

Mucocoadhesive Drug Delivery System: An Overview

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INTRODUCTION

In recent years, there has been increasing interest on the use of bioadhesive drug delivery system. 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. 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^{1, 2}. Transmucosal routes of drug delivery involve the delivery of the drug through the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity³.

BIOADHESIVE DRUG DELIVERY^{4, 5, 32}

Adhesion can be defined as the bond produced by contact between a pressure - sensitive adhesive and a surface or the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action or both.

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.

Drug delivery across the oral mucosa, can be divided into three different types.

1. **Sublingual** delivery, consisting of administration through the membrane of the ventral 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.

ADVANTAGES OF DRUG DELIVERY⁶

- 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.

LIMITATIONS OF BUCCAL DRUG DELIVERY⁶

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

STRUCTURE OF THE HUMAN ORAL MUCOSA⁷

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, lamina propria followed by the submucosa as the innermost layer. 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 epithelium⁸. 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, the floor of the mouth, the ventral tongue and the gingiva 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 keratinized⁹. The non-keratinized epithelia are more permeable to water than the keratinized epithelia¹⁰.

Fig. 1 Structure of the human oral mucosa

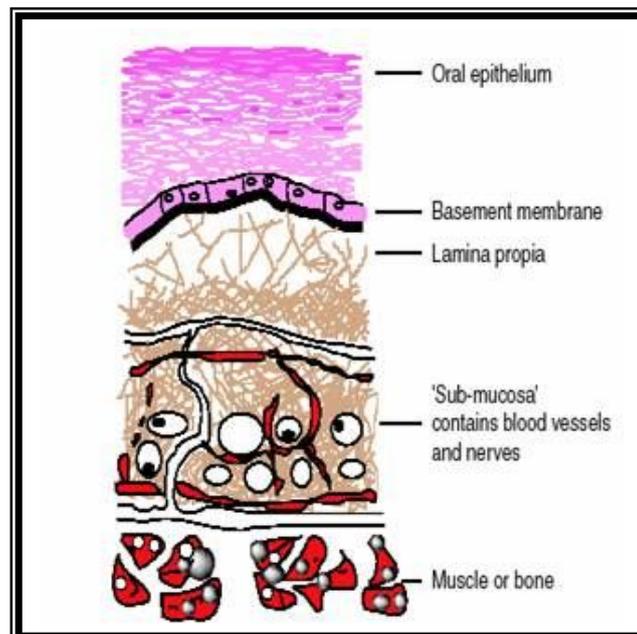


Fig. 2 Diagram to show the anatomic location and extent of masticatory, lining, and specialized mucosa in the oral cavity

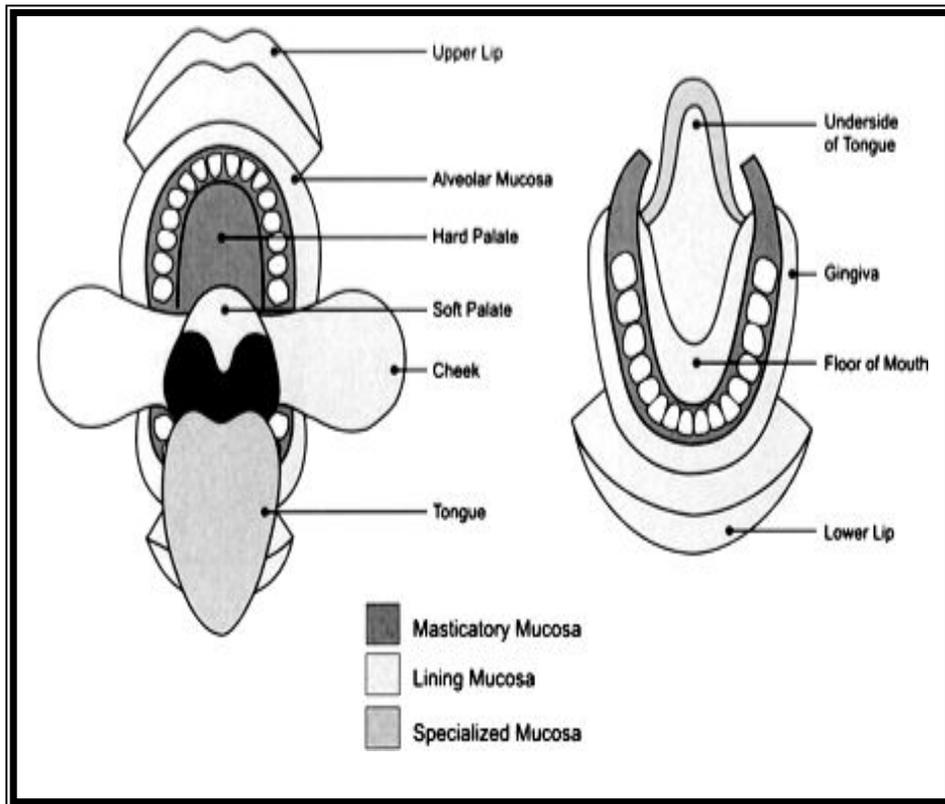
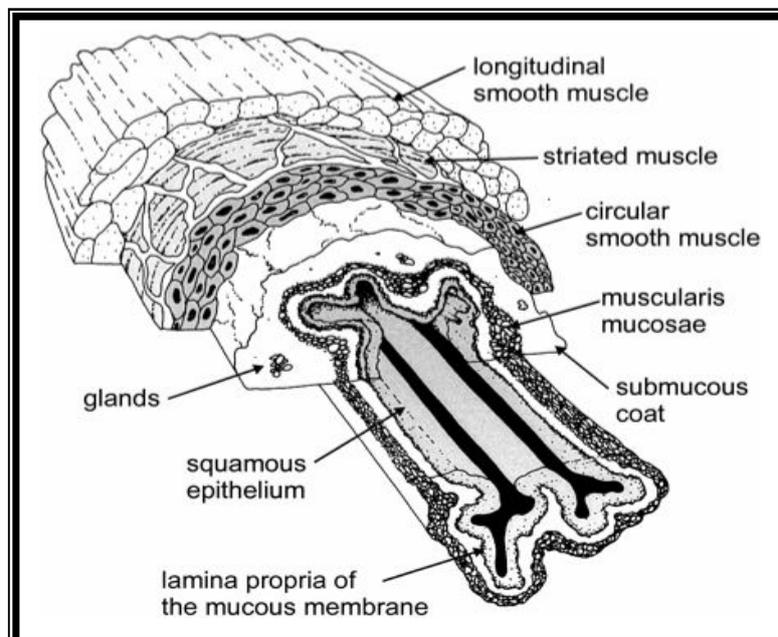


Fig. 3 General Structure of oral mucosae



VASCULAR SYSTEM OF THE ORAL MUCOSA^{11,33}

The blood flow in the various regions of the oral mucosa has been studied in the rhesus monkey and is represented as:

Table 1. 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 MUCUS¹²

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.

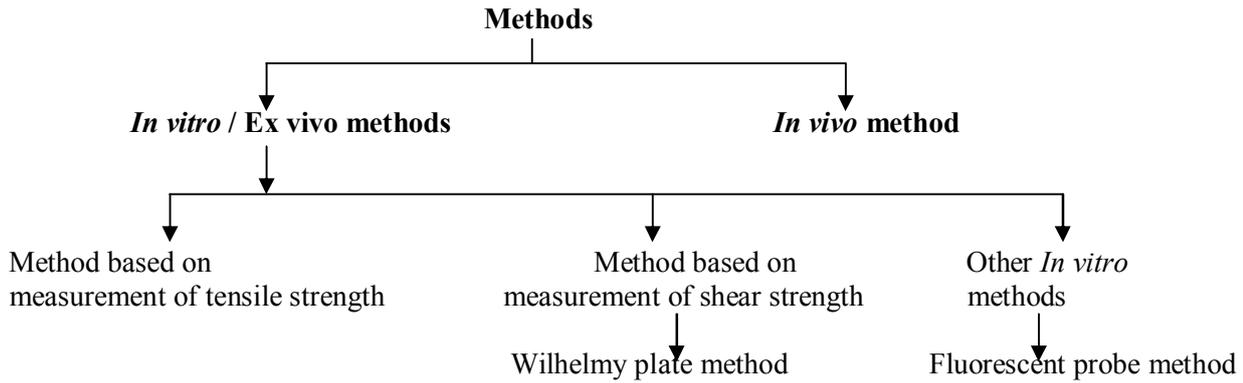
Mucus is a glycoprotein, chemically consisting of a large peptide backbone with pendant oligosaccharide side chains whose terminal end is either sialic or sulfonic acid or L-fructose. The oligosaccharide chains are covalently linked to the hydroxy amino acids, serine and threonine, along the polypeptide backbone. 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.

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. 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.

BIOADHESION IN DRUG DELIVERY^{13, 14}

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. 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.

METHOD USED TO STUDY BIOADHESION²⁰



A. Tensile strength measurement

Park and Robinson employed a method in which the force required to separate the bioadhesive sample from freshly excised rabbit stomach tissue was determined using a modified tensiometer. A section of the tissue, having the mucus side exposed, was secured on a weighed glass vial placed in a beaker containing USP simulated gastric fluid. Another section of the same tissue was placed over a rubber stopper again with the mucus side exposed and secured with a vial cap and a small quantity of polymer was placed between the two mucosal tissues. The force was used to detach the polymer from the tissue was then recorded.

B. Wilhelmy plate method

In this method, the plates are coated with a polymer to be tested and immersed in a temperature controlled mucus solution. The force required to pull the plate out of the solution is determined under constant experimental conditions.

C. Fluorescent probe method

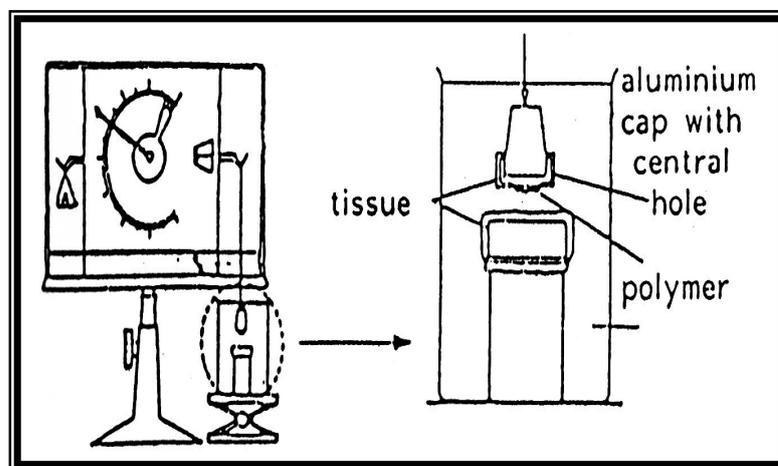
Park and Robinson, studied polymer interaction with the conjunctival epithelial cell membrane using fluorescent probes. The membrane lipid bilayer and membrane proteins were labeled with pyrene and fluorescein isothiocyanate, respectively. The cells were then mixed with candidate bioadhesives and the changes in fluorescence spectra were monitored. This gives a direct indication of polymer binding and its influence on polymer adhesion.

D. In vivo methods

In vivo techniques for measuring the bioadhesive strength are relatively few. Some of the reported methods are based on the measurement of the residence time of bioadhesives at the application site. The three main *in vivo* techniques to monitor bioadhesion include

- Gamma scintigraphy
- Isolated loop techniques
- Transit with radiolabelled or fluorescent coupled dosage forms.

Fig. 4 Apparatus for determination of ex vivo bioadhesion



METHODS TO INCREASE DRUG DELIVERY VIA BUCCAL ROUTE

Absorption enhancers²¹

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 *f. 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.

EVALUATION OF BUCCOADHESIVE DRUG DELIVERY SYSTEM²²⁻³⁰

a. Average weight and Weight Variation

b. Average Thickness

e. Determination of mucoadhesive strength

e. Drug content estimation

g. In-vitro Diffusion Studies

h. In vivo methods

DRUGS DELIVERED VIA BUCCAL ROUTE³¹

In an effort to determine the feasibility of buccal ROUTE as a novel route of drug delivery, several drugs have been studied. The variation in class of compounds illustrates that the pharmaceutical industries have an alternative and novel routes of administration for existing drugs.

Table 2: List of Permeation Enhancers

Sr. no	Permeation Enhancers	Sr. no	Permeation Enhancers
1	2,3-Lauryl ether	14	Phosphatidylcholine
2	Aprotinin	15	Polyoxyethylene
3	Azone	16	Polysorbate 80
4	Benzalkonium chloride	17	Polyoxyethylene
5	Cetylpyridinium chloride	18	Phosphatidylcholine
6	Cetyltrimethyl ammonium bromide	19	Sodium EDTA
7	Cyclodextrin	20	Sodium glycocholate
8	Dextran sulfate	21	Sodium glycodeoxycholate
9	Glycol	22	Sodium lauryl sulfate
10	Lauric acid	23	Sodium salicylate
11	Lauric acid/Propylene	24	Sodium taurocholate
12	Lysophosphatidylcholine	25	Sodium taurodeoxycholate
13	Menthol	26	Sulfoxides

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