Buccal Bioadhesive Drug Delivery System: An Overview


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ABSTRACT

Buccal administration of drugs provides a convenient route of administration for both systemic and local drug actions. However, the preferred site for retentive oral transmucosal delivery systems and for sustained- and controlled-release delivery devices is the buccal mucosa, mainly because of the differences in permeability characteristics between the two regions and the buccal mucosa’s expanse of smooth and relatively immobile mucosa. Key advantages and limitations related to the buccal drug delivery system has also been discussed in the review. In the development of these buccal drug delivery systems, mucoadhesion of the device is a key element. Mucoadhesive polymers have been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the buccal mucosa. This article reviews current status of various buccal bioadhesive dosage forms such as tablets, patches, hydrogels and chewing gums and describes the strategies to improve permeation of drugs through the Buccal mucosa. Recent innovations in the dosage form development and in vivo and in vitro mucoadhesion testing methods has also been focused. Lastly, different dissolution testing methods for buccoadhesive dosage forms developed by different researchers have also been discussed.

Key Words: Buccal, Bioadhesive, Permeation, Dissolution

INTRODUCTION

Bioadhesive drug delivery formulations were introduced in 1947 when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa; this was eventually to become Orabase® [1]. Recently, considerable attention has been focused on the development of alternative drug delivery systems for proteins and peptide drugs. As the peroral administration has disadvantages such as the hepatic first pass metabolism and enzymatic degradation within the gastrointestinal tract, proteins and peptides are usually not suitable for peroral administration and are mostly delivered by parenteral [2]. Nasal, ocular, vaginal, rectal and buccal mucosal membranes have been evaluated as potential alternative routes for peptide absorption. Buccal administration of drugs provides a convenient route of administration for both systemic and local drug actions [3].

Buccal mucosa as a site for drug delivery [4]

There are two permeation pathways for passive drug transport across the oral mucosa: Paracellular and transcellular routes. Permeants may traverse these two routes simultaneously, but one route usually is more effective than the other, depending on the physicochemical properties of the diffusant. Because the intercellular spaces are less lipophilic in character than the cell membrane, hydrophilic compounds have higher solubilities in this environment. The cell membrane, however, is highly lipophilic in nature, and hydrophilic solutes have great difficulty permeating the cell membrane because of a low partition coefficient. Therefore, the intercellular spaces pose the major barrier to passive permeation of lipophilic compounds, and the cell membrane acts as the major transport barrier for hydrophilic compounds. Because the oral epithelium is stratified, solute permeation may...
involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.

Three different categories of drug delivery fall within the oral cavity: sublingual, buccal, and local. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailabilities of many drugs, and is convenient, accessible, and generally well accepted. The sublingual route is by far the most widely studied of these routes. Sublingual dosage forms are most often one of two designs: those composed of rapidly disintegrating tablets and those consisting of soft gelatin capsules filled with liquid drug. Such systems create a very high drug concentration in the sublingual region before they are systemically absorbed across the mucosa. The buccal mucosa is considerably less permeable than the sublingual area, and is generally not able to provide the rapid absorption and good bioavailability seen with sublingual administration. Local delivery to tissues of the oral cavity has a number of applications, including the treatment of toothaches, periodontal disease, bacterial and fungal infections, and aphthous and dental stomatitis, and in facilitating tooth movement with prostaglandins. Even though the sublingual mucosa is relatively more permeable than the buccal mucosa, it is not suitable for a retentive oral transmucosal delivery system. The sublingual region lacks an expanse of smooth and relatively immobile mucosa and is constantly washed by a considerable amount of saliva, making device placement difficult. Because of the high permeability and the rich blood supply, transport via the sublingual route results in a rapid onset of action, making it appropriate for highly permeable drugs with short delivery period requirements and an infrequent dosing regimen. However, the preferred site for retentive oral transmucosal delivery systems and for sustained- and controlled-release delivery devices is the buccal mucosa, mainly because of the differences in permeability characteristics between the two regions and the buccal mucosa’s expanse of smooth and relatively immobile mucosa.

Advantages of Drug Delivery via the Buccal Lining

1. 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
2. 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.
4. 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.
5. Increased ease of drug administration
6. 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.
7. 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.
8. Transmucosal delivery occurs is less variable between patients, resulting in lower intersubject variability as compared to transdermal patches.
9. The large contact surface of the oral cavity contributes to rapid and extensive drug absorption

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.

1. 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.
2. 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.
3. For both local and systemic action, patient acceptability in terms of taste, irritancy and ‘mouth feel’ is an issue.
For systemic delivery the relative impermeability of oral cavity mucosa with regard to drug absorption, especially for large hydrophilic biopharmaceuticals, is a major concern.

**Buccal Drug Delivery and Mucoadhesivity**

In the development of these Buccal drug delivery systems, mucoadhesion of the device is a key element. The term ‘mucoadhesive’ is commonly used for materials that bind to the mucin layer of a biological membrane. Mucoadhesive polymers have been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosas. These dosage forms include tablets, patches, tapes, films, semisolids and powders. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as

I. Predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups
II. Suitable surface property for wetting mucus/mucosal tissue surfaces
III. Sufficient flexibility to penetrate the mucus network or tissue crevices

The polymers which have been tried and tested over the years include Carboxymethyl cellulose, Carbopol, Polycarbophil, Poly(acrylic acid/ divinyl benzene), Sodium Alginate, Hydroxyethyl cellulose, Hydroxypropyl methylcellulose, Hylauronic acid, Gelatin, Guar Gum, Thermally modified Starch, Pectin, Polyvinyl pyrrolidone, Acacia, Polyethylene glycol, Psyllium Amberlite-200 resin, Hydroxypropyl cellulose, Chitosan, Hydroxyethyl methacrylate.

There are some Novel Mucoadhesive Polymers under development, these include Copolymer of PAA and PEG monooethyl ether, PAA complexed with PEGylated drug conjugate, Hydrophilic pressure-sensitive adhesives (PSAs), AB block copolymer of oligo(methyl methacrylate) and PAA, Polymers with thiol groups (cysteine was attached covalently to polycarbophil by using carbodiimide as a mediator.

**CURRENT STATUS OF BUCCAL BIOADHESIVE DOSAGE FORM**

Dosage forms such as mouthwashes, erodible/ chewable buccal tablets, and chewing gums allow only a short period of release, and reproducibility of drug absorption is poor. Application of bioadhesive semi-solid gels creates considerable technical problems. Bioadhesive buccal films/patches and tablets are the less developed type of dosage forms. These bioadhesive buccal films/patches and tablets were usually fabricated in different geometry, as shown in Fig. A. Type I is a single-layer device, from which drug can be released multidirectionally. Type II device has an impermeable backing layer on top of the drug-loaded bioadhesive layer, and drug loss into oral cavity can be greatly decreased. Type III is a unidirectional release device, from which drug loss will be avoided and drug can penetrate only via the buccal mucosa.

![Diagram of release geometries](image)

**Buccal patches**

Buccal patches can be of

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

2. Reservoir type: The buccal patch 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 patch deformation and disintegration while in the mouth; and to prevent drug loss. Additionally, the patch can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.

Transmucosal drug delivery systems can be bi-directional or unidirectional. Bi-directional (Figure 1) patches release drug in both the mucosa and the mouth while, Unidirectional (Figure 2) patches release the drug only into the mucosa.

The adhesive part of the system can be used as a drug carrier or as an adhesive for the retention of a drug loaded non-adhesive layer. The use of an impermeable backing layer will maximize the drug concentration gradient and prolong adhesion because the system is protected from saliva. Bioadhesive films/patches are commonly manufactured by solvent casting methods using adhesive coating machines, which involve dissolving a drug in a casting solution, casting film, and drying and laminating with a backing layer or a release liner. The processing technology is quite similar to the conventional tablets and are prepared by wet granulation, dry granulation, or direct compression processes. Drug is released upon the hydration and adhesion of the device. Buccal tablets should be fabricated and optimized for swelling behavior and drug release to ensure a prolonged period of bioadhesion and sustained or controlled release. Generally, the tablets are formulated with flat punches with dimensions less than 10 mm in diameter and 2 mm thick to aid in establishing intimate contact with buccal mucosa and reduce their interference with normal activities. In addition to mucoadhesive components, most of the tablets contained water-soluble excipients such as high-molecular-weight polyethylene glycols and mannitol.

Specialized tablet formulations with two layers are being designed to promote unidirectional drug absorption, minimize drug leakage into buccal cavity, and to achieve biphasic drug release. Iga and Ogawa formulated a slowly disintegrating...
gingival tablet for sustained release of isosorbide dinitrate and nitroglycerin. Flatfaced tablets 8 mm in diameter were prepared using lactose and hydroxypropyl cellulose. In order to control the deformation of the tablet caused by softening and mouth movements, they were covered with a bioadhesive containing polyethylene film with a 5 mm hole in the center of the top surface. When evaluated in dogs, these tablets remained in position for about 10 hours, whereas plain tablets disintegrated within 3–6 hours. Constant blood drug levels were maintained for about 10 hours from covered tablets. It has been shown that the rate of tablet disintegration, which in turn refers the buccal residence and the drug blood levels, can be controlled by changing the size of hole. A size larger than 50% of the top surface of tablets is suggested to obtain a constant disintegration rate.

**METHODS TO INCREASE DRUG DELIVERY VIA BUCCAL ROUTE**

**Absorption enhancers**
Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates. These may act by a number of mechanisms, such as increasing the fluidity of the cell membrane, extracting inter/intracellular lipids, altering cellular proteins or altering surface mucin. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism.

**Prodrugs**
Hussain et al delivered opioid agonists and antagonists in bitterless prodrug forms and found that the drug exhibited low bioavailability as prodrug. Nalbuphine and naloxone bitter drugs when administered to dogs via the buccal mucosa, the caused excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in prodrug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds, which is generally 5% or less.

**pH**
Shojaei et al evaluated permeability of acyclovir at pH ranges of 3.3 to 8.8, and in the presence of the absorption enhancer, sodium glycocholate. The in vitro permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at both pH extremes (pH 3.3 and 8.8), as compared to the mid-range values (pH 4.1, 5.8, and 7.0).

**Patch Design**
Several in vitro studies have been conducted regarding on the type and amount of backing materials and the drug release profile and it showed that both are interrelated. Also, the drug release pattern was different between single-layered and multi-layered patches.

**RECENT INNOVATIONS**

**Related to dosage forms:**
1. **Biobadhesive Spray:**
Buccoadhesive sprays are gaining popularity over other dosage forms because of flexibility, comfort, high surface area and availability of drug in solution form. The fentanyl Oralet ™ is the first FDA-approved (1996) formulation developed to take advantage of oral transmucosal absorption for the painless administration of an opioid in a formulation acceptable to children. In 2002, the FDA approved Subutex (buprenorphine) for initiating treatment of opioid dependence (addiction to opioid drugs, including heroin and opioid analgesics) and Suboxone (buprenorphine and naloxone) for continuing treatment of addicts. In 2005, Oral-lyn buccal spray was approved for commercial marketing and sales in Ecuador.

2. **Gel Forming Liquids:**
This type of a formulation is liquid upon instillation and undergoes a phase transition to form a viscoelastic gel in response to stimulus such as temperature, ionic strength or pH. Carbomers become more viscous upon increased pH. Poloxamers and smart hydrogel (Advanced medical solution) gel at approximately body temperature. Gellan gum and alginate both form gel in response to increased ionic strength (particularly with Ca$^{2+}$ ions). Gel forming formulations are currently used for sustained ocular delivery. Recent work has examined the oesophageal retention of smart Hydrogel®, a liquid that gels in response to both high force and temperature, with its gelling temperature at about 32°C.
1. Thiolated tablet:
Another obstacle for delivering peptides across the buccal mucosa is the proteolytic hydrolysis of peptidic molecules. However, there are few proteolytic enzymes such as pepsin, trypsin and chymotrypsin present in gastric and intestinal secretion which are known to contribute to peptide hydrolysis \[21\]. Aminopeptidases appear to be the only peptidases active on the buccal mucosa, therefore representing a major metabolic barrier to the buccal delivery of peptide drugs \[22\]. The absence of endopeptidase and carboxypeptidase activities will be advantageous for the buccal delivery of peptides which are susceptible to these activities. Recently, it could be observed that thiolation of polycarboxphil (PCP) enhances the inhibitory potency of PCP towards aminopeptidase N and membrane bound peptidases involved in the digestion of leu-p-nitroanilide (leu-pNA) and leucin-enkephalin (leu-enkephalin). A combination of different properties within a unique system, for instance mucoadhesive and enzyme inhibiting properties could be obtained by the use of thiolated PCP in a buccal drug delivery system. The covalent attachment of cysteine to the anionic polymer PCP leads to an improvement of the stability of matrix-tablets consisting of thiolated polymer. The mucoadhesive properties are also enhanced, which is confirmed by two different in vitro test systems. In addition, thiolation increases the inhibitory potency of PCP towards buccal enzymes, and thereby the stability of leu-enkephalin and leu-pNA is raised. Due to these features matrix-tablets based on thiolated PCP represent a promising type of buccal drug delivery systems.

Related to evaluation methods
Experimental Methodology for Buccal Permeation Studies
Before a buccal drug delivery system can be formulated, buccal absorption/permeation studies must be conducted to determine the feasibility of this route of administration for the candidate drug. These studies involve methods that would examine in vitro and/or in vivo buccal permeation profile and absorption kinetics of the drug.

A. In vitro Methods
At the present time, most of the in vitro studies examining drug transport across buccal mucosa have used buccal tissues from animal models. Animals are sacrificed immediately before the start of an experiment. Buccal mucosa with underlying connective tissue is surgically removed from the oral cavity, the connective tissue is then carefully removed and the buccal mucosal membrane is isolated. The membranes are then placed and stored in ice-cold (4°C) buffers (usually Krebs buffer) until mounted between side-by-side diffusion cells for the in vitro permeation experiments. Buccal cell cultures have also been suggested as useful in vitro models for buccal drug permeation and metabolism \[23\]. However, to utilize these culture cells for buccal drug transport, the number of differentiated cell layers and the lipid composition of the barrier layers must be well characterized and controlled.

B. In vivo Methods
In vivo methods were first originated by Beckett and Triggs with the so-called buccal absorption test. Using this method, the kinetics of drug absorption was measured. The methodology involves the swirling of a 25 ml sample of the test solution for up to 15 minutes by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined in order to assess the amount of drug absorbed. The drawbacks of this method include salivary dilution of the drug, accidental swallowing of a portion of the sample solution, and the inability to localize the drug solution within a specific site (buccal, sublingual, or gingival) of the oral cavity \[24\]. Other in vivo methods include those carried out using a small perfusion chamber attached to the upper lip of anesthetized dogs \[25\]. The perfusion chamber is attached to the tissue by cyanoacrylate cement. The drug solution is circulated through the device for a predetermined period of time and sample fractions are then collected from the perfusion chamber (to determine the amount of drug remaining in the chamber) and blood samples are drawn after 0 and 30 minutes (to determine amount of drug absorbed across the mucosa).

C. Experimental Animal Species \[9\]
Aside from the specific methodology employed to study buccal drug absorption/permeation characteristics, special attention is warranted to the choice of experimental animal species for such experiments. For in vivo investigations, many researchers have used small animals including rats and hamsters for permeability studies. However, such choices seriously limit the value of the data obtained since, unlike humans, most laboratory
animals have an oral lining that is totally keratinized. The rabbit is the only laboratory rodent that has non-keratinized mucosal lining similar to human tissue but it is hard to isolate the desired non-keratinized region due to sudden transition to keratinized tissue at the mucosal margins. The oral mucosa of larger experimental animals that has been used for permeability and drug delivery studies include monkeys, dogs, and pigs which are having non-keratinized tissue.

**METHODS FOR MUCOADHESION TESTING**

A direct-staining method was established to evaluate the bioadhesion of polymeric aqueous dispersion on buccal cells both in vitro and in vivo by employing Alcian blue to bind to anionic polymers and Eosin to bind to the amine groups in polymers. Unbound dye was removed by washing with 0.25M sucrose. The extent of polymer adhesion was quantified by measuring the relative staining intensity of control and polymer-treated cells by image analysis. This method is only suitable for assessing the liquid dosage forms, which are widely employed to enhance oral hygiene and to treat local disease conditions of the mouth such as oral candidiasis and dental caries [26].

A lectin-binding inhibition technique involving an avidin–biotin complex and a colorimetric detection system was developed to investigate the binding of bioadhesive polymers to buccal epithelial cells without having to alter their physicochemical properties by the addition of “marker” entities [27]. The lectin from Canavalia ensiformis (Concanavalin A) has been shown to bind to sugar groups present on the surface of buccal cells [28]. Therefore, if polymers bind to buccal cells, they would mask the surface glycocconjugates, thus reducing or inhibiting Canavalia ensiformis lectin binding.

Atomic force microscopy was used to determine the bioadhesion of polymer onto the buccal cell surfaces [29]. Changes in surface topography were indicative of the presence of polymer bound onto buccal cell surfaces. Unbound cells showed relatively smooth surface characteristics with many small craterlike pits and indentations spread over cell surfaces, while polymer-bound cells lost the crater and indentation characteristics and gained a higher surface roughness.

**DISSOLUTION AND DRUG RELEASE FORM BIOADHESIVE DOSAGE FORMS**

USP 29 states the use of disintegration test for ergoloid mesylate and ergotamine tartrate sublingual tablets and apparatus 2 with water as dissolution medium for isosorbide-dinitrate sublingual tablet. Since such medications are designed to dissolve the drug in a short time period, it is obvious that disintegration and not necessarily dissolution is the true rate-limiting step for drug release of these dosage forms. Therefore, several studies have been performed to investigate drug dissolution in smaller volumes or using different apparatuses.

Fabregas and Garcia used USP apparatus 3 at a rate of 20 strokes/min for conducting in vitro dissolution studies of hydrocortisone hemisuccinate mucoadhesive tablets [30].

Dor and Fix developed a special disintegration test using a Texture Analyzer Instrument to accurately determine the rate of drug release from sublingual/buccal medications. In this method, the tablet is attached to a cylindrical probe and placed under a constant force to promote disintegration. The tablet is then submerged into a defined volume of medium and the time for complete tablet disintegration versus distance traveled is determined [31].

Drug release studies for buccal tablets are normally performed using USP apparatus 2 [32]. However some authors wanted to mimic the intended drug release in one direction only (buccal mucosa) and proposed to use an intrinsic dissolution apparatus to analyze the drug release from one surface only [33]. In order to expose a single face with constant area to the medium, they coated all surfaces except one using a water impermeable coating.

Ikinci et al. used an alternative method to study the release of nicotine from buccal tablets. They used modified Franz diffusion cells for this purpose. The dissolution medium was 22 ml phosphate buffer saline (PBS) (pH 7.4) at 37°C. Uniform mixing of the medium was provided by magnetic stirring at 300 rpm. To provide unidirectional release, each bioadhesive tablet was embedded into paraffin wax which was placed on top of a bovine buccal mucosa as membrane [34].

Mumtaz and Ch’ng introduced another method for studying the dissolution of buccal tablets. The device that they introduced is based on the circulation of pre-warmed dissolution medium through a cell as shown in Fig.B. Here the buccal tablet was attached on chicken pouches. Samples were removed at different time intervals for drug content analysis. They stated “the results obtained...
by using this apparatus for the release of drug from bioadhesive tablets concurred with the predicted patterns.\cite{35}

![Schematic drawing of the dissolution apparatus](image)

**Figure**: Schematic drawing of the dissolution apparatus used by Mumtaz and Ch’ng (1995) for studying the dissolution of buccal tablets

**Slug mucosal irritation assay**

Those formulations remain in contact with the mucosal surface for a longer time period, therefore it is important to assess their mucosal irritation potency. The Slug Mucosal Irritation (SMI) assay was developed at the University of Ghent (Belgium) in the Laboratory of Pharmaceutical Technology. The slug mucosal irritation assay can be used as an alternative test to predict the mucosal and ocular tolerance of new pharmaceuticals early in the research and development phase, thereby replacing the use of laboratory mammals. The principle of this assay is that the body wall of slug (Arion lustanicus) has a highly mucosal surface as a test organism. Slugs that are placed on an irritant substance will produce mucus and tissue damage results in the release of proteins and enzymes. Based on estimation of the levels of protein & enzymes irritation potency can be predicted. The irritation potency is predicted based on the total amount of mucus produced (total MP) during the repeated 30-min contact periods. The mucus production is expressed as a percentage of the body weight of the slugs.

**Table**: some currently available marketed buccal formulations in UK

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Bioadhesive agent</th>
<th>Pharmaceutical form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccastem®</td>
<td>Reckitt Benckiser</td>
<td>PVP, Xanthum gum</td>
<td>Buccal tablet</td>
</tr>
<tr>
<td>Corlan pellets®</td>
<td>Celltech</td>
<td>Acacia gum</td>
<td>Oromucosal pellets</td>
</tr>
<tr>
<td>Suscard®</td>
<td>Forest</td>
<td>HPMC</td>
<td>Buccal tablet</td>
</tr>
<tr>
<td>Gaviscon liquid®</td>
<td>Reckitt Benckiser</td>
<td>Sodium alginate</td>
<td>Oral liquid</td>
</tr>
<tr>
<td>Orabase®</td>
<td>Convatech</td>
<td>Pectin, Gelatin</td>
<td>Oral paste</td>
</tr>
<tr>
<td>Corsodyl gel®</td>
<td>GalaxoSmithKline</td>
<td>HPMC</td>
<td>Oromucosal gel</td>
</tr>
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