Buccal Delivery Systems

Dr. Sushil Raut

Introduction

- The oral cavity is an attractive site for drug delivery due to ease of administration and avoidance of possible drug degradation in the gastrointestinal tract and first-pass metabolism
- There are four potential regions for drug delivery in the oral cavity, namely buccal, sublingual, palatal, and gingival
- Buccal drug delivery specifically refers to the delivery of drugs within/through the buccal mucosa to affect local/systemic pharmacological actions.

Introduction

- Buccal-delivered drugs may be used for treatment of diseases in the oral cavity or for systemic use

- Limitations of buccal delivery include:
  - short residence time
  - small absorption area
  - barrier property of the buccal mucosa

Anatomy and Biochemistry of Oral Mucosa

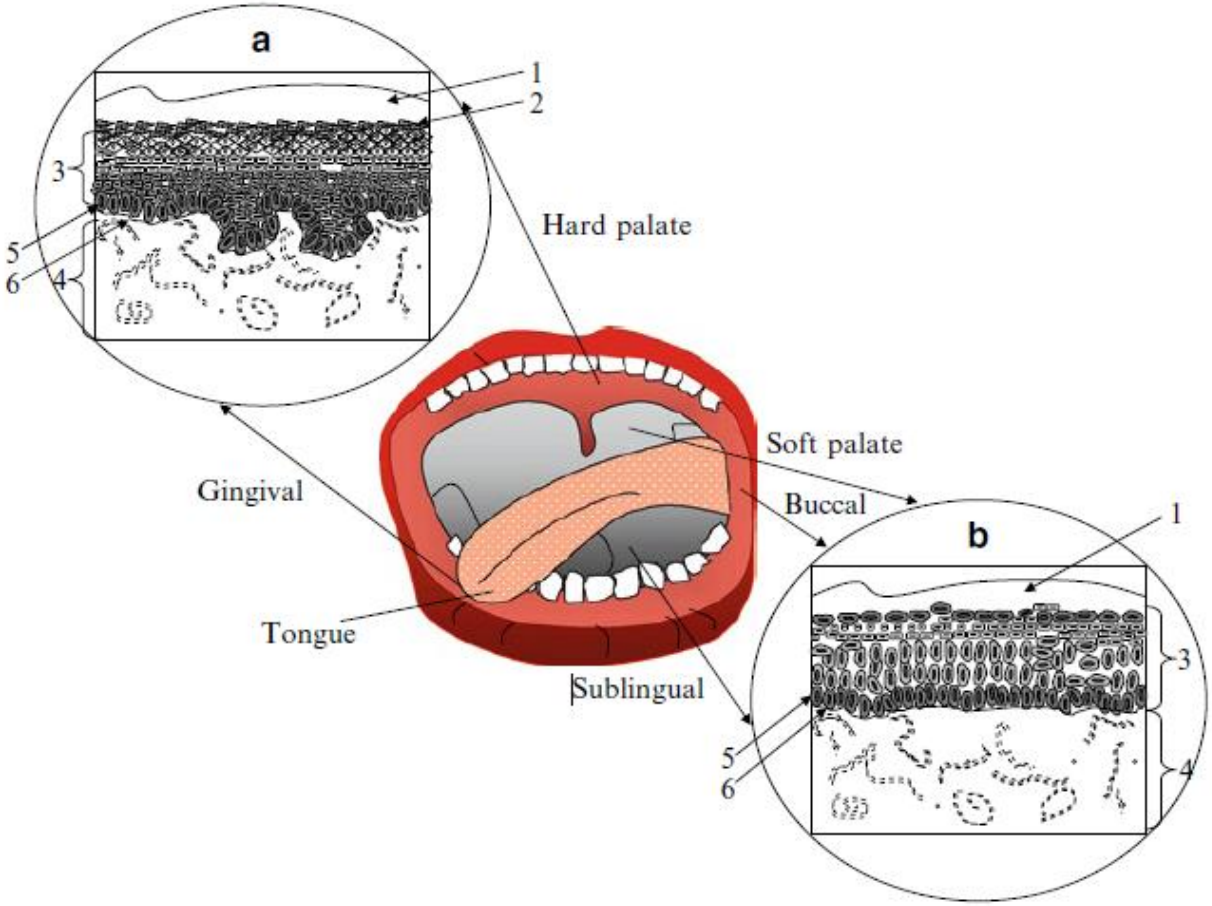


Fig. 16.1 Mucosal regions of the mouth with insets showing the compositions of (**a**) keratinized and (**b**) nonkeratinized mucosal epithelium lining various mucosal regions: 1. Mucus layer, 2. Parakeratinized layer, 3. Epithelium, 4. Lamina propria, 5. Stratum basale, 6. Basal lamina

Anatomy and Biochemistry of Oral Mucosa

- The lining mucosa of the oral cavity is covered by a stratified, nonkeratinized squamous epithelium
- Although the surface area of the oral mucosa is relatively small in comparison to the skin and the GI tract, its high vasculature lends itself to potential drug absorption.
- The oral cavity may be divided into three sections depending on variations in the thickness and nature of the mucosal lining:
  - The sublingual mucosa
  - The buccal mucosa
  - The soft palate

Sublingual mucosa

- The sublingual mucosa lines the floor of the mouth and is the thinnest and the most permeable region in the oral cavity
- It is supplied with high blood flow and has sufficient surface area to make it a location of choice when rapid absorption/onset of drug action is necessary
- However, its surface is constantly washed by saliva and this plus tongue activity which makes it difficult to keep the dosage form in contact with the mucosa

Buccal mucosa

- The buccal mucosa lines the interiors of the cheek and can be used for systemic as well as local delivery
- The surface of buccal mucosa is smooth, relatively immobile, and more permeable than other mucosal tissues makes it a location of choice for controlled release systems that need to stay adhered for an extended period
- Buccal mucosa is also more robust and tolerant to irritation and permanent damage from adhesion

Buccal mucosa

- Salivary production and composition may contribute to chemical modification of certain drugs
- Involuntary swallowing can result in drug loss from the site of absorption
- Constant salivary scavenging within the oral cavity makes it difficult for dosage forms to be retained for an extended period of time to facilitate absorption
- The relatively small absorption area and barrier properties can limit this route of delivery

Soft palate

- The soft palate is suspended from the posterior border of the hard palate connecting the oral and nasal parts of the pharynx in the roof of the oral cavity
- The palatal mucosa found in the oral cavity is highly vascularized, thin and mostly covered with stratified squamous epithelium

Formulation Considerations

- Mucoadhesive polymers
- Penetration enhancers (covered previously)
- Enzyme Inhibitors

Mucoadhesive polymers

- Mucoadhesives are synthetic or natural polymers that interact with the mucus layer covering the mucosal epithelial surface and main molecules constituting a major part of mucus

- The concept of mucoadhesives has alerted many investigators to the possibility that these polymers can be used to overcome physiological barriers in long-term drug delivery

Mucoadhesive polymers

- The polymers most commonly used in buccal dry or partially hydrated dosage forms include polyacrylic acid (PAA), polyvinyl alcohol (PVA), sodium carboxy methylcellulose (NaCMC) and sodium alginate

- New generation of mucoadhesive polymers (with the exception of thiolated polymers) can adhere directly to the cell surface, rather than to the mucus. They interact with the cell surface by means of specific receptors or covalent bonding instead of non-specific mechanisms, which are characteristic of the previous polymers. Examples of such are the incorporation of L-cysteine into thiolated polymers and the target-specific, lectin-mediated adhesive polymers

Mucoadhesive polymers

- Thiolated polymers are mucoadhesive polymers, which display thiol bearing side chains. These polymers are obtained by addition of conjugated sulfhydryl groups

- The presence of thiol groups allows the formation of covalent bonds with cysteine-rich sub domains of the mucus gel layer, leading to increased residence time and improved bioavailability

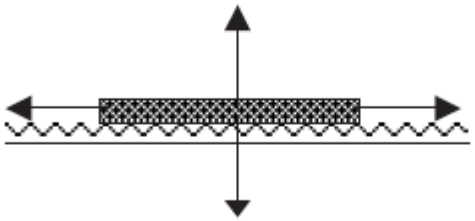
Enzyme Inhibitors

- The co-administration of a drug with enzyme inhibitors is another strategy for improving the buccal absorption of drugs, particularly peptides.
- Enzyme inhibitors, such as aprotinin, bestatin, puromycin and some bile salts stabilize protein drugs by different mechanisms, including:
  - affecting the activities of the enzymes
  - altering the conformation of the peptides or proteins
  - rendering the drug less accessible to enzymatic degradation
- It has been shown that some mucoadhesive polymers can act as an enzyme inhibitor

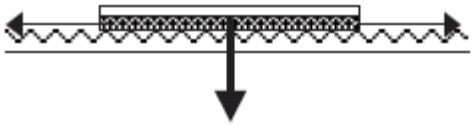
Enzyme Inhibitors

- Investigations have demonstrated that polymers, such as poly(acrylic acid), operate through a competitive mechanism with proteolytic enzymes
- This stems from their strong affinity to divalent cations (Ca^{2+}, Zn^{2+}). These cations are essential cofactors for the metalloproteinases, such as trypsin
- Studies suggest that Ca^{2+} depletion, mediated by the presence of some mucoadhesive polymers, causes the secondary structure of trypsin to change, and initiates a further autodegradation of the enzyme

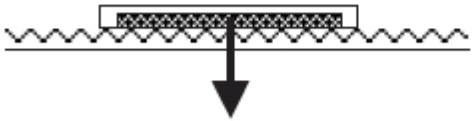
Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry illustrated in the following:



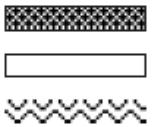
Type I Single-layer device



Type II Double-layer device



Type III Unidirectional release design



Drug-loaded bioadhesive layer
Impermeable backing layer
Mucus layer

Buccal Dosage Forms

- **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:** In this type, an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer, creating a double-layered device and preventing drug loss from the top surface of the dosage form into the oral cavity

Buccal Dosage Forms

- **Type III:** This is a unidirectional 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

Buccal dosage forms

- Buccal Tablets
- Buccal patches
- Buccal films
- Buccal gels and ointments
- Innovative Drug Delivery Systems

Fentanyl Buccal Tablet (Effentora™)

Buccal Tablets

- Buccal tablets are small, flat, and oval shaped dosage form and unlike conventional tablets allow for drinking and speaking without major discomfort.
- They soften, adhere to the mucosa and are retained in position until dissolution and/or release is complete
- Can be used for both local and systemic drug delivery

Buccal patches

- Buccal patches are described as laminates which comprise an impermeable backing layer, a drug-containing reservoir layer which releases the drug in a controlled manner, and a bioadhesive surface for mucosal attachment

Buccal film: Zuplenz 8 mg (approved by FDA, July 7, 2010)

Buccal films

- Buccal films are preferable over mucoadhesive tablets in terms of patient comfort and flexibility and they ensure more accurate drug dosing and longer residence time compared to gels and ointments

- Buccal films also reduce pain by protecting the wound surface and hence increase the treatment effectiveness

Buccal films

- An ideal buccal film should be flexible, elastic, and soft yet strong enough to withstand breakage due to stress from activities in the mouth
- Moreover, it should also possess good mucoadhesive strength so that it is retained in the mouth for the desired duration

Buccal gels and ointments

- These are semisolid dosage forms having the advantage of easy dispersion throughout the oral mucosa
- The problem of poor retention of gels at the application site has been overcome by using bioadhesive formulations
- Certain bioadhesive polymers for example, sodium carboxymethylcellulose undergo a phase change from a liquid to a semisolid. This change enhances or improves the viscosity, resulting in sustained or controlled release of drugs.

Innovative Drug Delivery Systems

- A novel liquid aerosol formulation (Oral-lyn, Generex Biotechnology) has been recently developed, and it is now in clinical phase III trials
- This system allows precise insulin dose delivery via a metered dose inhaler in the form of fine aerosolized droplets directed into the mouth
- This oral aerosol formulation is rapidly absorbed through the buccal mucosal epithelium, and it provides the plasma insulin levels necessary to control postprandial glucose rise in diabetic patients
- This novel, pain-free, oral insulin formulation has a number of advantages including rapid absorption, a simple (user-friendly) administration technique, precise dosing control (comparable to injection within one unit) and bolus delivery of drug.