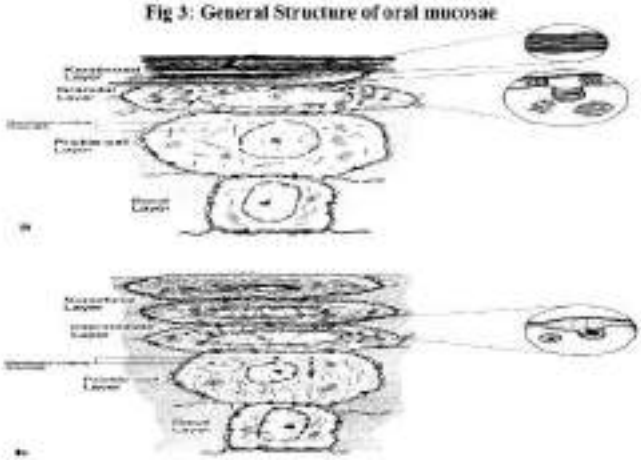


Fig 4: Principal ultra structural features of differentiation in (a) Keratinized oral epithelium and (b) Non keratinized oral and esophageal epithelium

Thickness of epithelium in different regions of oral mucosa

The below table shows thickness of epithelium in different regions of buccal mucosa[17] (Table 1)

Table 1: Thickness of epithelium in different regions of buccal mucosa

Region	Average Epithelial Thickness (µm)
Skin (mammary region)	100-120
Hard palate	250
Attached gingival	200
Buccal mucosa	500-600
Floor of mouth	100-200

Biochemical composition

A notable feature of the oral mucosa is the large amount of protein present in the form of monofilaments in the cells of layers, in both Keratinised and nonkeratinized epithelia. Comparatively little is known about the lipid composition of the oral mucosae. The keratinized oral epithelium shows a lipid pattern of mainly neutral lipids, i.e. ceramides, whereas the non-keratinized epithelium contains few neutral but polar lipids, particularly cholesterol sulphate and glucosylceramides[18].

The cells of the oral epithelia are surrounded by an intercellular ground substance, the principal components of which are carbohydrate, protein complexes, some of which may be intimately associated with particular sites on the cell surfaces. It is thought that this matrix may play a role in cell-cell adhesion, as well as a lubricant, allowing cells to move relative to one another. Another aspect of the biochemical composition of the oral mucosae is the so-called "membrane-coating granules", and their role in the biochemical changes which occur during the maturation of the epithelium[19].

Secretion of saliva

The surface of the mucous membrane is constantly washed by a stream of about 0.5 to 2 L of saliva daily produced in the salivary glands. The chief secretion is supplied by three pairs of glands, namely, the parotid, the sub maxillary, and the sublingual glands. Minor salivary glands are situated in the buccal, palatal, and retro molar regions of the oral cavity The presence of saliva in the mouth is impotant for two main reasons:

a) Drug permeation across moist (mucous) membranes occurs much readily than across non-mucous membranes; compared to drug absorption across the GI tract and skin.

b) Drugs are commonly administered to the mouth in the clinical setting in a solid form. The drug must therefore first dissolve in saliva before it can be absorbed across the oral mucosa; that is, the drug cannot be absorbed directly from a tablet[20].

Vascular system of the oral mucosa

The blood flow in the various regions of the oral mucosa has been studied in the rhesus monkey[21] (Table 2).

Table 2: Blood flow in the various regions of the oral mucosa.

Tissue	Blood flow ml / min / 100 cm^2
Buccal	2.40
Sublingual	3.14
Floor of mouth	0.97
Ventral tongue	1.17
Frenulum	1.00
Gingival(+)	1.47
Palatal(-)	0.89

Where,
(+) average value of maxillary and mandibular attached gingival mucosa
(-) average value of the anterior and posterior hard palatal mucosa

The mucous membranes of the buccal cavity have a highly vascular nature, and drugs diffusing across the membranes have easy access to the systemic circulation via the internal jugular vein. The blood supply to the mouth is delivered principally via the external carotid artery. The maxillary artery is the major branch, and the two minor branches are the lingual and facial arteries. The lingual artery and its branch, the sublingual artery, supply the tongue, the floor of the mouth, and the gingiva and the facial artery supplies blood to the lips and soft palate. The maxillary artery supplies the main cheek, hard palate, and the maxillary and mandibular gingiva. The internal jugular vein eventually receives almost all the blood derived from the mouth and pharynx.

Characteristics of mucus

The composition of mucus varies widely depending on animal species, anatomical location and whether the tissue is in a normal or pathological state. Native mucin, in addition to mucus, also contains water, electrolytes, sloughed epithelial cells, enzymes, bacteria, bacterial by products and other debris. The glycoprotein fraction of the mucus imparts a viscous gel like characteristic to mucus due to its water retention capacity.

Mucus is a glycoprotein, chemically consisting of a large peptide backbone with pendant oligosaccharide side chains whose terminal end is either sialic or sulfonic acid or L–fructose. The oligosaccharide chains are covalently linked to the hydroxy amino acids, serine and threonine, along the polypeptide backbone (Fig.5). About 25% of the polypeptide backbone is without sugars, the so-called 'naked' protein region, which is especially prone to enzymatic cleavage. The remaining 75% of the backbone is heavily glycosylated. The terminal sialic groups have a pKa value of 2.6 so that the mucin molecule should be viewed as a polyelectrolyte under neutral or acid condition. At physiological pH the mucin network may carry a significant negative charge because of the presence of

sialic acid and sulfate, residues and this high charge density plays an important role in mucoadhesion[22].

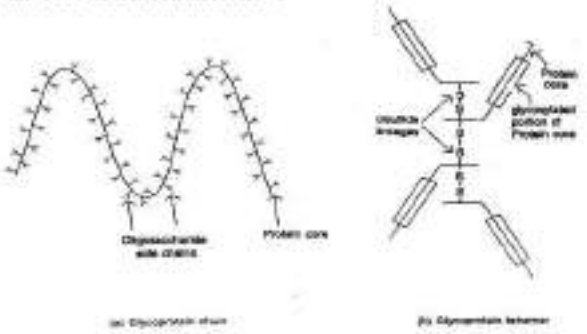


Fig 5: Schematic representation of the mucus Permeability of the oral mucosae

A primary function of the oral mucosa is to provide a barrier. At the same time, the oral mucosa shares with the gut the ability to maintain a moist surface. The permeability of the oral mucosa in general is probably intermediate between that of the epidermis and that of the intestinal mucosa. Galey estimated the permeability of the buccal mucosa to be 4 – 4000 times greater than that of the skin. In general, the permeability of the oral mucosa decreases in the order: sublingual > buccal > palatal.

Transport of material across the oral mucosa

The majority of drugs move across epithelia, by passive mechanisms, which are governed primarily by the laws of diffusion. In the case of simple diffusion, two potential routes of material transport across the epithelium are the paracellular and transcellular pathways. The paracellular route involves the passage of molecules through intercellular space, while the transcellular route involves transport into and across cells. The most important property that determines whether a given non-electrolyte will pass rapidly across the oral mucosa seems to be its relative partition between lipid and water. Substances with a high solubility in lipid are expected to traverse the oral mucosa more easily by moving along, or across the lipid rich plasma membrane of the epithelial cells, while water–soluble substances and ions probably move through the intercellular spaces (Fig.6).

Although passive diffusion is undoubtedly the major transport mechanism for drugs, the nutrients from mouth are shown to be absorbed by carrier systems i.e. facilitated diffusion[23].

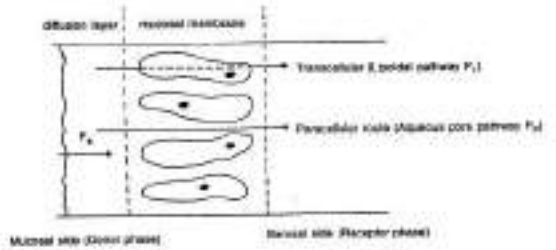


Fig 6: Mechanism of transmucosal permeation

Membrane storage during buccal absorption of drugs

The absorption of a drug from the mouth is not synonymous with drug entry into the systemic circulation. Instead, the drug appears to be stored in the buccal membranes due to drug binding in or on the oral epithelium.

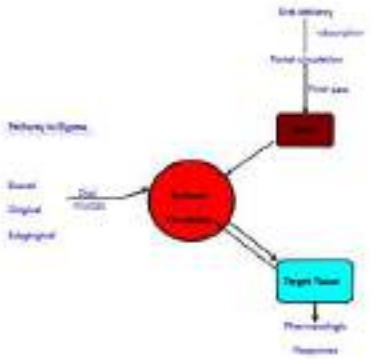


Fig 7: Schematic representation of the absorption kinetics of buccal administered drugs

Evidence for the existence of a storage compartment is easily found in the published literature because drug lost from solutions placed in the mouth could be recovered from the buccal mucosa by rinsing the mouth with a buffer of the appropriate pH. Due to this phenomenon, buccal partitioning has been suggested as a more accurate term to describe the diffusion of drugs across the oral mucosa (Fig.7)[18].

BIOADHESION IN DRUG DELIVERY

Since the early 1980's, there has been renewed interest in the use of bioadhesive polymers to prolong contact time in the various mucosal routes of drug administration. The ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local disease treatment as well as systemic drug bioavailability. Normal contact time for mucosal routes of drug delivery ranges from a few minutes for the front of the eye to ~3h for the small intestine, with intermediate times for the other routes[17].

The term bioadhesion defined as attachment of synthetic or natural macromolecules to mucus and / or an epithelial surface. In the case of polymer attached to the mucin layer of mucosal tissue the term "Mucoadhesion" is employed. In most instances the bioadhesive polymer is in contact with a soft tissue (buccal, intestinal, nasal etc.) and thus the tissue layer responsible for formation of the adhesive interface is mucus[24].

Mechanism of bioadhesion

The process of bioadhesion can be viewed as occurring in two steps. First intimate contact between the polymer and membrane followed by formation of bonds. The bonding occurs chiefly through both physical and mechanical bonds results from entanglement of the adhesive material and the extended mucus chains. Secondary chemical bonds may be due to electrostatic interactions, hydrophobic interactions, hydrogen bonding and dispersion forces. Electrostatic interactions and hydrogen bonding appear to be important as a result of the large number of charged and hydrophilic species, e.g. hydroxylic (-OH),carboxylic (-COOH), sulfate (SO_3H) and amino ($-NH_2$) groups. Several theories of bioadhesion have been proposed to explain fundamental mechanisms of attachment[25].

a. Electronic theory

The adhesive polymer and mucus typically have different electronic characteristics when these two surfaces come in contact, a double layer of electrical charges form at the interface and then adhesion develops due to the attractive force from electron transfer across the electrical double layer[26].

b. Adsorption theory

In the adsorption theory, a bioadhesive polymer adheres to mucus because of secondary surface forces such as Van der Waals forces, hydrogen bonds or hydrophobic interactions. For a bioadhesive polymer with a carboxyl group, hydrogen bonding is considered to

be the dominant force at the interface. On the other hand, hydrophobic interactions can explain the fact that a bioadhesive polymer may bind to a hydrophobic substrate more tightly than to a hydrophilic surface.

This theory describes the adhesion of liquid or paste to biological surface. According to this theory moderately wettable polymers showed optimal adhesion, spreading and proliferation to the cells and the adhesion decreased or disappeared with either very hydrophilic or very hydrophobic polymer. In a homologous series of cellulose polymers the authors observed an increase in bioadhesive strength as the contact angle increased[27].

c. Diffusion theory

The essence of this theory is that chains of the adhesive and the substrate interpenetrate one another to a sufficient depth to create a semi permanent adhesive bond. The penetration rate depends on the diffusion coefficients of both interacting polymers and the diffusion coefficient is known to depend on molecular weight and cross linking density. In addition, segment mobility, flexibility of the bioadhesive polymer, mucus glycoprotein and the expanded nature of both net works are important parameters that need to be considered[28].

d. Wetting theory

Wetting theory is predominantly applicable to liquid bioadhesive systems and analyses adhesive and contact behaviour in terms of the ability of a liquid or a paste to spread over a biological system.

The work of adhesion (expressed in terms of surface and interfacial tension), Y being defined as the energy per cm^2 released when an interface is formed. The work of adhesion is given by:

$$W_A = Y_A + Y_B - Y_{AB}$$

Where 'A' and 'B' refer to the biological membrane and the bioadhesive formulation respectively. The work of cohesion is given by:

$$W_C = 2\ Y_A \text{ or } Y_B$$

For a bioadhesive material B spreading on a substrate A, the spreading coefficient is given by:

$$S_{B/A} = Y_A - (Y_B + Y_{AB})$$

$S_{B/A}$ should be positive for a bioadhesive material to adhere to a biological membrane[29].

e. Absorption theory

According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished: Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because their high strength may result in permanent bonds. Secondary chemical bonds having different forces of attraction, including electrostatic forces, Van der Waals forces and hydrogen and hydrophobic bonds[30].

f. Fracture theory

This theory attempts to relate the difficulty of separation of two surfaces after adhesion. Fracture theory equivalent to adhesive strength is given by:

$$G = (E\ c/L)^{1/2}$$

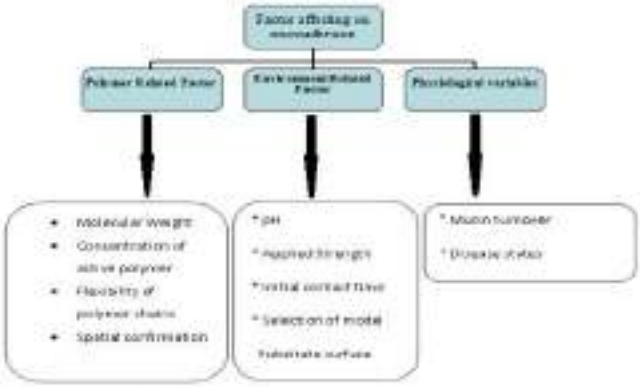
Where

E is the Young's modulus of elasticity.

c is the fracture energy, and

L is the critical crack length when two surfaces are separated[19].

Factors important to Mucoadhesion



A. Polymer related factor

Molecular weight

The optimum molecular weight for maximum bioadhesion depends on the type of bioadhesive polymer. It is generally understood that the threshold required for successful bioadhesion is atleast 100,000 molecular weight. For example, polyethylene glycol (PEG) with a molecular weight of 20,000 has little adhesive character, whereas PEG with 200,000 molecular weight has improved, and a PEG with 400,000 has superior adhesive properties. The fact that bioadhesiveness improves with increasing molecular weight for a linear polymer implies two things:

1. Interpenetration is more critical for lower molecular weight polymers to be a good bioadhesive and
2. Entanglement is important for higher molecular weight polymers. Adhesiveness of a nonlinear structure, by comparison follows a quite different trend. The adhesive strength of dextran, with a very high molecular weight of 19,500,000 is similar to that of 200,000. The reason for this similarity may be that the helical conformation of dextran may shield many of the adhesive groups, which are primarily responsible for adhesion, unlike the conformation of PEG[31].

Concentration

There is an optimum concentration of a bioadhesive polymer to produce maximum bioadhesion. In highly concentrated system, beyond the optimum level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become[31].

Chain flexibility

Chain flexibility is critical for interpenetration and entanglement. As water soluble polymers become cross linked, mobility of individual polymer chain decreases and thus the effective length of the chain that can be penetrate into the mucus layer decreases, which reduces bioadhesive strength[32].

Spatial conformation

Besides molecular weight or chain length, spatial conformation of a molecule is also important. Despite a high molecular weight of 19,500,000 for dextrans, they have similar adhesive strength to that of polyethylene glycol with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation[32].

B. Environment related factors.

These are the environmental factor described below: [28]

pH

pH can influence the formal charge on the surface of mucous as well as certain ionizable bioadhesive polymers.

Applied strength

The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interaction with mucin.

Initial contact time

Bioadhesive strength increases as the initial contact time increases.

Swelling

Swelling characteristics are related to the bioadhesive itself and its environment. Swelling depends on the polymer concentration, ionic strength as well as the presence of water.

POLYMERS IN BUCCAL DRUG DELIVERY

Polymers remain the most versatile class of biomaterials, being extensively applied in medicine and biotechnology as well as in the food and cosmetic industries. Applications include surgical devices, implants and supporting materials (e.g. artificial organs, prostheses and sutures), drug–delivery systems with different routes of administration and design, carriers of immobilized enzymes and cells, biosensors, components of diagnostic assays, bioadhesives, ocular devices, and materials for orthopaedic applications. Classifying the properties of polymers for their selection as biomaterials is challenging, because a wide variety of materials are available for a particular application (e.g. surgery, drug delivery) and no single, simple set of methods can be used to characterize polymers.[33]

Polymers used as biomaterials can be naturally occurring, synthetic or a combination of both (Table 3). Polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad categories: -

- Polymers that become sticky when placed in water and owe their bioadhesion to stickiness.
- Polymers that adhere through non-specific, non-covalent interactions, which are primarily electrostatic in nature.
- Polymers that bind to specific receptor sites on the cell surface.

Characteristics of an ideal polymer for mucoadhesive drug delivery system.

An ideal polymer should possess the following characteristics: [34]

- The polymer and its degradation products should be non-toxic and non-absorbable from the GI tract.
- It should be non-irritant to the mucous membrane.
- It should preferably form a strong non-covalent bond with mucin-epithelial cell surfaces.
- It should preferably adhere quickly to moist tissue and should possess some site specificity.
- It should allow easy incorporation of the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The cost of the polymer should not be high so that the prepared dosage form remains competitive.

Table 3: List of polymers used in buccal drug delivery system

Criteria	Categories	Examples
Source	Semi-natural/natural	Agarose, chitosan, gelatin/hyaluronic acid Various gums (guar, karaya, xanthan, pullan, carrageenan, pectin, and sodium alginate)
	Synthetic	**Cellulose derivatives** [CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methylhydroxyethylcellulose] **Polyacrylic acid)-based polymers** [CP, PC, PAA, polyacrylates, poly (methylvinylether-co-methacrylic acid), poly (2-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexylacrylate), poly (methacrylate), poly (alkylcyanoacrylate) poly (isobutylcyanoacrylate), poly (isobutylcyanoacrylate), copolymer of acrylic acid and PEO] **Others**: Poly PHPMAm, polyoxyethylene, PVA, PVP, thiolated polymers
Aqueous solubility	Water-soluble	CP, HEC, HPC (water/50 8C), HPMC (cold water), PAA, sodium CMC, sodium alginate
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, (DEAE)-dextran, TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan
Potential Bioadhesive forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylated methacrylates, poly(methacrylic acid)], CP, PC, PVA
	Electrostatic interaction	Chitosan

PERMEATION ENHANCER

Membrane permeation is the limiting factor for many drugs in the development of buccal adhesive delivery devices. The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. As most of the penetration enhancers were originally designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers must be a priority in drug delivery. The goal of designing penetration enhancers, with improved efficacy and reduced toxicity profile is possible by understanding the relationship between enhancer structure and the effect induced in the membrane and of course, the mechanism of action. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers. The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. Penetration enhancement to the buccal membrane is drug specific. Effective penetration enhancers for transdermal or intestinal drug delivery may not have similar effects on buccal drug delivery because of structural differences; however, enhancers used to improve drug permeation in other absorptive mucosae improve drug penetration through buccal mucosa. These permeation enhancers should be safe and non toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic.

Table 4: List of different permeation enhancers

.	Name of permeation enhancer		
1	23-lauryl ether	14	Methyloleate
2	Aprotinin	15	Oleic acid
3	Azone	16	Phosphatidylcholine
4	Benzalkonium chloride	17	Polyoxyethylene
5	Cetylpyridinium chloride	18	Polysorbate 80
6	Cetyltrimethylammonium bromide	19	Sodium EDTA
7	Cyclodextrin	20	Sodium glycocholate
8	Dextran sulfate	21	Sodium glycodeoxycholate
9	Lauric acid	22	Sodium lauryl sulfate
10	Lauric acid/Propylene glycol	23	Sodium salicylate
11	Lysophosphatidylcholine	24	Sodium taurocholate
12	Menthol	25	Sulfoxides
13	Methoxysalicylate	26	Various alkyl glycosides

However, examination of penetration route for transbuccal delivery is important because it is fundamental to select the proper penetration enhancer to improve the drug permeability[35]. The different permeation enhancers available are listed in (Table 4).

BUCCAL MUCOADHESIVE DOSAGE FORMS

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry: [29]

Type I:

It is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

Type II:

It is a device in which 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 into the oral cavity.

Type III:

It is a unidirectional drug release device, from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa. (Fig.8)

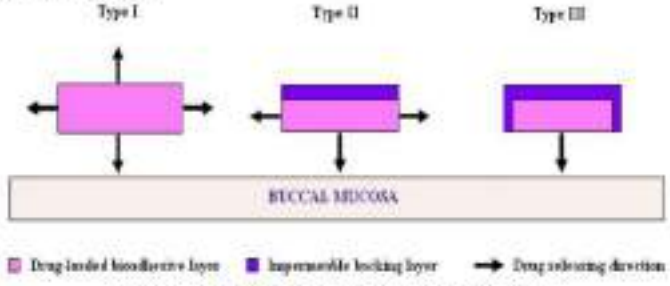


Fig 8: Design of buccal mucoadhesive dosage forms.

Solid forms

Several solid lozenges formulations have been developed and are commercially available, including nitroglycerin sublingual tablet, fentanyl lozenge on a handle and prochlorperazine buccal tablets. Although these formulations vary in shape and size, they share many common characteristics. This method of delivery is simple for patients to use. The solid formulations dissolve in the oral cavity. The drugs are released and exposed to the entire mucosa and the top third of the esophageal mucosa. The limitation of this delivery form is the short residence time. Depending on the size and formulation, the lozenge or tablet is usually dissolved within 30 min, thus limiting the total amount of drug that can be delivered. The dissolution or disintegration is usually controlled by the patient, i.e. how hard they suck the unit. Increased sucking and saliva production causes swallowing and loss of drug down the esophagus and the gastrointestinal tract. Thus, solid dosage forms generally have a much higher inter- and intraindividual variation in absorption and bioavailability. In addition, since these formulations are open systems, the delivery medium is not well controlled. Although the formulation offers some control, Oral transmucosal technology. Difficult to control drug or other ingredient concentrations because the media is constantly diluted by saliva. This makes it difficult to effectively use permeation enhancers in this type of system. Taste of the drug is another hurdle for this delivery system. Unless the drug is tasteless or the taste can be masked by sweetening and flavorings agents, it is difficult to achieve high patient acceptability of this type of product[36].

Gum

Chewing gum is one of the modern approaches to oral transmucosal drug delivery and is a useful means for systemic drug delivery. The advantages of chewing gum over other oral mucosal drug delivery systems are the possibility of controlled drug release over an extended time and the potential to improve the variability in drug release and retention times. One of the advantages of chewing gum is convenience. Furthermore, an individual may be able to control the drug intake by simply changing the rate and vigour of chewing, or expelling the gum altogether. Since chewing gum is also an open system, it shares many of the same limitations of the other solid formulations[37].

Patches

Flexible adhesive patches have been developed in an effort to overcome some of the drawbacks of other dosage forms. Transmucosal delivery patches have unique characteristics, including relatively rapid onset of drug delivery, sustained drug release and rapid decline in the serum drug concentration when the patch is removed. Also, a buccal patch is confined to the buccal area over which it is attached and therefore the absorption profile may have less inter- and intraindividual variability. In general, oral mucosal patches can be classified into three categories: patches with a dissolvable matrix, patches with a non-dissolvable backing, and patches with a dissolvable backing. Patches with a dissolvable matrix are designed to release drug into the oral cavity. They work similarly to, and share many of the limitations of, the solid dos e form. The mucoadhesive layer, either in the drug matrix or attached to drug matrix as an additional layer, prolongs the duration of drug matrix in the oral cavity. Therefore, compared with other open dosage forms, these types of patches are longer acting and can potentially deliver more drugs. They also use the entire oral cavity mucosa as compared with other closed systems that typically use smaller areas. These types of patches are also suitable for treating local diseases such as candidiasis or mucositis. Patches with non-dissolvable backing are usually designed for systemic delivery. Since they are closed systems and the formulations are protected from saliva, the drug concentrations are controlled and drug is continuously delivered for 10 to 15 h. The disadvantages of these systems are that they use only a small mucosal area and the backings have to be removed by the patient after drug administration. Patches with dissolvable backing share many characteristics of patches with non-dissolvable backing, but they have the advantage of the entire patch dissolving in the oral cavity. Patches with dissolvable backings are shorter acting than patches with non-dissolvable backing. Oral mucosal dosage forms are convenient, easy to use, and have the potential to offer a low-cost and painless alternative to more invasive routes of administration. Each delivery form offers very distinct delivery characteristics that can be used in a broad range of therapies. The majority of patches provide a longer period over which to deliver the formulated as either solventcast mucoadhesive polymer discs or drug to and through the buccal mucosa[38].

Gel-forming liquids and *in situ* gel

Viscous liquids have been investigated primarily to coat the mucosa to act as a protectant or a vehicle for drug delivery for the treatment of local disorders, including motility dysfunction, fungal infections. Using sodium alginate suspension as a novel bioadhesive liquid, researchers showed that the esophageal surface can be coated to protect against reflux and can deliver therapeutic agents to the damaged mucosa. The retention behavior of various bioadhesive formulations was evaluated on the esophageal surface under conditions mimicking the salivary flow. Both polycarbophil and xanthum gum demonstrated excellent bioadhesive potential, and carmellose sodium and theromosensitive poloxamer (Lutrol 407) demonstrated poor retention. A thermosensitive hydrogel of poloxamer covalently linked to polyacrylic acid and carbopol. This "esophageal bandage", upon oral administration, demonstrated significant retention within the esophagus[39].

Commercial mucoadhesive dosage forms

Some commercially available mucoadhesive dosage forms[30] are listed in table 5

Table 5: Commercial mucoadhesive dosage forms

Delivery formulation	Generic name	Commercial name	Manufacturer and marketing company	Special technology or properties
Tablet/ Lozenge /troches	Fentanyl buccal tablet Oral transmucosal fentanyl citrate lozenge Nicotine replacement therapy	Fentora[TM] Actiq ® nicorette® gum nicorette® lozenge	Cephalon, inc.,frazer, PA,USA Teva pharmaceutical, Sellersville,PA,USA Multigal international, companies wyeth ayerst laboratories,USA	OraVescent® drug delivery technology Effervescent Lozenge also referred to as 'lollipops Sugar-free therapeutic nicotine chewable gum or dissolving lozenge
Wafer/film	Rizatriptan Fentanyl buccal dissolvable film	Maxalt Wafers® Onsolis®	Merck & Co. Inc., Whitehouse, Station, NJ, USA. Meda Pharmaceuticals Inc., Somerset, NJ, USA	Rapidly dissolving BioErodible MucoAdhesive technology from BioDelivery Sciences

CONCLUSION

In the past few decades, research in buccal drug delivery has revealed remarkable growth and advances. The transmucosal route is becoming more and more popular because it is having significant advantages like avoidance of first pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. Despite the advantages of delivering drugs through buccal mucosa, this route is still very challenging, with the main obstacles being the limited absorption area and the barrier properties of the mucosa. The strategies studied to overcome such obstacles include use of materials that combine mucoadhesive, penetration enhancer properties and the design of novel formulations, which besides improving patient compliance favor in intimate and prolonged contact of the drug with the absorption mucosa. New and unforeseen challenges are expected in the use of mucoadhesives for the delivery of new drugs and in the search of ideal mucoadhesives.

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REFERENCES

1. Elnay JC, Swarbick J, Boylan JC. Encyclopedia of pharmaceutical technology. 2nd ed. New York: Marcel Dekkar.1990;189.
2. N. S. Miller, M. Chittchang, T. P. Johnston. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Delivery Review.2005; 57:1666- 91.
3. N. K. Jain. Controlled and novel drug delivery. 1st ed. CBS Publishers, New Delhi, 2002.
4. Chowdary KPR, Srinivas L. Mucoadhesive drug delivery systems: A review of current status. Indian drugs 2000;37(9):400-06.
5. Khanna R, Agarwal SP, Ahuja A. Mucoadhesive buccal drug delivery: A potential alternative to conventional therapy. Indian Journal of Pharmaceutical Science 1998;60(l):1-11.
6. Senel S, Kremer M, Nagy K, Squier C. Delivery of bioactive peptides and proteins across oral (buccal) mucosa. Curr Pharm Biotechnol 2001;2:175-86.
7. Khairnar GA, Sayyad FJ. Development of buccal drug delivery system based on mucoadhesive polymers. International Journal of PharmTech Research. 2010; 2(1): 719-735
8. Wani MS. Current status in buccal drug delivery [Online]. [cited 2007 Nov 15];[11screens]. Available from:URL: www.pharmainfo.net.
9. Ghaly ES, Ruiz G. Mucoadhesive delivery systems using carrageenan and eudragit RL [Online]. [cited 2006 Aug 6];[9 screens]. Available from: URL: www. AAPS Pharm Sci Tech.
10. Nicholas HGH, Leslie ZB. Pharmacokinetics and pharmacodynamics: rational dose selection and the time course of drug action, in basic and clinical pharmacology. Indian Journal of Pharmaceutical Science. 1995; 59-66.
11. Madhusudan RY, Vani G, Rameshachary BR. Design and evalution of mucoadhesive drug delivery system. Indian Drug. 1998; 35(9): 134-141.
12. Roy S, Pal K, Anis A, Prabhakar B. Polymer in mucoadhesive drug delivery system: A brief note. Design monomers and polymers. 2009; 12:483-95.
13. Tomlison E. Site specific drug delivery using particulate systems. In: Banker GS, editors. Modern Pharmaceutics. 2nd ed. New York: Marcel Dekker Inc; 1990; 673.
14. Smart JD. An *In vitro* assessment of some mucosa-adhesive dosage forms. International Journal of Pharmacy. 1991; 73(1):69-74.
15. Gandhi RE, Robinson JR. Bioadhesion in drug delivery. Indian Journal of Pharmaceutical Science. 1988; 50: 145-52.
16. Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. Journal of Pharmaceutical Science. 1992; 81:1-10.
17. Vyas SP, Khar RK. Controlled drug delivery concepts and advances. Vallabh prakasan. First edition. 2002: 102.
18. Hearnden V, Sankar V, Hull K, Juras DV, Greenberg M, Kerr RA, Lockhart PA. New developments and opportunities in oral mucosal drug delivery for local and systemic disease. Advance drug delivery reviews. 2011; 1-13.
19. Squier CA, Cox P, Wertz PW. Lipid content and water permeability of skin and oral mucosa. The J Invest, Dermat 1991;96:123-26.
20. Johnson JB, Davis DA, Davies F. Gray's anatomy. 32nd ed. London (England): Longmans Green And Co; 1958. p.737.
21. Squier CA, Nany D. Buccal drug delivery system. Arch oral Biol 1985; 30: 313-18.
22. Varma S, Kaul M, Rawat A, Sisni S. An overview on buccal drug delivery system. International journal of pharmaceutical science and research. 2011;2(6): 1303-1321
23. Pimlott SJ, Addy M. Site dependent absorption study on buccal mucosae. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1985; 59:145-48.
24. Jin Whan Lee, Jae Han Park, Joseph R. Robinson. Bioadhesive-based dosage forms. Journal of Pharmaceutical Science. 2000; 89(7):850-65.
25. Serra L, Domenech J, Nicholas AP. Engineering design and molecular dynamics of mucoadhesive drug delivery system as targeting agents. European journal of pharmaceutics and biopharmaceutics. 2009; 71: 519-528.
26. Longer MA, Robinson JR. Fundamental aspects of bioadhesion. Int J Pharm 1986; 7: 114-17.
27. Deryagain BV, Toporov YP, Mueler VM, Alenikova IN. On the relationship between the electrostatic and molecular component of the adhesion of elastic particles to a solid surface. Journal of Colloid Interface Science 1997; 58: 528-33.
28. Javier OM, Jason TM. Manufacture and characterization of mucoadhesive buccal film. European Journal of Pharmaceutical Science and Biopharmaceutics 2011; 77: 187-199
29. Helfand E, Tagami Y. Theory of the intern between immiscible polymers. J Chem Phys 1972; 57: 1812-13.
30. Bhalodia R, Basu B, Garala K. Buccoadhesive drug delivery systems- a review. International Journal of Pharmacy and Biosciences. 2010; 2: 1-31.
31. Campion RP. The influence of structure on adhesion (self-tack) and other forms of diffusion into polymers. J Adhesion 1975; 7: 1–23.
32. Duchene D, Touchard,F, Peppas NA. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug Dev Ind Pharm 1988; 14:283.
33. Bandyopadhyay AK, Yajaman S, Kstouastuo K. Buccal bioadhesive drug delivery – a promising option for orally less efficient drugs. Journal of Control Release 2006; 114: 15-40.
34. Punitha S, Girish Y. Polymers in mucoadhesive buccal drug delivery system – A review. International Journal of PharmTech Research. 2010; 1(2): 170-186.
35. Park H, Robinson JR. Mucosal drug delivery system. Journal of Control Release 1985; 2:47.
36. Satheesh NVM, Shakya AK, Shakya P, Singh K. Orotransmucosal drug delivery system: a review. Journal of controlled released. 2009; 140: 2-11.
37. Savaliya P, Kanigar A, Ramanna MV,Patel M,chewing gum : a modern era of drug delivery system. International research journal of pharmacy.2011; 2(10): 7-11.
38. Semalty M, Semalty A, Kumar G, Juyal V. Development of mucoadhesive mucoal films of glipizide, International Journal of Pharmaceutical Sciences and Nanotechnology. 2008; 1(2): 184-190.
39. Patel VF, Jiang L, Brown MB. Advance in oral transmucosal drug delivery. Journal of control release.2011; 1-11