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Mucoadhesive Buccal Drug Delivery System

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ABSTRACT

The buccal region of the oral cavity is an attractive target for administration of the drug of choice, particularly in overcoming deficiencies associated with the latter mode of administration. Problems such as high first-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented by administering the drug via the buccal route. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin are held together for extended periods of time by the help of interfacial forces. The mucosa has a buccal dosage forms will be reviewed with an emphasis on bioadhesive polymeric based delivery systems. The mucoadhesive interaction is explained in relation to the structural characteristics of mucosal tissues and the theories & properties of the polymers. To prevent accidental swallowing of drugs adhesive mucosal dosage forms were suggested for oral delivery, which included adhesive tablets, adhesive gels, adhesive patches and many other dosage forms with various combinations of polymers, absorption enhancers. In addition to this, studies have been conducted on the development of controlled or slow release delivery systems for systemic and local therapy of diseases in the oral cavity.

KEYWORDS

Mucoadhesive; Buccal; Polymers; Retention time; Drug delivery system.

INTRODUCTION

Mucoadhesion is defined as the ability of material adheres to biological tissue for an extended period of time. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms. Buccal delivery of the desired drug using mucoadhesive polymers has been the subject of interest since the early 1980s. Mucoadhesive are synthetic or natural polymer, which interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules constituting a major part of mucus.

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Mucoadhesive drug delivery system utilize the property of bioadhesion of certain water soluble polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time.

Mucoadhesion has been widely promoted as a way of achieving site-specific drug delivery through the supply of blood and lymph vessels; beneath this is a thin layer of smooth muscle tissue.

The buccal mucosa has been investigated for local and 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. Buccal delivery offers a safer mode of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity .A suitable buccal drug

delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a unidirectional way toward the mucosa, in a controlled and predictable manner, to elicit the required therapeutic response.

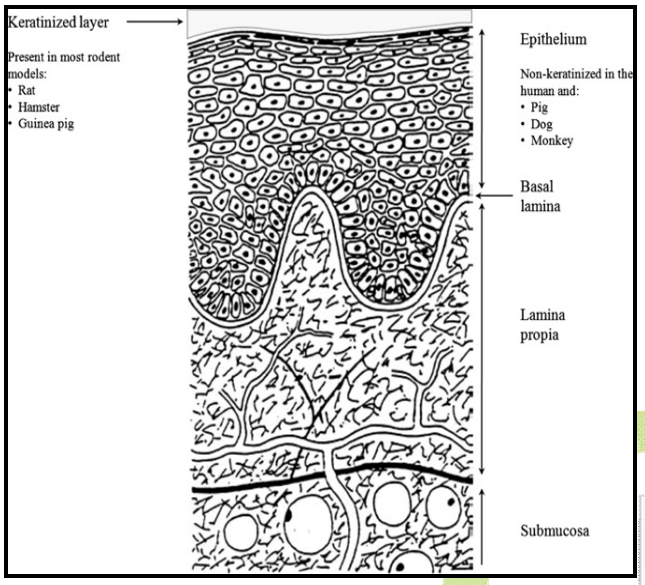

Figure 1: Structure of the Buccal mucosa

RATIONALE FOR BUCCAL MUCOSAL DRUG DELIVERY

Because it has number of features that makes it desirable for drug delivery:

1) A rich blood supply that drains directly into the jugular vein, thus by passing the liver and sparing the drug from first-pass metabolism.

2) Ease of drug delivery even in unconscious patients and those who are permitted nothing by mouth.

ADVANTAGES OF MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM

It has several advantages:

- Oral mucosal drug delivery systems are easy and painless to administer and well accepted by the patient.
- Precise dosage form localization is possible and there is ability to terminate delivery when required.
- Flexibility in physical state, shape, size and surface.
- For patient suffering with nausea or vomiting or in the state of unconsciousness, with an upper gastrointestinal tract disease or surgery which affects oral drug absorption, the oral cavity a useful site for drug delivery for upper symptoms.
- Maximized absorption rate due to intimate contact with the absorbing membrane and decreased diffusion barriers.
- Excellent route for the systemic delivery of drug with high first pass metabolism, thereby offering a greater bioavailability.
- A significant reduction in dose can be achieved, thereby reducing dose dependent side effects.
- Drugs which are unstable in the acidic environment of the stomach or are destroyed by the enzymatic or alkaline environment of the intestines can be administered by this route.
- It offers a passive system for drug absorption and does not require any activation.
- It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, selective use of therapeutic agents like peptides, proteins and ionised species can be achieved.
- The oral mucosa lacks prominent mucus secreting goblets cells and therefore there is no problem of diffusion limited mucus buildup beneath the applied dosage form.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
- It satisfied several features of the controlled release system.
- It can be made unidirectional to ensure only buccal absorption.

- The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.
- Bioadhesion prolongs the residence time at the site of drug absorption, and thus improves bioavailability and dosing interval.
- Rapid onset of action.

LIMITATIONS OF BUCCAL DRUG ADMINISTRATION

Drug administration via this route has certain limitations

- Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour cannot be administered by this route.
- Drugs which are unstable at buccal pH cannot be administered by this route.
- Only drugs with a small dose requirement can be administered.
- Drug contained in the swallowed saliva follows the peroral route and advantages of buccal route are lost.
- Only those drugs which are absorbed by passive diffusion can be administered by this route.
- Eating and drinking may become restricted.
- There is an ever present possibility of the patient swallowing the tablet.
- Overhydration may lead to formation of slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration of bioadhesive polymer.

MECHANISMS OF BIOADHESION

A. The Bioadhesive Interface

Adhesive bonds between a polymer and a soft tissue require contributions from the surface of the potentially bioadhesive polymer. The first layer of the natural tissue and the interfacial layer between adhesive and tissue. Mucus is highly a viscous product, which coats lining of hollow organs in contact with external media. The main components of the mucous layer are glycoproteins or mucins, inorganic salts, proteins, lipids and muco polysaccharides and its composition Varies depending on its source. The mucin composition also depends on the pathological conditions. It was found those mucins secreted by abnormal tissues are histochemically different from the corresponding mucins produced by the normal tissues.

B. Chemical and Physical Interactions

Adhesion of polymers to tissues may be achieved by:

1. Primary ionic or covalent chemical bonds.
2. Secondary chemical bonds or
3. Physical or mechanical bonds.

Primary chemical bonds are the result of chemical reaction of functional groups of the adhesive material with the substrate' they are hardly desirable for most soft tissue uses where a semipermanet adhesive bond strength is needed lasting from a few minutes to a few hours. Secondary chemical bonds contribute to bioadhesive bonds through vander walls dispersive interactions or hydrogen bonding. Hydrogen bonds are also important in bioadhesion as in other form of adhesion. Physical or mechanical bonds are obtained by inclusion of the adhesive material in the crevices of the tissue. Thus, the surface roughness of the substrate becomes an important factor in bioadhesion. Only highly fluid materials or suspensions that can be incorporated within these anomalies of the tissue can be considered successful adhesive systems.

THEORIES OF BIOADHESION

The theoretical framework for polymer-polymer adhesion can be easily extended to describe the bioadhesion of polymeric materials with biological surfaces. Pertinent theories include the electronic, the adsorption, the wetting, the diffusion and the fracture theory.

A. Electronic Theory

The electronic theory indicates that there is likely to be electron transfer on contact of the bioadhesive polymer and the glycoproteinic net work which have different electronic structures, which will in turn lead to the formation of a double of electrical charge at the bioadhesive interface.

B. Adsorption Theory

According to the adsorption theory, bioadhesive systems adhere to tissue because of vander walls, hydrogen bonding, and related forces.

C. Wetting Theory

Intimate molecular contact is a pre - requisite for development of strong adhesive bond, requiring examination of the wetting equilibrium and dynamic behavior of the bioadhesive candidate material with the mucus. Some important characteristic for liquid bioadhesive materials include:

I. a zero or near zero contact angle
II. a relatively low viscosity and
III. an intimate contact that exclude air entrapment.

The specific work of adhesion between bioadhesive controlled release system and the tissue is equal to the sum of the two surface tensions and less than the interfacial tension.

D. Diffusion Theory

Interpenetration of the chains of polymer and mucus may lead to formation of a sufficiently deep layer of chains. The diffusion mechanism is the intimate contact of two polymers or two pieces of the same polymer. During chain interpenetration the molecules of the polymer and the dangling chains of the glycoproteinic network are brought in intimate contact. Due to the concentration gradient, the bioadhesive polymer chains penetrate at rates that are dependent on the diffusion coefficient of a macromolecule through a cross-linked network and the chemical potential gradient. In addition, good solubility of the bioadhesive medium in the mucus is required in order to achieve bioadhesion. Thus the difference of the solubility parameters of the bioadhesive medium and the glycoprotein should be as close to zero as possible. Thus the bioadhesive medium must be of similar chemical structure to the glycoproteins.

E. Fracture Theory

The facture theory of bioadhesion relates the difficulty of separation of two surfaces after adhesion to the adhesive bond strength.

FACTORS AFFECTING MUCO-ADHESION 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.

1. Polymer-related factors

Molecular weight

In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above 100,000. As one example, the direct correlation between the bioadhesive strength of polyoxyethylene polymers and their molecular weights, in the range of 200,000 to 7,000,000.

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. A recent publication demonstrated the use of tethered poly (ethylene glycol)–poly (acrylic acid) hydrogels and their copolymers with improved mucoadhesive properties. The increased chain interpenetration was attributed to the increased structural flexibility of the polymer upon incorporation of poly(ethylene glycol). 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.

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. They have also confirmed that flexibility of the polymer is important to improve this hydrogen bonding potential. Polymers such as poly (vinyl alcohol), hydroxylated methacrylate, and poly(methacrylic acid), as well as all their copolymers, are polymers with good hydrogen bonding capacity.

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. 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. Flory has reported this general property of polymers, in which the degree of swelling at equilibrium has an inverse relationship with the degree of cross-linking of a polymer.

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. Peppas and Buri have demonstrated that strong anionic charge on the polymer is one of the required characteristics for mucoadhesion. It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium. Additionally, some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties.

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. 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. One of the studies addressing this factor demonstrated that high concentrations of flexible polymeric films based on polyvinyl pyrrolidone or poly (vinyl alcohol) as film-forming polymers did not further enhance the mucoadhesive properties of the polymer. On the contrary, it decreased the desired strength of mucoadhesion.

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. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network. However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bioadhesion occurs.

2. 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. The residence time of dosage forms is limited by the mucin turnover time, which has been calculated to range between 47 and 270 min in rats and 12–24 h in humans.

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.

Bioadhesive Polymers

Bioadhesive polymers have properties to get adhered to the biological membrane and hence capable of prolonging the contact time of the drug with a body tissue. The use of bioadhesive polymers can significantly improve the performance of many drugs. This improvement ranges from better treatment of local pathologies to improved bioavailability and controlled release to enhance patient compliance.

Ideal Characteristics of a Buccal Adhesive Polymer

- Polymer and its degradation products should be nontoxic, non-irritant and free from leachable impurities.
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- Should adhere quickly to buccal mucosa and should sufficient mechanical strength.
- Should possess peel, tensile and shear strengths at the bioadhesive range
- Should have required spatial conformation.
- Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- Should not aid in development of secondary infections such as dental caries

BUCCAL MUCOADHESIVE DOSAGE FORMS

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry. Type I is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing. In type II devices, 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 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 can also be classified as either a “reservoir” or “matrix” type. In the reservoir type, an excessive amount of the drug is present in the reservoir surrounded by a polymeric membrane, which controls the drug’s release rate. In the matrix-type systems, the drug is uniformly dispersed in the polymer matrix, and drug release is controlled by diffusion through the polymer network.

In addition, the mucoadhesive tablet was generally well-tolerated and caused fewer incidences of gastrointestinal disorders and drug-related adverse events than those observed when ketoconazole was administered systemically. The authors suggested that this

particular dosage form is the first and only once-daily topical treatment option for this condition.

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. 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 the 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. 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.

EVALUATIONS

Two imperical evaluating parameters of mucoadhesive drug delivery system include release studies in vitro and in vivo and bioadhesive strength.

In Vitro Release Studies

No standard in vitro method has yet been developed for the dissolution studies of buccal formulations. Different workers have used apparatus of varying designs, depending on the shape and applications of the dosage form developed.

1. Machida and Nagaiin in 1977 used J.P. IX disintegration tester without the attached disc, with 800 ml of the dissolution medium for dissolution rate measurement of directly compressed tablets of di–isoprotenol hydrochloride meant for controlled release.

2. Nagai et al in 1978, prepared disc like dosage forms for the treatment of uterine cancer and measured the dissolution rate using Toyamo-Sangyo TR-553, dissolution tester. For this 900ml of purified water was used as dissolution medium, rotating the basket at 100 rpm. This apparatus was used for the evaluation of oral mucosal dosage form of insulin.

3. Tshida et al used an apparatus similar to that used for evaluation of insulin dosage forms, with a slight modification of providing a water jacket for the maintenance of temperature. This apparatus was used for the dissolution rate measurement of mucosal adhesive dosage form of lidocaine for toothache. Collin and Deasy studied the release of cetyl pyridinium chloride into the simulated saliva (isotonic phosphate buffer pH 6.6) in an apparatus consisting of a water jacket and an internal compartment containing 50 ml of the dissolution medium. The compound formulated was placed in a metal die sealed as its lower end by paraffin wax; hence the drug could be released only from the upper convex face of the device. The medium was stirred with rotating stirrer at a rate of 250 rpm.

In Vivo Release Studies

Various techniques of in vivo testing have been reported to quantitatively evaluate drug absorption through the oral mucosal membrane

1. Becket and Triggs, introduced a buccal absorption test which involved swirling a buffered drug solution around the mouth. After known time period the solution was expelled and the subjects rinsed their mouth with buffers. Drug solution and the buffers were then combined, analyzed for drug content and the amount of drug absorbed estimated from the difference between the entered and recovered.

2. In 1988, Tucker reported an improvement over this traditional buccal absorption test, which enables kinetic data to be collected in a single 15 min. trial. The method involved multiple samples being withdrawn from the mouth using a positive displacement pipetter.

3. In 1974, Kaaber developed a method for investigating the trnsport of water and ions through known regions and fixed areas of the oral mucosa. In 1985, pimlott and Addy, used a similar method to Kobber to study steroid absorption across kerotinised and non kerotinised oral mucosal sites,

4. Barsuhn et al, in 1988 devised a closed perfusion cell apparatus to study the tranport of flubiprofen across the human buccal membrane.

5. In 1991, Rothbone, offered a buccal perfusion cell apparatus, which offers larger areas over which drug transfer can take place, no leakage problem and continuous monitoring of drug loss as a function of time.

6. Kurosaki et al have recently investigated drug permeability using hamster cheek pouch.

7. Anmo etal have developed an in situ recirculating perfusion device and demonstrated its usefulness in beagle dogs. Some preliminary studies on buccal absorption using a small perfusion chamber on mongrel dogs.

Mucoadhesive strength

- ➔ Three different types of stress, tensile, shear and peel stress are measured.
- ➔ For simulation of actual application conditions, the ideal substrate would be the tissue to which the mucoadhesive system will be applied and the force required to separate mucoadhesives from mucosal

tissue is measured using modified automatic surface tensiometer.

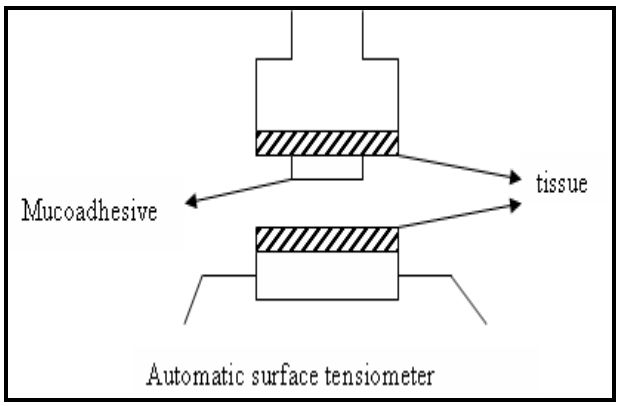

Figure 2: Automatic surface tensiometer

➔ The results from measuring tensile strength provides information regarding the effects of charge density, hydrophobicity and experimental conditions such as pH, ionic strength, mucolytic agents and applied pressure on bioadhesion.

CONCLUSION

The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. 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. However, the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery.

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