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Mucoadhesive Drug Delivery System – A Novel Approach For Oral Cavity Drug Delivery

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ABSTRACT

The mucosal layer represents a potential site for the attachment of bio-adhesive drug delivery systems, as it lines several parts of the body such as the gastrointestinal tract, urogenital tract, vaginal tract, eyes, ears, and nose. Among these, oral transmucosal drug delivery has gained more attention compared to other mucoadhesive systems like vaginal, rectal, nasal, and ocular delivery. The buccal mucosa, in particular, is rich in vascular and lymphatic systems, which allows drugs to be absorbed directly into the systemic circulation, bypassing the first-pass metabolism in the liver and avoiding pre-systemic elimination in the gastrointestinal tract. Moreover, buccal drug delivery can be quickly discontinued in case of toxicity, making it a safer and more convenient method of drug administration. This system takes advantage of the physicochemical properties of both the drug formulation and the mucosal lining. It's important to note that the mucoadhesive properties of a dosage form are only effective on moist surfaces.

Keywords: Oral transmucosal, Buccal mucosa

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INTRODUCTION

Bio-adhesion is defined as the condition where two materials, one of which is biological in nature, remain attached for extended periods due to interfacial forces. In drug delivery, bio-adhesion refers to the attachment of a drug carrier to a specific biological site. This biological site can be either an epithelial tissue or the mucus layer covering the tissue. When the adhesion occurs with the mucus layer, it is referred to as muco-adhesion. The mucosal layer, which lines various parts of the body such as the gastrointestinal tract, urogenital tract, vaginal tract, eyes, ears, and nose, serves as potential sites for the attachment of bio-adhesive systems. Among the different muco-adhesive systems, oral transmucosal drug delivery has recently gained more prominence compared to vaginal, rectal, nasal, and ocular delivery systems.

Mucoadhesive Drug Delivery in the Oral Cavity[2]

Drug delivery through the membranes of the oral cavity can be categorized into three main types:

- **Sublingual Delivery**: Drugs are administered through the mucosal membrane under the tongue, allowing absorption directly into systemic circulation.
- **Buccal Delivery**: Drugs are absorbed through the mucosal membrane by placing the drug between the gums and cheeks.
- **Local Delivery**: Drugs are delivered directly into the oral cavity.

Advantages of Buccal Drug Delivery[3, 4]

The buccal mucosa offers several benefits as a drug delivery route:

- It is easy to administer and therapy can be terminated quickly if needed.
- The drug can be localized in the buccal cavity for an extended period.
- It is suitable for unconscious patients and for systemic delivery of drugs that undergo extensive first-pass metabolism or degradation in the gastrointestinal environment.
- The dose required is reduced, minimizing side effects.
- Drugs with poor oral bioavailability can be delivered effectively via this route.
- Buccal administration does not require any activation process, as it relies on passive drug absorption.
- The presence of saliva provides adequate moisture for drug dissolution, unlike other routes such as rectal or transdermal.
- Rapid systemic absorption occurs due to the thin buccal mucosa and its rich blood supply.
- It provides an alternative delivery route for drugs like hormones, steroids, narcotic analgesics, and cardiovascular agents.

Disadvantages of Buccal Drug Delivery[5,6]

- Local ulceration may occur due to prolonged contact with drugs that have ulcerogenic properties.
- The development of buccal delivery systems is hampered by the lack of suitable in vitro models for drug screening.
- Drugs that irritate the oral mucosa, have an unpleasant taste or odor, or are unstable at buccal pH cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Drugs may be swallowed with saliva, reducing the effectiveness of buccal delivery.
- Buccal mucosa has a limited surface area for drug absorption and is less permeable than other sites like the intestine or rectum.

Classification of buccal bio-adhesive dosage form[7-8]

Buccal Bio-adhesive Tablets

Buccal bio-adhesive 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 bio-adhesive polymers and excipients. These tablets are solid dosage forms that ate 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 Bio-adhesive Semisolid Dosage Forms Buccal bio-adhesive semisolid dosage forms consist of finally powdered natural or synthetic polymers dispersed in a polyethylene or in aqueous solution example: Arabase.

Buccal Bio-adhesive Patches and Films

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

Buccal Bio-adhesive Powder Dosage Forms

Buccal bio-adhesive powder dosage forms are a mixture of bio-adhesive 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.

Bio-adhesive 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 bioavailability[9-10]

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 that 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 expense 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 systems[11]

Mucoadhesive drug delivery systems can be applied to various sites within the body to deliver pharmacologically active agents. These sites include the oral cavity, the eye's conjunctiva, the vagina, the nasal cavity, and the gastrointestinal tract. Below is an overview of these key application areas.

The buccal cavity, though limited in surface area (around 50 cm^2), offers easy access, making it a favored location for drug delivery. The buccal route also allows for systemic drug delivery while bypassing hepatic first-pass metabolism. Additionally, it enables the localized treatment of oral lesions. The sublingual mucosa, more permeable than the buccal mucosa due to its large number of smooth muscles and immobile nature, is suitable for rapid drug release. Meanwhile, mucoadhesive formulations are designed for controlled release in the buccal mucosa, highlighting its significance in drug delivery.

The nasal cavity also presents an excellent site for mucoadhesive drug formulations, particularly due to its mucosal surface area of 150-200 cm^2. The residence time of particulate matter in the nasal cavity typically ranges from 15 to 30 minutes, largely because of mucociliary activity, which intensifies in response to foreign particles.

Ophthalmic applications of mucoadhesive drug systems are also promising, particularly due to the challenges associated with tear formation and blinking, which typically reduce drug bioavailability. This challenge can be addressed by using ocular inserts or patches to enhance drug retention and efficacy.

The vaginal and rectal lumens have also been explored for both systemic and localized drug delivery. These routes avoid hepatic first-pass metabolism, making them advantageous for certain

therapies. However, migration of the delivery system within these lumens can sometimes hinder the targeted delivery of the active agent.

Mucoadhesive polymers[12]

Mucoadhesive polymers, which can be either water-soluble or water-insoluble, consist of swellable networks that are interconnected by cross-linking agents. These polymers possess the necessary polarity to ensure adequate wetting by mucus, along with the right fluidity that allows mutual adsorption and interpenetration between the polymer and mucus. Based on their adhesive mechanisms, mucoadhesive polymers that adhere to the mucin-epithelial surface can be broadly categorized into three main types:

1. Polymers that become adhesive upon contact with water, with their stickiness being the primary factor contributing to mucoadhesion.
2. Polymers that adhere through nonspecific, non-covalent interactions, primarily relying on electrostatic forces, although hydrogen bonding and hydrophobic interactions may also play a role.
3. Polymers that bind to specific receptor sites on the cell surface.

Classification of mucoadhesive polymers

Natural and modified natural polymers.

Agarose, Chitosan, Gelatin, Pectin, Sodium alginate, CMC, NaCMC, HPC, HPMC, Methyl cellulose.

Synthetic polymers.

Carbopol, Polycarbpphil, Polyacrilic acid, Polyacrylates.

Cationic and anionic.

Aminodextran, Chitosan, Chitosan –EDTA, Dimethylamino-ethyldextran (Table 1)[13]

Characteristics of ideal mucoadhesive polymer[14-15]

Polymers used in drug delivery systems should meet several important criteria:

- They should be non-toxic, non-irritating, and non-absorbable in the gastrointestinal tract.
- The polymer should exhibit favorable characteristics such as wetting, swelling, solubility, and biodegradability.
- It should adhere quickly and effectively to the buccal mucosa, demonstrating sufficient mechanical strength.
- The polymer should maintain adequate tensile and shear strengths within the bioadhesive range.
- It should be cost-effective and easily accessible.

- The polymer must retain bioadhesive properties in both dry and liquid states.
- It should possess penetration-enhancing capabilities and inhibit local enzymatic activity.
- The polymer should remain stable throughout its shelf life and storage period without degrading.
- It must have a narrow distribution and optimal molecular weight.
- Cross-linking should be sufficient without suppressing the bond-forming groups.
- The polymer should not cause secondary infections, particularly in dental caries.

The basic components of Buccal bio-adhesive drug delivery system are[16]

- Drug substance
- Bio-adhesive polymers
- Backing membrane
- Penetration enhancers

Drug substance

When selecting drug substances for bucco-adhesive drug delivery systems, the choice depends on whether the drug is intended for rapid or prolonged release and whether the desired effect is local or systemic. The drug should have the following characteristics:

- It should have a biological half-life of 2 to 8 hours, making it suitable for controlled drug delivery.
- The conventional single dose should be relatively small.
- The drug should be absorbed passively when administered orally.
- The drug may experience first-pass metabolism or pre-systemic elimination through the oral route.
- It should have a neutral taste and be free from irritants, allergens, and properties that cause discoloration or erosion of teeth.

Bio-adhesive polymers

The second step in developing bucco-adhesive dosage forms is selecting and characterizing suitable bio-adhesive polymers. These polymers are crucial in bucco-adhesive drug delivery systems, often being used in matrix devices where they control the release duration of the drug embedded within. An ideal polymer for such systems should possess the following characteristics:

- It should be inert and environmentally compatible.
- Both the polymer and its degradation products should be non-toxic and absorbable by the mucous membrane.

- It should adhere quickly to moist tissue surfaces and demonstrate some level of site specificity.
- The polymer should remain stable during storage and throughout the shelf life of the dosage form.
- It should be readily available and cost-effective.

Backing membrane

The backing membrane plays a crucial role in attaching bioadhesive devices to the mucous membrane. The materials used for this membrane should be inert and impermeable to both the drug and penetration enhancers. Common materials for backing membranes include carbopol, magnesium stearate, HPMC, HPC, CMC, and Polycarbophils. The primary function of the backing membrane is to ensure unidirectional drug flow towards the buccal mucosa. It prevents the drug from dissolving in saliva, thus minimizing the possibility of it being swallowed and avoiding any interaction between the drug and saliva. The backing membrane material must remain inert and impermeable to ensure the proper function of the drug delivery system

Penetration enhancers

To enhance the permeation rate of co-administered drugs in pharmaceutical formulations, certain agents are incorporated. These agents improve the bioavailability of drugs that have poor membrane penetration without causing toxicity or damaging the membrane. The effectiveness of these penetration enhancers depends on whether they are used alone or in combination, as well as the characteristics of the vehicle used in the formulation.

Categories and examples of membrane permeation enhancers

Bile salts: Sodium glycocholate, Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxy-cholate, Sodium glycodeoxy-cholate

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

Fatty acids: Oleic acid, Capric acid, Lauric acid, Lauric acid/propylene glycol, Methyl oleate, Lys phosphatidylcholine, Phosphatidylcholine

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

Non-surfactants: Unsaturated cyclic urea's

Inclusion complexes: Cyclodextrins

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

Thiolate polymers: Chitosan-4-thiobutylamide, Chitosan-4-thiobutylamide/gash, Chitosan-cysteine (Table 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 tests[18]

- Techniques for measuring tensile strength
- Methods for assessing shear stress
- Adhesion weight assessment
- Fluorescent probe analysis
- Flow channel analysis
- Mechanical spectroscopy
- Falling liquid film assessment
- Colloidal gold staining technique
- Viscosity measurement
- Thumb adhesion test
- Adhesion numerical analysis
- Electrical conductivity measurement
- Swelling property evaluation
- In vitro drug release assessment
- Muco retentability testing

***In vivo* methods**[19]

- Application of radioisotopes
- Utilization of gamma scintigraphy
- Implementation of pharmacoscintigraphy
- Employment of electron paramagnetic resonance (EPR) oximetry

These techniques are often used in the evaluation and tracking of drug delivery systems, allowing researchers to assess bioavailability and the distribution of drugs within the body.

Table 1: Mucoadhesive polymers with their mucoadhesive property[13]

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 2: List of Some drugs investigated for buccal drug delivery[17]

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

CONCLUSION

Buccal drug delivery offers numerous advantages for administering medications. The buccal mucosa is well-supplied with vascular and lymphatic systems, allowing drugs to enter systemic circulation directly while bypassing first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. This method enables prompt termination of drug delivery in cases of toxicity, making it a safe and convenient option. Furthermore, this delivery system is tailored to meet specific needs by leveraging the physicochemical properties of both the dosage form and the mucosal lining. It's essential that the dosage form maintains a moist surface to ensure its mucoadhesive properties. Research in buccal drug delivery is promising, especially for the systemic delivery of drugs that are poorly absorbed orally, as well as for non-invasive administration of potent peptide and protein drugs. Currently, commercially successful formulations include solid dosage forms, liquids, sprays, and gels applied to the oral cavity. Future developments in buccal adhesive drug delivery are expected to focus on vaccine formulations and the delivery of small proteins and peptides.

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