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Review Article

A Review on Buccal Drug Delivery System

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Abstract

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to biological surface for an extended period of time. Within the oral mucosal cavity, the buccal region offers an adorable route of administration for systemic drug delivery. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily approachable site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage form. Because buccal drug delivery system prolong the residence time of dosage form at the site and thus contribute to improved and/or better therapeutic performance of the drug. In this paper main focus on oral mucosa, pathway, barriers to penetration of drug, different dosage forms, evaluation methods; this will be useful to circumvent the difficulties associated with the formulation design.

Keywords: Buccal drug delivery system, Bioadhesion, barriers, Pathway, Dosage form.

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1.0 Introduction

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to biological surface for an extended period of time. Among the various routes of drug delivery the oral route is perhaps the most preferred by patients and clinicians alike. However, peroral administration of drugs has disadvantages, such as hepatic first-pass metabolism and enzymatic degradation within the gastrointestinal (GI) tract, that prohibit oral administration of certain classes of drugs, especially peptides and proteins. Consequently, other absorptive mucosas are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities) offer distinct advantages over peroral administration for systemic effect. These advantages include possible bypass of first-pass effects and avoidance of presystemic elimination within the GI tract. [1]

Many research groups have investigated the nasal cavity as a site for systemic drug delivery; however, the potential irritation and the irreversible damage to the ciliary action of the nasal cavity from chronic application of nasal dosage forms make the nasal cavity less attractive for drug delivery. Similar to the nasal route, the oral cavity as a site for drug delivery also has reached commercial status with several drugs, including nitroglycerin as sublingual tablets for angina and fentanyl as a transmucosal buccal device (Actiq, Abbott Laboratories, Abbott Park, IL) for breakthrough cancer pain. However, drug delivery via the oral cavity is highly acceptable by patients. The mucosa is relatively permeable, has a rich blood supply, is robust, and shows short recovery times after stress or damage [1, 2, 3]. The oral cavity has been used as a site for local and systemic drug delivery. Local therapy is used to treat conditions such as gingivitis, oral candidosis, oral lesions, dental caries and xerostoma while systemic delivery is used for the treatment of asthma and angina. Systemic activity is researched for the treatment of diseases like angina and asthma [1, 3].

2.0 Bioadhesive Delivery of Drug System in Oral Cavity

2.1 sublingual delivery, which is systemic delivery of drugs through the mucosal linings of the oral cavity from chronic application of nasal dosage...
2.3 **local delivery**, which is drug delivery into the oral cavity [2].

### 3.0 Advantages [6-11]
- Significant reduction in dose related side effects.
- It provides direct entry of drug into systemic circulation.
- Drug degradation in harsh gastrointestinal environment can be circumvented by administering the drug via buccal route.
- Drug absorption can be terminated in case of emergency.
- It offers passive system, which does not require activation.
- Rapid cellular recovery following local stress or damage.
- Ability to withstand environmental extremes like change in pH, temperature etc.
- Sustained drug delivery.
- The potential for delivery of peptide molecules unsuitable for the oral route.

### 4.0 Limitations [6, 12, 13]
- Once placed at the absorption site, the dosage form should not be disturbed.
- Eating and drinking are restricted.
- There is ever present possibility that the patient may swallow the formulation.
- Drug swallowed with saliva is lost.
- Drugs which are unstable at buccal pH and which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor cannot be administered by this route.
- Over hydration may lead to formation of slippery surface and structural integrity of formulation may get disrupted.

#### 5.0 Buccal Mucosal Structure and Its Suitability [4, 21]

Buccal region is that part 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. Maxillary artery supplies blood to buccal mucosa and blood flow is faster and richer (2.4ml/min/cm²) than that in the sublingual, gingival and palatal regions, thus facilitates passive diffusion of drug molecules across the mucosa. The thickness of the buccal mucosa is measured to be 500–800 μm and is rough textured, hence suitable for retentive delivery systems. The turnover time for the buccal epithelium has been estimated at 5–6 days. Buccal mucosa composed of several layers of different cells as shown in (Fig. 1). The epithelium is similar to stratified squamous epithelia found in rest of the body and is about 40–50 cell layers thick. Lining epithelium of buccal mucosa is the nonkeratinized stratified squamous epithelium that has thickness of approximately 500–600 μ and surface area of 50.2 cm². Basement membrane, lamina propria followed by the submucosa is present below the epithelial layer. Lamina propria is rich with blood vessels and capillaries that open to the internal jugular vein.

#### 6.0 Buccal Mucosa: Environment [2, 11]

The cells of oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. At physiological pH the mucus network carries a negative charge (due to sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer. On the other hand, saliva is the protective fluid for all tissues of the oral cavity. It protects soft tissues from abrasion by rough material and from chemicals. Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is flow rate. It ranges from 0.21 to 1.18 ml/min with a mean of 0.65 ml/min. The salivary pH ranges from 5.5 to 7 depending on the flow rate. The daily salivary volume is between 0.5 to 2 litres and it is this volume of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric devices as vehicle for oral mucosal drug delivery systems is this water rich environment of the oral cavity.

#### 7.0 Buccal Absorption Pathways [4, 11]

Studies with microscopically visible tracers such as small proteins and dextrans suggest that the major pathway across stratified epithelium of large molecules is via the intercellular spaces and that there is a barrier to penetration as a result of modifications to the intercellular substance in the superficial layers. However, rate of penetration varies depending on the physicochemical properties of the molecule and the type of tissue being traversed. This has led to the suggestion that materials uses one or more of the following routes simultaneously to cross the barrier region in the process of absorption, but one route is predominant over the other depending on the physicochemical properties of the diffusant.

#### 8.0 Barriers to Penetration across Buccal Mucosa [4, 10, 20, 21]

The barriers such as saliva, mucus, membrane coating granules, basement membrane etc retard the rate and extent of drug absorption through the buccal mucosa. The main penetration barrier exists in the outermost quarter to one third of the epithelium [4].

### 8.1 Membrane coating granules or cored granules: The permeability barrier property of the oral mucosa is
predominantly due to intercellular materials derived from the so-called “membrane coating granules” (MCGs). MCGs are spherical or oval organelles that are 100–300 nm in diameter and found in both keratinized and non-keratinized epithelia. 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.

8.2 Saliva [21]: It moistens the mouth, initiates digestion and protects the teeth from decay. It also controls bacterial flora of the oral cavity. Because saliva is high in calcium and phosphate, it plays a role in mineralization of new teeth repair and precarious enamel lesions. It protects the teeth by forming “protective pellicle”. A constant flowing down of saliva within the oral cavity makes it very difficult for drugs to be retained for a significant amount of time in order to facilitate absorption in this site. Permeability’s between different regions of the oral cavity vary greatly because of the diverse structures and functions. In general, keratinization of these tissues in the order of sublingual> buccal>palatal. The permeability of the buccal mucosa was estimated to be 4–4000 times greater than that of the skin.

8.3 Basement membrane [21]: Although the superficial layers of the oral epithelium represent the primary barrier to the entry of substances from the exterior, it is evident that the basement membrane also plays a role in limiting the passage of materials across the junction between epithelium and connective tissue. A similar mechanism appears to operate in the opposite direction. 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.

8.4 Mucus [21]: The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness varies from 40-300µm. It serves as an effective delivery vehicle by acting as a lubricant allowing cells to move relative to one another and is believed to play a major role to adhesion of bioadhesive drug delivery system. Mucus is composed of mucins and inorganic salts suspended in water. Mucins are a family of large, heavily glycosylated proteins composed of oligosaccharide chain attached to a protein core. Three quarters of the protein core are heavily glycosylated and impart a gel like characteristic to mucus. The dense sugar coating of mucins gives considerable water holding capacity and also makes resistant to proteolysis, which may be important in maintaining mucosal barriers.

9.0 Physiochemical Properties of Drug [7]

9.1 Molecular size: For hydrophilic substances, the rate of absorption is a function of molecular size. Small molecules (<75-100Da) appear to cross the mucosa rapidly, but permeability falls off rapidly as molecular size increases.

9.2 Lipid solubility: For any series of unionizable compounds, their relative permeabilities are function of their oil water partition coefficient, with the more lipid compounds having higher permeabilities.

9.3 Ionization: The degree of ionization of permeant is a function of both its pKa and pH at mucosal surface. For many weak acids and bases, only the unionized form possesses appreciable lipid solubility. The absorption of many compounds has been shown to be maximal at which they are mostly unionized tailing off as the degree of ionization increases.

10.0 Physiological factors affecting buccal bioavailability [20]

10.1 Inherent permeability of the epithelium The permeability of the oral mucosal epithelium is intermediate between that of the skin epithelium, which is highly specialized for barrier function and the gut, which is highly specialized for an adsorptive function. Within the oral cavity, the buccal mucosa is less permeable that the sublingual mucosa.

10.2 Thickness of epithelium: The thickness of the oral epithelium varies considerably between sites in the oral cavity. The buccal mucosa measures approximately 500-800µm in thickness.

10.3 Blood supply: A rich blood supply and lymphatic network in the lamina propria serve the oral cavity, thus drug moieties which traverse the oral epithelium are readily absorbed into the systemic circulation. The blood flow in the buccal mucosa is 2.4mL min⁻¹ cm⁻².

10.4 Metabolic activity: Drug moieties adsorbed via the oral epithelium are delivered directly into the blood, avoiding first pass metabolism effect of the liver and gut wall. Thus oral mucosal delivery may be particularly attractive for the delivery of enzymatically labile drugs such as therapeutic peptides and proteins.

10.5 Saliva and mucous: The activity of the salivary gland means that the oral mucosal surfaces are constantly washed by a stream of saliva, approximately 0.5-2L per day. The sublingual area in particular, is exposed to a lot of saliva which can enhance drug dissolution and therefore increase bioavailability.

10.6 Ability to retain delivery system: The buccal mucosa comprises an expense of smooth and relatively immobile surface and thus is ideally suited to the use of retentive delivery systems.

10.7 Species differences: Rodents contain a highly keratinized epithelium and thus are not very suitable as animal models when studying buccal drug delivery.

10.8 Transport routes and mechanism: Drug permeation across the epithelium barrier is via two main routes:

- The paracellular route: between adjacent epithelial cells;
- The transcellular route: across the epithelial cells, which can occur by any of the following mechanisms:
  - Passive diffusion, carrier mediated transport and via endocytic processes.

11.0 Buccal Adhesive Dosage Form [11, 20]

Buccal mucosa presents a relatively smooth and immobile surface for the placement of a bioadhesive dosage form. The amount of drug can be incorporated is limited by the size limitation of the buccal dosage form. In general, a drug with a daily requirement of 25mg or less is suitable for buccal delivery. Drugs with short half lives, requiring sustained and controlled delivery, with poor aqueous solubility, which are sensitive to enzymatic degradation may be successfully delivered across the buccal mucosa.
Table 1: Research work on buccoadhesive dosage forms [15-22]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymer</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transforming growth factor-b (TGF-b)</td>
<td>Chitosan-H</td>
<td>Gel</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>PVP, Carboxymethylcellulose sodium salt (NaCMC)</td>
<td>Patch</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Carbomer, Hydroxypropylmethylcellulose</td>
<td>Double-Layered tablet</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Ethyl cellulose, polyvinyl pyrrolidone K-30, hydroxpropyl methyl cellulose-15cps, hydroxyl ethyl cellulose-10cps</td>
<td>Film</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>Carbopol-934P, Hydroxypropylcellulose-M</td>
<td>Film</td>
</tr>
<tr>
<td>Miconazole nitrate</td>
<td>Hydroxypropylmethylcellulose, Sodium carboxymethylcellulose, Carbopol 934P, and sodium alginate.</td>
<td>Slow-Release Tablets</td>
</tr>
<tr>
<td>Benzocaine</td>
<td>Sodium carboxymethylcellulose, Xanthan gum</td>
<td>Liquid gel</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Carbopol 934P, White petrolatum</td>
<td>Ointment</td>
</tr>
</tbody>
</table>

Table 2: Commercially available buccal adhesive formulations

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>Bioadhesive polymer</th>
<th>Company</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccastem</td>
<td>PVP, Xanthum gum, Locust bean gum</td>
<td>Rickitt Benckier</td>
<td>Tablet</td>
</tr>
<tr>
<td>Suscard</td>
<td>HPMC</td>
<td>Forest</td>
<td>Tablet</td>
</tr>
<tr>
<td>Gavisoon</td>
<td>Sodium alginate</td>
<td>Rickitt Benckiser</td>
<td>Oral liquid</td>
</tr>
<tr>
<td>Orabase</td>
<td>Pectin, gelatin</td>
<td>Conva Tech</td>
<td>Oral paste</td>
</tr>
<tr>
<td>Corcodyl gel</td>
<td>HPMC</td>
<td>Glaxosmithkline</td>
<td>Oral mucosal gel</td>
</tr>
<tr>
<td>Corlan pellets</td>
<td>Acacia</td>
<td>Celltech</td>
<td>Oral mucosal pellets</td>
</tr>
<tr>
<td>Fentanyl oraleTM</td>
<td></td>
<td>Lexicomp</td>
<td>lozenge</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Losartan</td>
<td>Bioalliance</td>
<td>Tablet</td>
</tr>
<tr>
<td>EmemineTM</td>
<td>BDSI’s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEMA Fentanyl</td>
<td>Bexarion</td>
<td>Ardana</td>
<td></td>
</tr>
<tr>
<td>StraintTM SR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilactin</td>
<td>Zila</td>
<td>Buchal</td>
<td></td>
</tr>
<tr>
<td>Luborant</td>
<td>Sodium CMC</td>
<td>Antigen</td>
<td>Artificial saliva</td>
</tr>
<tr>
<td>Saliveze</td>
<td>Sodium CMC</td>
<td>Wyvem</td>
<td>Artificial saliva</td>
</tr>
<tr>
<td>Tibozole</td>
<td></td>
<td>Tibotec</td>
<td></td>
</tr>
</tbody>
</table>

The dosage forms developed for this purpose includes tablets, adhesive patches, adhesive gels and adhesive ointment. Adhesive tablets and patches can be formulated to release the drug unidirectionally or multidirectionally by varying the extent and permeability of the backing.

In a matrix type system, the drug is uniformly dispersed in the polymer and the matrix controls drug release. Drug molecules dispersed in the polymer have to dissolve in the medium and then diffuse through the polymer network. Therefore, a drug dispersion and drug depletion zone always exists in the matrix. A thin hydrodynamic diffusion layer also exists at the interface of the drug and the matrix. A matrix system may result in a constant release profile only at early times when the drug depletion zone is rather insignificant.

12.0 Evaluation of Buccoadhesive Dosage Form [20, 21]

- In vitro methods
- Shear strength
- Tensile strength
- Other method
  - Adhesion weight method
  - Fluorescent probe method
  - Flow channel method
  - Mechanical spectroscopic method
  - Falling liquid film method
  - Colloidal gold staining method
  - Isometric method
  - Thumb method
  - Adhesion number
  - Electrical conductance

- In vivo method
  - Radioisotopes
  - Gamma scintigraphy
  - Pharmaco scintigraphy
  - Electron paramagnetic resonance
  - Isolated loop technique
13.0 Developments in Buccal Adhesive Drug Delivery [4, 5, 14-19]

Retentive buccal mucoadhesive formulations may prove to be an alternative to the conventional oral medications as they can be readily attached to the buccal cavity retained for a longer period of time and removed at any time. Buccal adhesive drug delivery systems using matrix tablets, films, layered systems, discs, microspheres, ointments and hydrogel systems has been studied and reported by several research groups. However, limited studies exist on novel devices that are superior to those of conventional buccal adhesive systems for the delivery of therapeutic agents through buccal mucosa. A number of formulation and processing factors can influence properties and release properties of the buccal adhesive system. There are numerous important considerations that include biocompatibility (both the drug/device and device/environment interfaces), reliability, durability; environmental stability, accuracy, delivery scalability and permeability are to be considered while developing such formulations. While biocompatibility is always an important consideration, other considerations vary in importance depending on the device application. Bioadhesive formulation designed for buccal application should exhibit suitable rheological and mechanical properties, including pseudoplastic or plastic flow with thixotropy, ease of application, good spreadability, appropriate hardness, and prolonged residence time in the oral cavity. These properties may affect the ultimate performance of the preparations and their acceptance by patients. An ideal buccal adhesive system must have the following properties:

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

14.0 Research on Buccal Adhesive Drug Delivery Systems [4, 5, 14-19]

Buccal adhesive delivery devices are broadly classified into

- Solid buccal adhesive dosage forms
  - Tablets
  - Microparticles
  - Wafer
  - Lozenges
- Semi-solid buccal adhesive dosage
  - Gels
  - Patches/films
- Liquid buccal adhesive dosage form
  - Viscous liquids

The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. Microparticulate bioadhesive systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component [4].

15.0 Commercial Buccal Adhesive Drug Delivery Systems [4]

Research work on buccoadhesive dosage forms (Table 1). Some of the commercially available buccal adhesive formulations (Table 2).

16.0 CONCLUSION

The buccal mucosa is a promising delivery route for drugs that need to avoid the gastrointestinal tract due to degradation by the gastric pH, intestinal enzymes, or due to substantial hepatic first pass effect. The buccal cavity provides a highly vascular mucous membrane site for the administration of drugs. The epithelial lining of the oral cavity differs both in type (keratinized and non-keratinized) and thickness in different areas, and differences give rise to regional variations in permeability to drugs. So far, the oral mucosa has been utilized for the delivery of small drugs molecules, since their adsorption occurs more reproducibly and rapidly. The advantages are presently clinically relevant for only a limited number of drugs. However, with the developments of new formulations, such as bioadhesive preparations may increase in the future.

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