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**APPROACHES TO MUCOADHESIVE DRUG DELIVERY SYSTEM IN ORAL
CAVITY-A DETAILED REVIEW**

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ABSTRACT

Buccal mucosa is the preferred site for both systemic and local drug action. The mucosa has a rich blood supply and it is relatively permeable. In buccal drug delivery systems mucoadhesion is the key element so various mucoadhesive polymers have been utilized in different dosages form. 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. In this review we have discussed the various approaches to achieve mucoadhesion through oral cavity, various types of mucoadhesive dosage forms along with new generation mucoadhesive polymers.

KEYWORDS

Bucco-adhesive drug delivery, Mucoadhesion, Mucoadhesive Polymer, Dosage Form and Permeation enhancers.

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INTRODUCTION¹

Bioadhesion may be defined as the state in which two materials, at least one of which is of a biological nature, are held together for extend periods of time by interfacial forces. For drug delivery purposes, bioadhesion term implies the attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue or the mucous coat on the surface of a tissue. If the adhesive attachment is to a mucous coat, then the phenomenon is known as mucoadhesion. Mucosal

layer represents potential sites for the attachment of any bioadhesive systems because mucosal layer lines number of the body including the gastro intestinal tract, the urogenital tract, vaginal tract, eye, ear, and nose. Recently the oral transmucosal drug delivery gaining important than other mucoadhesive delivery systems like vaginal delivery, rectal delivery, nasal delivery, ocular delivery.

Mucoadhesive drug delivery system in oral cavity²

Drug delivery via the membranes of the oral cavity can be subdivided as follows:

Sublingual Delivery

Drugs are delivered through mucosal membrane lining the floor of mouth into systemic circulation.

Buccal Delivery

Drugs are delivered through mucosal membrane into systemic circulation by placing drug in between cheeks and gums.

Local Delivery

Drugs are delivered into the oral cavity.

Advantages of Buccal Drug Delivery Systems³⁻⁴

Drug administration via buccal mucosa offers several distinct advantages,

- Ease of administration.
- Termination of therapy is easy.
- Permits localization of drug to the buccal cavity for a prolonged period of time.
- Can be administered to unconscious patients.
- Offers an excellent route, for the systemic delivery of drugs which undergo extensive first-pass metabolism or degradation in harsh gastrointestinal environment.
- A significant reduction in dose can be achieved thereby reducing dose related side effects.
- Drugs, which show poor bioavailability via the oral route, can be administered conveniently.
- It offers a passive system of drug absorption and does not require any activation.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal or transdermal routes.
- Systemic absorption is rapid as buccal mucosa is thin and highly perfused with blood.

- Provides an alternative route for the administration of various hormones, narcotic analgesics, steroids, enzymes, cardiovascular agents etc.
- It allows the local modification of tissue permeability, inhibition of protease activity and reduction in immunogenic response. Thus, delivery of therapeutic agents like peptides, proteins and ionized species can be done easily.

Disadvantages of Buccal drug delivery system⁵⁻⁶

- Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property.
- One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.
- Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste or odour; cannot be administered by this route.
- Drugs, which are unstable at buccal pH, cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Drugs may get swallowed with saliva and loses the advantages of buccal route.
- Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
- Surface area available for absorption is less.
- The buccal mucosa is relatively less permeable than the small intestine, rectum, etc.

Classification of buccal bio-adhesive dosage form⁷⁻⁸

Buccal Bioadhesive Tablets

Buccal bioadhesive tablets are dry dosage forms that are to be moistened after placing in contact with buccal mucosa. Double and multilayered tablets are already formulated using bioadhesive polymers and excipients. These tablets are solid dosage forms that are prepared by the direct compression of powder and can be placed into contact with the oral mucosa and allowed to dissolve or adhere depending on the type of excipients incorporated into the dosage form. They can deliver drug multi-directionally into the oral cavity or to the mucosal surface.

Buccal Bioadhesive Semisolid Dosage Forms

Buccal bioadhesive semisolid dosage forms consist of finally powdered natural or synthetic polymers dispersed in a polyethylene or in aqueous solution example: Arabase.

Buccal Bioadhesive Patches and Films

Buccal bioadhesive patches consists of two ply laminates or multilayered thin film that are round or oval in shape, consisting of basically of bioadhesive polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bioadhesive films are formulated by incorporating the drug in alcohol solution of bioadhesive polymer.

Buccal Bioadhesive Powder Dosage Forms

Buccal bioadhesive powder dosage forms are a mixture of bioadhesive polymers and the drug and are sprayed onto the buccal mucosa the reduction in diastolic B.P after the administration of buccal tablet and buccal film of Nifedipine.

Buccal chewing gum

Some commercial products of buccal chewing gum are available in the market like Caffeine chewing gum, Stay Alert, was developed recently for alleviation of sleepiness. It is absorbed at a significantly faster rate and its bioavailability was comparable to that in capsule formulation. Nicotine chewing gums (e.g., Nicorette and Nicotinell) have been marketed for smoking cessation. The permeability of nicotine across the buccal mucosa is faster than across the skin.

Bioadhesive spray

Bucco-adhesive sprays are gaining important over other dosage forms because of flexibility, comfort, high surface area and availability of drug in solution form. The first FDA-approved (1996) formulation was developed by fentanyl Oralet™ 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.

Physiological factors affecting buccal bioavailability⁹⁻¹⁰

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 than the sublingual mucosa.

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.

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.

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.

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.

Ability to retain delivery system

The buccal mucosa comprises an expanse of smooth and relatively immobile surface and thus is ideally suited to the use of retentive delivery systems.

Species differences

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

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 mechanism: passive diffusion, carrier mediated transport and via endocytic processes.

Sites for mucoadhesive drug delivery systems¹¹

The common sites of application where mucoadhesive drug delivery systems have the ability to delivery pharmacologically active agents include oral cavity, eye conjunctiva, vagina, nasal cavity and gastrointestinal tract. The current section of the review will give an overview of the above-mentioned delivery sites.

The buccal cavity has a very limited surface area of around 50 cm² but the easy access to the site makes it a preferred location for delivering active agents. The site provides an opportunity to deliver pharmacologically active agents systemically by avoiding hepatic first-pass metabolism in addition to the local treatment of the oral lesions. The sublingual mucosa is relatively more permeable than the buccal mucosa (due to the presence of large number of smooth muscle and immobile mucosa), hence formulations for sublingual delivery are designed to release the active agent quickly while mucoadhesive formulation is of importance for the delivery of active agents to the buccal mucosa where the active agent has to be released in a controlled manner. This makes the buccal cavity more suitable for mucoadhesive drug delivery.

Like buccal cavity, nasal cavity also provides a potential site for the development of formulations where mucoadhesive polymers can play an important role. The nasal mucosal layer has a surface area of around 150-200 cm². The residence time of a particulate matter in the nasal mucosa varies between 15 and 30 min, which have been attributed to the increased activity of the mucociliary layer in the presence of foreign particulate matter. Ophthalmic mucoadhesives also is another area of interest. Due to the continuous formation of tears

and blinking of eye lids there is a rapid removal of the active medicament from the ocular cavity, which results in the poor bioavailability of the active agents. This can be minimized by delivering the drugs using ocular insert or patches.

The vaginal and the rectal lumen have also been explored for the delivery of the active agents both systemically and locally. The active agents meant for the systemic delivery by this route of administration bypasses the hepatic first-pass metabolism. Quite often the delivery systems suffer from migration within the vaginal/rectal lumen which might affect the delivery of the active agent to the specific location.

Mucoadhesive polymers¹²

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes:

- Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- Polymers that adhere through nonspecific, non-covalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor site on tile self surface.

Classification of mucoadhesive polymers

- Natural and modified natural polymers. Agarose, Chitosan, Gelatin, Pectin, Sodiumalginate, CMC, NaCMC, HPC, HPMC, Methyl cellulose.
- Synthetic polymers. Carbopol, Polycarbophil, Polyacrylic acid, Polyacrylates.
- Cationic and anionic. Aminodextran, Chitosan, Chitosan –EDTA, Dimethylaminoethyl dextran (Table No.1)¹³.

Characteristics of ideal mucoadhesive polymer¹⁴⁻¹⁵

- Polymer and its degradation products should be non-toxic, non-irritant and non- absorbable in the gastrointestinal tract.
- The polymer should have good properties like wetting, swelling, solubility and biodegradability properties.
- The polymer should show sufficient mechanical strength by adhere quickly to the buccal mucosa.
- The polymer should show sufficient tensile and shear strengths at the bioadhesive range.
- Polymer should not be of high cost and must be easily available.
- The polymer must have bioadhesive properties in both dry and liquid state.
- The polymer should have properties like penetration enhancement and local enzymatic inhibition.
- The polymer does not decompose during the shelf- life of dosage form and during storage.
- Should have narrow distribution and optimum molecular weight.
- The polymer should not have degree of suppression of bond forming group but should have sufficient cross-linkage.
- Should not produce the secondary infection in the dental caries.

The basic components of Buccal bioadhesive drug delivery system are¹⁶

- Drug substance
- Bioadhesive polymers
- Backing membrane
- Penetration enhancers

Drug substance

The drug substances are decided on the basis of, does drug used for rapid release/prolonged release and for local/systemic effect? Before formulating buccoadhesive drug delivery systems, one has to decide whether the intended. The drug should have following characteristics;

- The drugs having biological half-life between 2-8 hours are good candidates for controlled drug delivery.

- The conventional single dose of the drug should be small.
- The drug absorption should be passive when given orally.
- Through oral route, the drug may exhibit first pass effect or presystemic drug elimination.
- Drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.

Bioadhesive polymers

The second step in the development of buccoadhesive dosage forms is the selection and characterization of appropriate bioadhesive polymers in the formulation." Bioadhesive polymers play a major role in buccoadhesive drug delivery systems of drugs. Polymers are also used in matrix devices in which the drug is embedded in the polymer matrix, which controls the duration of release of drugs an ideal polymer for buccoadhesive drug delivery systems should have following Characteristics.

- It should be inert and compatible with the environment
- The polymer and its degradation products should be non-toxic absorbable from the mucous layer.
- It should adhere quickly to moist tissue surface and should possess some site specificity.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The polymer should be easily available in the market and economical.

Backing membrane

Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. The commonly used materials in backing membrane include carbopol, magnesium separate, HPMC, HPC, CMC, polycarbophil etc. The main function of backing membrane is to provide unidirectional drug flow to buccal mucosa. It prevents the drug to be dissolved in saliva and hence swallowed avoiding the contact between drug and saliva. The material used for the

backing membrane must be inert and impermeable to drugs and penetration enhancers.

Penetration enhancers

To increase the permeation rate of the membrane of co-administered drug they are added in the pharmaceutical formulation. Without causing toxicity and damaging the membrane they improve the bioavailability of drugs that have poor membrane penetration. The capability to enhance the penetration is dependent upon they are used in combination or alone, nature of vehicle.

Categories and examples of membrane permeation enhancers

Bile salts: Sodium glycocholate, Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxycholate, Sodium glycodeoxycholate

Surfactants: Sodium lauryl sulphate, Polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxyethylene-20-cetylether, Benzalkonium chloride

Fatty acids: Oleic acid, Capric acid, Lauric acid, Lauric acid/ propylene glycol, Methyloleate, Lysophosphatidylcholine, Phosphatidylcholine

Chelators: EDTA, Citric acid, Sodium salicylate, Methoxy salicylates

Non-surfactants: Unsaturated cyclic ureas

Inclusion complexes: Cyclodextrins

Others: Aprotinin, Azone, Cyclodextrin, Dextran sulfate, Menthol, Polysorbate 80, Sulfoxides and various alkyl glycosides

Thiolated polymers: Chitosan-4-thiobutylamide, Chitosan-4-thiobutylamide/gsh, Chitosan-cysteine (Table No.2)¹⁷.

Method of evaluation

Mucoadhesive polymers and drug delivery systems can be evaluated by testing their adhesion strength by both *in vitro* and *in vivo* tests.

***In vitro* tests / *ex vivo* tests¹⁸**

- Methods determining tensile strength
- Methods determining shear stress
- Adhesion weight method
- Fluorescent probe method
- Flow channel method
- Mechanical spectroscopic method
- Falling liquid film method
- Colloidal gold staining method
- Viscometer method
- Thumb method
- Adhesion number
- Electrical conductance
- Swelling properties
- *In vitro* drug release studies
- Mucoadhesiveness studies.

***In vivo* methods¹⁹**

- Use of radioisotopes
- Use of gamma scintigraphy
- Use of pharmacoscintigraphy
- Use of electron paramagnetic resonance (EPR) oximetry
- X-ray studies
- Isolated loop technique.

Table No.1: Mucoadhesive polymers with their mucoadhesive property¹³

S.No	Polymer	Mucoadhesive property
1	Carbopol 934	+++
2	Carboxymethylcellulose	+++
3	Polycarbophil	+++
4	Tragacanth	+++
5	Sodium alginate	+++
6	Hydroxyethyl cellulose	+++
7	Hydroxypropyl methylcellulose	+++
8	Gum karaya	++
9	Guar gum	++
10	Polyvinylpyrrolidone	+
11	Polyethylene glycol	+
12	Hydroxypropyl cellulose	+

Note: +++ excellent, ++ fair, +poor

Table No.2: List of drugs investigated for buccal drug delivery¹⁷

Acitretin	Metoprolol tartrate
Acyclovir	Metronidazole
Arecoline	Miconazole nitrate
Benzydamine	Morphine
Buprenorphine	Morphine sulphate
Carbamazepine	Nalbuphine
Cetylpyridium chloride	Nicotine
Chitosan	Nifedipine
Chlorhexidine	Ofloxacin
Chlorhexidine diacetate	Omeprazole
Chlorhexidine digluconate	Oxytocin
Chlorpheniramine maleate	Pentazocine
Cyanocobalamine	Pindolol
Danazol	Piroxicam
Denbufylline	Propolis
Diclofenac sodium	Propranolol

CONCLUSION

The buccal drug delivery provides a several advantages for the delivery of drug. The buccal mucosa is rich in both vascular and lymphatic system through which drugs are directly drainage in systemic circulation and first-pass metabolism in liver and pre-systemic elimination in gastrointestinal tract are avoided. Additionally buccal drug can be terminated in case of toxicity thereby provide a safe and easy method for administration of drugs, and also this delivery system shows specific needs by utilizing the physiochemical characters of both the dosage form and the mucosal lining. It has to be noted that only a moist surface can bring the mucoadhesive nature of the dosage form. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. Currently solid dosage forms, liquids, spray and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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