

Recent Trend In Oral Local Drug Delivery Using Buccal Mucoadhesive Formulation: A Review

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Abstract

In this 21st century pharmaceutical science has been focused on the delivery of drugs through the oral mucosa. The buccal mucosa has been investigated for mucoadhesive local drug therapy and the systemic delivery of therapeutic peptides and other drugs that are subjected to first-pass metabolism or are unstable within the rest of the gastrointestinal tract. This review focuses on the permeability features of oral mucosa and new potential mucoadhesive local delivery systems to treat oral diseases.

Key Words: Drug delivery; Mucoadhesive; Buccal Mucosa; Oral Diseases.

Introduction

Considerable attention has been focused in recent years on the delivery of drugs through the oral mucosa which have a high first pass metabolism or degrade in the gastrointestinal tract.¹

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Difficulties associated with parenteral delivery and poor oral availability promoted the impetus for exploring alternative routes for the delivery of drugs. Among the various transmucosal routes i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities, buccal mucosa has an excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of controlled release dosage forms and has a high patient acceptability compared to other non-oral transmucosal routes of drug administration.² Mucoadhesive controlled-release devices can improve the effectiveness of a drug by maintaining the drug concentration between the effective and toxic levels, inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site.¹

Ideal Characteristics of Mucoadhesive Drug Delivery Mode³

1. Should have good adherence and strong interaction with the mucin epithelial tissue.
2. Should have good viscoelastic and biodegradability properties.
3. Should have peel, tensile and shear strengths at the bioadhesive range.
4. Should not affect by the hydrodynamic conditions, food and pH changes.
5. Should have good shelf life.
6. Should have optimum molecular weight.
7. Should incorporate in various dosage forms both in dry and liquid state.
8. Should have adhesively active groups and spatial conformation.

Advantages of Mucoadhesive Drug Delivery Mode ^{4,5}

1. It is preferred route, for the systemic delivery of drugs in severe gastrointestinal disturbances and unconscious patients.
2. Administration and termination of drug is easy.
3. Systemic absorption is fast and permits localization of drug to the buccal mucosa for a prolonged period of time.
4. It allows the delivery of therapeutic agents like peptides and proteins easily.
5. Drug dissolution due to presence of saliva is more as compared to rectal or transdermal routes.
6. Dose related side effects are less in comparison to other modes of administration.
7. Patients suffering from dysphagia, repeated emesis, paralysis and mental disorders prefer mucoadhesive dosage form as they are not capable swallowing large quantities of water.

Drawbacks of Mucoadhesive Drug Delivery Mode ^{4,6}

1. Patient may swallow the tablet while eating and drinking.
2. Mucoadhesive drugs cannot be used with unstable pH of buccal mucosa.
3. Large doses of drug are difficult to be administered.
4. Surface area for absorption is small.
5. Drugs which irritate the mucosa or have an unpleasant taste or an obnoxious odour cannot be used.

Theories of Bioadhesion

A complete and comprehensive theory that can predict adhesion based on the chemical and/or physical nature of a polymer is not yet available.⁷ The theoretical framework for polymer- polymer adhesion can be easily extended to describe the bioadhesion of polymeric materials with biological surfaces.⁸ Five theories of mucoadhesion that were originally developed are described below:

1. Electronic Theory: Mucoadhesion is based on electron transfer due to contact of the bioadhesive polymer and the glycoprotein network which have different electronic structures and lead to the formation of a double layer of electrical charge at the bioadhesive interface. Nikhil et al reported that mucoadhesion is analogous to a capacitor where the system is charged when the adhesive and substrates are in contact and discharged when they are separated.^{7,8}

2. Diffusion Theory: The interpenetration and entanglement of the bioadhesive polymer chains and mucous polymer chains is based on diffusion theory. The bond strength increases with the increase in the degree of the penetration depend on the concentration gradients and the diffusion coefficients.⁹

3. Adsorption Theory: According to the adsorption theory, bioadhesive systems adhere to tissue because of Vander walls, hydrogen bonding, electrostatic attraction, hydrophobic interactions and/or other related forces.^{7,8}

4. Fracture Theory: The fracture theory of bioadhesion related to the difficulty of separation of two surfaces after adhesion to the adhesive bond strength by measuring the maximum tensile stress produced during detachment.^{8,9}

5. Wetting Theory: The wetting theory emphasizes the intimate contact between the mucoadhesive polymer and the mucus in liquid systems which is based on interfacial tension to predict spreading and subsequent adhesion. Some important characteristics for liquid bioadhesive materials include a zero or near zero contact angle, a relatively low viscosity and an intimate contact that exclude air entrapment.^{7,8}

Factors Affecting Mucoadhesion

Anatomical Factors Affecting Mucoadhesion: The permeability of the oral mucosal epithelium is intermediate as compared to skin epithelium and gut.⁶ The permeability barrier in the oral mucosa depends on the intercellular material derived from the membrane coating granules which are present in the outermost 200µm of the superficial layer.¹⁰ The buccal mucosa thickness is approximately 500-800 µm and less permeable in comparison with sublingual mucosa.⁶ The drug transport through the buccal mucosa involves transcellular (intracellular) and paracellular (intercellular) pathways.²

Environmental Factors Affecting Mucoadhesion: Movement of the buccal tissues leads to the detachment of the dosage form while sleeping, eating, drinking, and talking should be considered during administration of drug and an optimum time span for the administration is necessary in order to avoid above mentioned interfering factors.¹

Physiological Factors Affecting Mucoadhesion: Drug moieties which traverse the oral epithelium are readily absorbed into the systemic circulation due to rich blood supply and lymphatic network in the lamina propria.⁶ Mucus forms viscoelastic layer of varying thickness that affects drug absorption.² Oral mucosal delivery is preferred for enzymatically labile drugs such as therapeutic peptides and proteins because these drug moieties adsorbed via the oral epithelium are delivered directly into the blood, avoiding first-pass metabolism effects of the liver and gut wall.⁶ With the use of various compounds like penetration enhancers, solubility modifiers and enzyme inhibitors increase the flux of drugs through the oral mucosa.²

Mechanism of Mucoadhesion

It has been stated that at least one of the following polymer characteristics are required to obtain adhesion (i) sufficient number of hydrogen bonding chemical groups (- OH and -COOH) (ii) anionic surface chain (iii) high molecular weight (iv) high chain flexibility (v) surface tension that will induce spreading into the mucus layer. Each of these characteristics favours the formation of bonds that are either chemical or mechanical in origin.¹³ Mucoadhesion is a complex phenomenon and several steps have been suggested in mucoadhesive bond formation are discussed below:¹¹

1. Spreading, wetting, and dissolution of mucoadhesive polymer at the interface.
2. Mechanical or physical entanglement between the polymer and the tissue surface mucus layer, resulting in an interpenetration layer.
3. Chemical interactions, such as covalent and ionic bonds, hydrogen bonding, and Vander Waals' interactions. Hydrogen bonds and hydrophobic interactions are the most desirable in developing mucoadhesive systems, as strong primary bonds (e.g., covalent bonds and ionic bonds) could cause irreversible damage of the mucosal surface.

Local Oral Drug Delivery

Local drug delivery provides a more targeted delivery and should be considered a delivery route appropriate for drugs exhibiting high therapeutic potency and relatively small quantity of drug can be delivered. Drug delivery via the oral mucosa can be categorized¹¹

1. Drug delivery via keratinized mucosa
 - a. Gingiva
 - b. Palate
2. Drug delivery via nonkeratinized mucosa.
 - a. Sublingual drug delivery
 - b. Buccal mucosa drug delivery

The keratinized mucosa, such as gingival and hard palatal mucosa should be considered as useful sites for local (direct) drug delivery only in treating oral diseases localized at the gingiva or palate. The sublingual mucosa is more permeable, thinner and rapid onset than the buccal mucosa used for the systemic delivery of drugs in treating acute disorders. The buccal mucosa is considerably less permeable than the sublingual mucosa; so it is preferred for the systemic treatment of chronic disorders where the sustained delivery of systemically acting drugs is required.¹¹

Recently, Chitosan-based delivery systems which are non-invasive mucosal routes used for administration of biotherapeutics to enhance the absorption and/or cellular uptake of peptides/proteins across mucosal sites and have immunoadjuvant properties. Chitosan is a mucoadhesive polysaccharide capable of opening the tight junctions between epithelial cells and it has functional groups for chemical modifications.¹² Many synthetic polymers biodegradability used for mucoadhesive is doubtful, so they are replaced by natural gums and mucilage as pharmaceutical excipients. Goswami et al concluded in their study that the gum of *Azadirachta indica* and *Moringa oleifera* can be used as a pharmaceutical excipient in oral mucoadhesive drug delivery systems.¹³

Dosage Forms: Dosage forms can be classified on the basis of mechanism by which a drug is released into the following categories:

1. Monolithic or matrix type
2. Reservoir or membrane-controlled type.

Mucoadhesive systems for oral local drug delivery include adhesive tablets, adhesive patches, adhesive films or pellicles, adhesive semisolid systems (gels, ointments), and adhesive liquid systems (sprays, mouthwashes).¹¹

Vijaybhaskar et al¹⁴ concluded that curcumin is effective and useful in oral submucous fibrosis in their in-vitro study of curcumin that exhibits antitumeric and antimutogenic activity as oral mucoadhesive semisolid gel for the treatment of oral submucous fibrosis. Cilarzo et al¹⁵ studied a mucoadhesive prolonged release tablet containing 24 lg clobetasol- 17 propionate (CP) for the management of oral lichen planus and concluded that the application of mucoadhesive tablet containing 24 lg CP 3 times a day appeared to be effective, avoiding the side effects of the generally used treatment.

Godara et al¹⁶ conducted the study on formulation of mucoadhesive buccal discs containing 10 mg Prednisolone by using polymers like Sodium carboxymethylcellulose (SCMC), Hydroxypropyl methylcellulose (HPMC K100M), Carbopol-934 and Chitosan. They concluded in their study that formulation with HPMC shows the best sustained result, whereas the formulation with the polymer SCMC and Chitosan shows the best ex-vivo mucoadhesion time.

Conclusion

Now a days there is huge work going in developing to novel dosage form to satisfy increased patient demand of more convenient dosage forms within aim to improve patient compliance and convenience are more important. Mucoadhesive dosage forms are more popular and convenient way of dosing medication, not only to dysphagia patients, but also to general population. The use of buccal-adhesive dosage forms offers an opportunity for optimizing the delivery of drugs both locally and systemically, and many different types of formulation have been developed. The presence of saliva within the oral cavity is important in providing the moisture to allow adhesion to occur, and to allow a medium for drug dissolution prior to absorption. For the delivery of large molecules, the use of a buccal-adhesive dosage form in conjunction with a suitable safe but effective penetration enhancer would appear to provide the optimum conditions for drug absorption if other routes of drug delivery are found to be inappropriate.

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