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Mucoadhesive Drug Delivery System: A Review

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Abstract: 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. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption. 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.

Mucoadhesive characteristics are a factor of both the bioadhesive polymer and the medium in which the polymer will reside. Buccal dosage forms can be of Matrix or Reservoir types. However, this route could become a significant means for the delivery of a range of active agents in the coming years, if the barriers to buccal drug delivery are overcome. © 2011 IGJPS. All rights reserved.

Keywords: Mucoadhesive Drug Delivery System; NDDS; Buccal Delivery.

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. Transmucosal delivery has also been considered for treatment of oral disorders and as a local anesthetic[1].

Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption[2]. Other routes, such as nasal, ocular, pulmonary, rectal, and vaginal drug administration, have provided excellent opportunities for the delivery of a variety of compounds. However, the mucosal lining of the oral cavity offers some distinct advantages. 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[3].

Permeability of drugs through buccal mucosa[4]

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa:

1. Transcellular (intracellular, passing through the cell)
2. Paracellular (intercellular, passing around the cell).

Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intercellular lipids produced by membrane-coating granules.

The buccal mucosa is a potential site for the controlled delivery of hydrophilic macromolecular therapeutic agents (biopharmaceuticals) such as peptides, oligonucleotides and polysaccharides. However, these high molecular weight drugs usually have low permeability leading to a low bioavailability, and absorption enhancers may be required to overcome this. The buccal mucosa also contains proteases that may degrade peptide-based drugs. In addition, the salivary enzymes may also reduce stability. Disease states where the mucosa is damaged would also be expected to increase permeability. This would be particularly true in conditions that result in erosion of the mucosa such as lichen planus, pemphigus, viral infections and allergic reactions.

Buccal drug delivery and mucoadhesivity[5]

In the development of these buccal drug delivery systems, mucoadhesion of the device is a key element. The term ‘mucoadhesive’ is commonly used for materials that bind to the mucin layer of a biological membrane. Mucoadhesive polymers have been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosae. These dosage forms include tablets, patches, tapes, films, semisolids and powders. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as:

1. Predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups.
2. Suitable surface property for wetting mucus/mucosal tissue surfaces.
3. Sufficient flexibility to penetrate the mucus network or tissue crevices.

Factors affecting mucoadhesion in the oral cavity

Mucoadhesive characteristics are a factor of both the bioadhesive polymer and the medium in which the polymer will reside. A variety of factors affect the mucoadhesive properties of polymers, such as molecular weight, flexibility, hydrogen bonding capacity, cross-linking density, charge, concentration, and hydration (swelling) of a polymer, which are briefly addressed below.

Polymer-related factor

1. Molecular weight

In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above

100,000[6].

2. Flexibility

Bioadhesion starts with the diffusion of the polymer chains in the interfacial region. Therefore, it is important that the polymer chains contain a substantial degree of flexibility in order to achieve the desired entanglement with the mucus. In general, mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients, where higher flexibility of a polymer causes greater diffusion into the mucus network[7].

3. Hydrogen bonding capacity

Hydrogen bonding is another important factor in mucoadhesion of a polymer. Park and Robinson found that in order for mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds[8]. They have also confirmed that flexibility of the polymer is important to improve this hydrogen bonding potential.

4. Cross-linking density

The average pore size, the number average molecular weight of the cross-linked polymers, and the density of cross-linking are three important and interrelated structural parameters of a polymer network[7]. Therefore, it seems reasonable that with increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin[7].

5. Charge

Some generalizations about the charge of bioadhesive polymers have been made previously, where nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium[9]. Additionally, some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties.

6. Concentration

The importance of this factor lies in the development of a strong adhesive bond with the mucus, and can be explained by the polymer chain length available for penetration into the mucus layer. When the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is small, and the interaction between polymer and mucus is unstable[10]. In general, the more concentrated polymer would result in a longer penetrating chain length and better adhesion. However, for each polymer, there is a critical concentration, above which the polymer produces an “unperturbed” state due to a significantly coiled structure. As a result, the accessibility of the solvent to the polymer decreases, and chain penetration of the polymer is drastically reduced. Therefore, higher concentrations of polymers do not necessarily improve and, in some cases, actually diminish mucoadhesive properties.

7. Hydration (swelling)

Hydration is required for a mucoadhesive polymer to expand and create a proper "macromolecular mesh" of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin[7].

Environmental factors

The mucoadhesion of a polymer not only depends on its molecular properties, but also on the environmental factors adjacent to the polymer. Saliva, as a dissolution medium, affects the behavior of the polymer. Depending on the saliva flow rate and method of determination, the pH of this medium has been estimated to be between 6.5 and 7.5.[11]

Movement of the buccal tissues while eating, drinking, and talking, is another concern which should be considered when designing a dosage form for the oral cavity. Movements within the oral cavity continue even during sleep, and can potentially lead to the detachment of the dosage form. Therefore, an optimum time span for the administration of the dosage form is necessary in order to avoid many of these interfering factors[12].

An ideal property of buccal adhesive system:

- Should adhere to the site of attachment for a few hours,
- Should release the drug in a controlled fashion,
- Should provide drug release in an unidirectional way toward the mucosa,
- Should facilitate the rate and extent of drug absorption,
- Should not cause any irritation or inconvenience to the patient and
- Should not interfere with the normal functions such as talking, drinking etc.

Structure and design of buccal dosage form[13]

Buccal Dosage form can be of

1. **Matrix type:** The buccal formulation designed in a matrix configuration contains drug, adhesive, and additives mixed together.
2. **Reserviour type:** The buccal formulation designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce formulation deformation and disintegration while in the mouth; and to prevent drug loss.

Additionally, the formulation can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.

Buccal mucoadhesive dosage forms[14]

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry.

Type I: A single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

Type II: 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.

Type III: 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 tablets

Tablets have been the most commonly investigated dosage form for buccal drug delivery to date. Buccal tablets are small, flat, and oval, with a diameter of approximately 5–8 mm[15]. Unlike conventional tablets, buccal mucoadhesive 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. These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek, as well as between the lip and the gum. Successive tablets can be applied to alternate sides of the mouth. The major drawback of buccal bioadhesive tablets is their lack of physical flexibility, leading to poor patient compliance for long-term and repeated use.

Buccal patches

Patches are laminates consisting of an impermeable backing layer, a drug-containing reservoir layer from which the drug is released in a controlled manner, and a bioadhesive surface for mucosal attachment. Buccal patch systems are similar to those used in transdermal drug delivery. Two methods used to prepare adhesive patches include solvent casting and direct milling. In the solvent casting method, the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymer(s) onto a backing layer sheet, and subsequently allowing the solvent(s) to evaporate. In the direct milling method, formulation constituents are homogeneously mixed and compressed to the desired thickness, and patches of predetermined size and shape are then cut or punched out. An impermeable backing layer may also be applied to control the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device during the application period.

Buccal films

Films are the most recently developed dosage form for buccal administration. Buccal films may be preferred over adhesive tablets in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. Moreover, in case of local delivery for oral diseases, the films also help protect the wound surface, thus helping to reduce pain and treat the disease more effectively. An ideal film should be flexible, elastic, and soft, yet adequately strong to withstand breakage due to stress from mouth movements. It must also possess good bioadhesive strength in order to be retained in the mouth for the desired duration of action. Swelling of film, if it occurs, should not be too extensive in order to prevent discomfort.

Buccal gels and ointments

Semisolid dosage forms, such as gels and ointments, have the advantage of easy dispersion throughout the oral mucosa. However, drug dosing from semisolid dosage forms may not be as accurate as from tablets, patches, or films. Poor retention of the gels at the site of application has been overcome by using bioadhesive formulations .Certain bioadhesive polymers, e.g. poloxamer 407, sodium carboxy methylcellulose, carbopol, hyaluronic acid, and xanthan gum, undergo a phase change from a liquid to a semisolid [16]. This change enhances the viscosity, which results in sustained and controlled release of drugs. However, these polymers have been investigated for this purpose primarily in ocular drug delivery.

Advantages of drug delivery via the buccal lining[13, 17]

1. Bypass 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.
2. 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.
3. Sustained drug delivery.
4. 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.
5. Increased ease of drug administration.
6. 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.
7. 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.
8. Transmucosal delivery occurs is less variable between patients, resulting in lower intersubject variability as compaired to transdermal patches.
9. The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.

Limitations of buccal drug delivery[13, 17]

Depending on whether local or systemic action is required the challenges faced while delivering drug via buccal drug delivery can be enumerated as follows:-

1. 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.
2. 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.
3. For both local and systemic action, patient acceptability in terms of taste, irritancy and ‘mouth feel’ is an issue.

For systemic delivery the relative impermeability of oral cavity mucosa with regard to drug absorption, especially for large hydrophilic biopharmaceuticals, is a major concern.

Toxicity and irritancy associated with buccal drug delivery[18]

Formulations that produce local damage at the site of application, such as ulceration of the mucosa, would preclude their widespread usage as a result of the associated pain and discomfort. This is particularly important in buccal drug delivery where the formulation is in contact with the mucosa for extended periods. Toxic effects can arise from the drug itself, the bioadhesive or from other components of the formulation. For example, carbomers have been reported to produce mucosal irritation believed to result from a localised low pH, whereas lectins have been shown to be cytotoxic. Excipients such as absorption enhancers (e.g., sodium dodecyl sulfate) have also been reported to be irritant.

List of drugs delivered via buccal route[2,19]

In an effort to determine the feasibility of buccal route as a novel route of drug delivery, several drugs (Table 2) 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.

List of Active Ingredients delivered via a buccal route[2, 19]

Sr. No.	Active Ingredients	Sr. No.	Active Ingredients
1.	Acitretin	25	Metronidazole
2	Acyclovir	26	Melatonin
3	Arecoline	27	Metoprolol tartrate
4	Buprenorpine	28	Morphine sulphate
5	Carbamazepine	29	Nalbuphine
6	Cetyl Pyridinium chloride	30	Nicotine
7	Chlorhexidine diacetate	31	Nifedipine
8	Chitosan	32	Omeprazole
9	Chlorpheniramine maleate	33	Oxytocin
10	Cyanocobalamin	34	Pentazocine
11	Danazol	35	Protirelin

12	Denbufylline	36	Pindolol
13	Diclofenac sodium	37	Piroxicam
14	Diltiazem Hydrochloride	38	Propranolol
15	Ergotamine tartrate	39	Propolis
16	Fluride	40	Recombinant human epidermal growth factor (Rh EFG)
17	Flurbiprofen	41	Salmon calcitonin
18	Glucagon-like peptide (GLP)-1	42	Sodium fluoride
19	Hydrocortisone acetate	43	Testosterone
20	Insulin	44	Terbutaline sulphate
21	Lactoferrin	45	Theophylline
22	Lignocaine	46	Thyotropin releasing hormone
23	Leu-enkephalin	47	Triamcinolone acetate
24	Luteinizing hormone releasing Hormone (LHRH)	48	Zinc sulphate

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