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Buccal Route As A Novel Delivery Route

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ABSTRACT

Buccal administration of drugs provides a convenient route of administration for both systemic and local drug actions. However, the preferred site for retentive oral transmucosal delivery systems and for sustained- and controlled-release delivery devices is the buccal mucosa, mainly because of the differences in permeability characteristics between the two regions and the buccal mucosa's expanse of smooth and relatively immobile mucosa. The buccal mucosa offers excellent possibilities for the (long-term) delivery of suitable drugs, especially for metabolically unstable drugs, such as peptides. In the development of these buccal drug delivery systems, mucoadhesion of the device is a key element. Mucoadhesive polymers have been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the buccal mucosa. Buccoadhesive drug delivery is relatively new drug delivery strategy; in this traditional polymers are replaced by novel bioadhesive polymers such as thiomers & lectins etc. to overcome limitation of traditional polymer.

Keywords: Buccal Drug Delivery, Oral mucosa, Buccal absorption, Mucoadhesion, Buccoadhesive Polymer, Buccoadhesive Dosage Form

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INTRODUCTION

The pharmaceutical industry has made remarkable interest making it a major participant in the healthcare industry. The progress and advances made by pharmaceutical industry have greatly contributed in terms of treatment of disease, thereby enhancing the quality of life.[1]

Bioadhesive drug delivery formulations were introduced in 1947 when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa; this was eventually to become Orabase.® [2]

Amongst various routes of drug delivery, the oral route is most convenient to the patient and the clinician alike. However, peroral administration of drugs has limitations such as hepatic first pass metabolism and enzymatic degradation within the gastro intestinal (GIT), that prevent oral administration of certain classes of drugs especially peptides and proteins. Other absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery (mucosal linings of oral, nasal, rectal, Vaginal and ocular cavity) offers distinct advantages over peroral administration for Systemic drug delivery. These advantages include bypass of first pass effect, avoidances of pre-systemic elimination within the gastrointestinal (GI) tract and better enzymatic flora for drug absorption. In buccal drug delivery, the buccal mucosa is the preferred region as compared to the sublingual mucosa.One of the reasons is that buccal mucosa is less permeable and is therefore not able to elicit a rapid onset of absorption and better suited for formulations that are intended for sustained release action. Further, the buccal mucosa being relatively immobile mucosa and readily accessible, it makes it more beneficial for retentive systems used for oral transmucosal drug delivery. [1]

Mucoadhesive Drug Delivery System in Oral Cavity: [3]

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

Sublingual delivery: is Systemic drug delivery through the mucosal membranes lining the floor of the mouth.

Buccal delivery: is administration of drug through the mucosal membranes lining the cheeks.

Local delivery**:** is delivery of drug into the oral cavity.

An ideal Property of Buccoadhesive Drug Delivery System: [4]

- Should adhere to the site of attachment for a few hours
- Should release drug in a controlled fashion
- Should provide drug release in an Unidirectional way toward the mucosa
- Should facilitate rate and extent of drug absorption

- Should not cause any irritation or inconvenience to the patient and
- Should not impede with the normal functions such as talking, drinking etc.

Advantages of Buccal Drug Delivery: [5]

1. Drugs bypass first pass metabolism so increases bioavailability.
2. Improved patient compliance due to the elimination of associated pain with injections.
3. Sustained drug delivery.
4. Rapid onset of action and termination of therapy is possible.
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. Transmucosal systems exhibit a rapid initiation and decline of delivery than do transdermal patches.
8. Transmucosal delivery occurs is less variable between patients, resulting in lower intersubject variability as compared to transdermal patches.
9. The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.

Limitations of Buccal Drug Delivery:[6]

1. Drugs which are unstable at buccal pH cannot be administered.
2. Drugs which irritate the oral mucosa or have an unpleasant or bitter taste or an obnoxious odour can not be administered by this route.
3. Drugs with small dose requirements can only be administered.
4. Those drugs which are absorbed by passive diffusion can only be administered by this route.
5. Drinking and eating may become restricted.

Structural Features of Oral Cavity:[3]

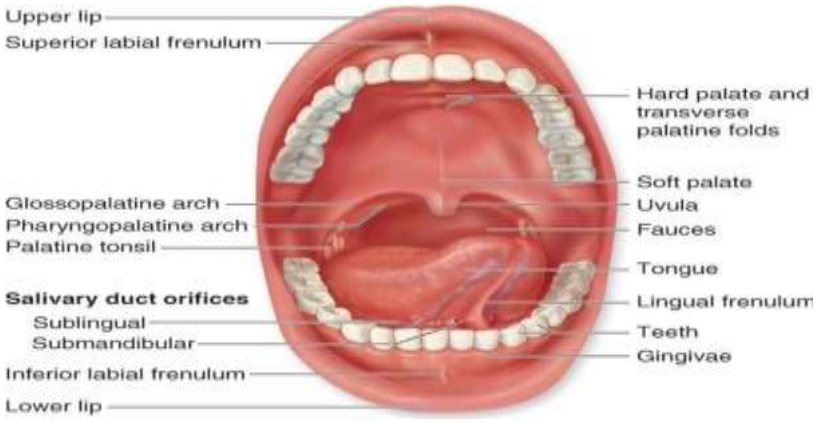

Figure 1: Anatomical Structure of Oral Cavity

Overview of the Oral Mucosa:

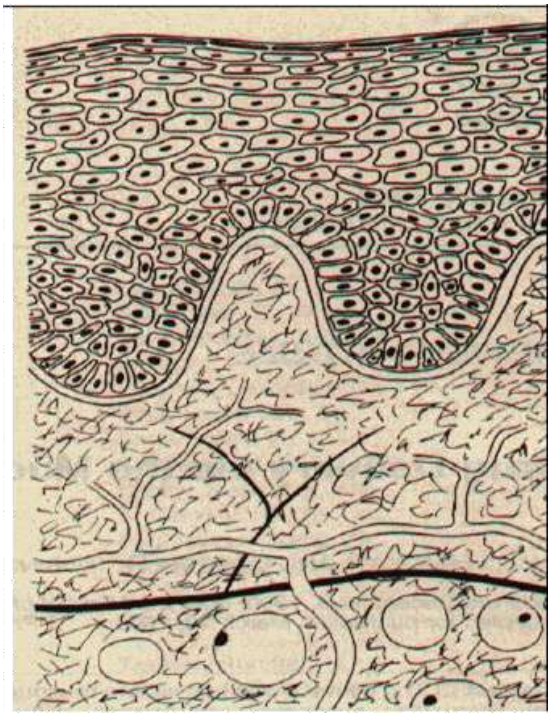

Figure 2: Structure of the Oral Mucosae

Structure of Oral Mucosa:[7]

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (Figure 2). Below this lies a basement membrane, a lamina propria followed by the Submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium . The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they differentiate from the basal layers to the superficial layers.

The turnover time for the buccal epithelium has been estimated at 5-6 days . The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 µm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of the gingivae and hard palate are keratinized and the mucosae of the soft palate, the buccal and the sublingual regions, are not keratinized. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are

relatively impermeable to water. whereas, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and only have small amounts of ceramides . They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

Mucus Layer:[3]

Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 µm in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially depending on the species, the anatomical location and the pathophysiological state. However, it has the following general composition:

- Water - 95%
- Glycoproteins and Lipids - 0.5 to 5%
- Mineral salts - 0.5 to 1%
- Free Proteins - 0.5 to 1%

Functions of Mucus Layer:[8]

- Protective: - Resulting particularly from its hydrophobic.
- Barrier: - acts as a barrier in tissue absorption of drugs and other substrates.
- Adhesion: - Mucus has strong adhesion properties and firmly binds to the epithelial cells surface as a continuous gel layer.
- Lubrication: - An important role of the mucus layer is to keep the mucosal membrane moist.

Permeability of Oral Mucosa: [7]

The oral mucosae in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the buccal mucosa permeability is 4-4000 times greater than that of the skin . In general, the permeability of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal . This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

It is presently believed that the permeability barrier in the oral mucosa is a result of intercellular material obtained from the so-called ‘membrane coating granules’ (MCG) . When

cells go through differentiation, MCGs start forming and at the apical cell surfaces they fuse with the plasma membrane and their contents are discharged into the intercellular spaces at the upper one third of the epithelium. This barrier exists in the outermost 200µm of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase and lanthanum nitrate. When applied to the outer surface of the epithelium, these tracers penetrate only through outermost layer or two of cells. When applied to the submucosal surface, they permeate up to, but not into, the outermost cell layers of the epithelium. In both keratinized and non-keratinized epithelia, the limit of penetration coincided with the level where the MCGs could be seen adjacent to the superficial plasma membranes of the epithelial cells. Since the same result was derived in both keratinized and non-keratinized epithelia, keratinization by itself is not expected to play a significant role in the barrier function. The components of the MCGs in keratinized and non-keratinized epithelia are different, however. The MCGs of keratinized epithelium are composed of lamellar lipid stacks, In contrast the non-keratinized epithelium contains MCGs that are non-lamellar. The MCG lipids of keratinized epithelia include sphingomyelin, glucosyl ceramides, ceramides, and other nonpolar lipids, however for non-keratinized epithelia, the major MCG lipid components are cholesterol esters, cholesterol, and glycosphingolipids.

Environment of Oral Mucosa: [7]

The oral cavity is marked by the presence of saliva produced by the salivary glands and mucus which is secreted by the major and minor salivary glands as part of saliva. Saliva is the protective fluid for all tissues of the oral cavity. It protects soft tissues from abrasion by rough materials and from chemicals. Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus, and the degree of stimulation .The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the pH. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. The main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

Role of Saliva: [3]

- Protective fluid for all tissues of the oral cavity.
- Continuous mineralization / demineralization of the tooth enamel.

- To hydrate oral mucosal dosage forms.

Buccal Routes of Drug Absorption: [3]

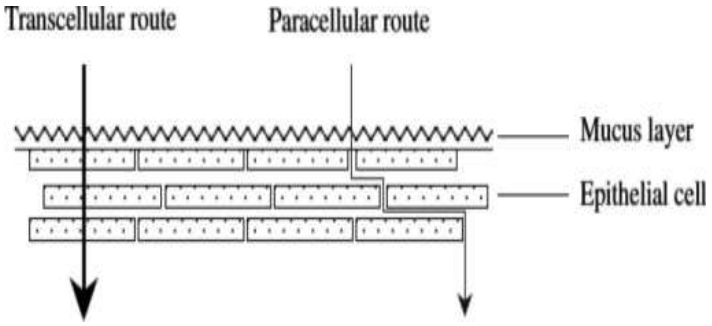

Figure 3: Mechanism of Drug Transport

There are two permeation pathways for passive drug transport across the oral mucosa: Transcellular and paracellular routes.

- Transcellular: it involves passage into and across the cells.
- Paracellular: involves transport of compounds through the intercellular space between the cells.

Bioadhesion /Mucoadhesion:

Bioadhesion may be defined as the state in which two materials, at least one of which is biological membrane, are held together by means of interfacial forces. In the pharmaceutical sciences, when the adhesive attachment of a polymer is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion.[9]

Bioadhesive is defined as a substance that is capable of interacting with biological material and being retained on them or holding them together for extended periods of time. [10]

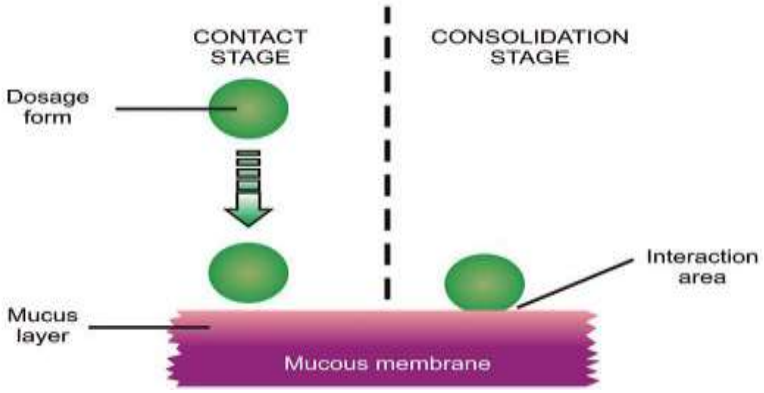

Figure 4: The Two Steps of the Mucoadhesion Process

Mechanism of Mucosal Adhesion: [3]

The mechanism of mucoadhesion is divided into two steps, first is contact step and second is consolidation step.

1. Contact step = the mucus layer come in contact with Mucoadhesive and mucous membrane and the formulation swell and spread over mucus membrane.
2. Consolidation step = the moisture activates the Mucoadhesive material, this plasticizes the system, this allow to Mucoadhesive molecules to break free and link up by weak Vander walls and hydrogen bonds. The diffusion and dehydration theory explain the consolidation step.

THEORIES OF MUCOADHESION

I Electronic Theory:

Because of different electronic structures of the adhesive polymer and the mucus glycoprotein, electron transfer between these two surfaces occurs. This results in the formation of an electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.[11]

II Adsorption Theory:

This theory states that, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces.

Two types of chemical bonds resulting from these forces are:

- Primary chemical bonds of covalent (permanent) nature.
- Secondary chemical bonds having various forces of attraction including Vander Waals forces, electrostatic forces and hydrogen and hydrophobic bonds. [11]

III Wetting Theory:

Wetting theory is predominantly applicable to liquid bioadhesive system and analyses adhesive and contact behaviour in terms of the ability of a liquid or a paste to spread over a biological system. [11]

The work of adhesion [expressed in terms of surface and interfacial tension , Y being defined as the energy per centimeter square released when an interface is formed.] The work of adhesion is given by:

$$Wc = 2YA \text{ or } YB$$

where 'A' and ' B' refer to the biological membrane and the bioadhesive formulation respectively. The work of cohesion is given by:

$$SB/A = YA - [YB + YAB]$$

For a bioadhesive material B spreading on a biological substrate coefficient is given by:

SB/A should be positive for a bioadhesive material to adhere to a biological membrane.[10]

$$Wa = YA + YB - YAB$$

IV Diffusion Theory:

According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus depends on the diffusion coefficient and the time of contact.[11] This diffusion coefficient, in turn, depends on the value of molecular weight between cross-links and decreases significantly as the linking density increases.[10]

V Fracture Theory:

This theory attempts to relate the difficulty of separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by:

$$G = (E\varepsilon / L)$$

Where : E is Young's modules of elasticity, ε is Fracture energy and L is Critical crack length when two surfaces are separated.[11]

FACTORS AFFECTING BUCCAL DRUG DELIVERY SYSTEM

- The rate of absorption of hydrophilic compounds is a function of the molecular size. Smaller molecules (75-100 Da) generally exhibit rapid transport across the mucosa, with permeability decreasing as molecular size increases. For hydrophilic macromolecules such as peptides, absorption enhancers have been used to successfully alter the permeability of the buccal epithelium, causing this route to be more appropriate for delivery of larger molecules.
- Only the nonionized forms of molecules have the ability to cross-lipoidal membranes in significant amounts. The more lipid soluble a compound is, the higher its permeability. The permeability for these compounds is direct functions of their oil-water partition coefficients. The partition coefficient is an important tool to determine the absorption potential of a drug.[12]
- In general, increasing a drug's polarity by ionization or the addition of carboxyl, hydroxyl, or amino groups, will increase the water solubility of any particular drug and cause a decrease in the lipid-water partition coefficient. Whereas, decreasing the polarity of a drug (e.g. adding methyl or methylene groups) results in an increased partition coefficient and decreased water solubility. The partition coefficient is also affected by pH at the site of drug absorption. With increasing pH, the partition coefficient of acidic drugs decreases, while that of basic drugs increases. The partition coefficient is also an important indicator

of drug storage in fat deposits. Obese individuals can store large amounts of lipid-soluble drug in fat stores. These drugs are dissolved in the lipid and are a reservoir of slow release from these fat deposits.

- The ionization of a drug is directly related to both its pKa and pH at the mucosal surface. Only the nonionized form of many weak acids and weak bases exhibit appreciable lipid solubility, and thus the ability to cross lipoidal membranes. As a result, maximal absorption of these compounds has been shown to occur at the pH at which they are unionized, with absorbability diminishing as ionization increases.[13]

METHODS TO INCREASE DRUG DELIVERY VIA BUCCAL ROUTE

Absorption enhancers:

Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates.[14]

MECHANISMS OF ACTION: [15]

Changing mucus rheology:

Drug absorption mainly affect by the thickness of mucus viscoelastic layer. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.

Increasing the fluidity of lipid bilayer membrane:

The most accepted mechanism of buccal mucosa drug absorption is intracellular route. Some permeation enhancer disturb the intracellular lipid packing by interaction with lipid or protein components.

Acting on the components at tight junctions:

Some permeation enhancers act on desmosomes, a major component at the tight junctions thereby enhances drug absorption.

By overcoming the enzymatic barrier:

By inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, modification in membrane fluidity also alters the enzymatic activity indirectly.

Increasing the thermodynamic activity of drugs:

Some permeation enhancers increase the solubility of drug thereby alters the partition coefficient.This leads to increase the thermodynamic activity resulting better drug absorption.

Table 1: List of Permeation Enhancers [14]

Sr.no	Permeation Enhancers	Sr.no	Permeation Enhancers
1	2,3-Lauryl ether	9	Glycol
2	Aprotinin	10	Polyoxyethylene
3	Azone	11	Polysorbate 80
4	Benzalkonium chloride	12	Sodium salicylate
5	Cetylpyridinium chloride	13	Phosphatidylcholine
6	Cetyltrimethyl ammonium bromide	14	Sodium EDTA
7	Cyclodextrin	15	Sodium glycocholate
8	Dextran sulfate	16	Sodium glycodeoxycholate

Prodrugs:[14]

Hussein et al delivered opioid agonists and antagonists in bitterness prodrug forms and found that the drug exhibited low bioavailability as prodrug. Nalbuphine and naloxone bitter drugs when administered to dogs via the buccal mucosa, the caused excess salivation and swallowing. As a result, the drug exhibited low bioavailability

pH:[14]

Shojaei et al evaluated permeability of acyclovir at pH ranges of 3.3 to 8.8, and in the presence of the absorption enhancer, sodium glycocholate. The in vitro permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at both pH extremes (pH 3.3 and 8.8), as compared to the mid-range values (pH 4.1, 5.8, and 7.0).

Patch design:[14]

Several in vitro studies have been conducted regarding on the type and amount of backing materials and the release of drug profile and it showed that both are interrelated. Also, the drug release pattern was different between single-layered and multi-layered patches.

Toxicity and Irritancy Associated With Buccal Drug Delivery:[16]

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 discomfort and pain. This is particularly useful 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 localized 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.

BUCCOADHESIVE POLYMER:[11]

Buccoadhesive polymers are water soluble and water insoluble polymers, which are swellable networks, jointed by crosslinking agent. These polymers possess optimal polarity to make sure that they permit adequate wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to replace.

Ideal Characteristics Of Buccoadhesive Polymer:[17]

The Buccoadhesive polymers should possess following characteristics:

1. Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
2. It should preferably form a strong noncovalent bond with the mucin epithelial cell surfaces.
3. It should adhere quickly to moist tissue and should possess some site specificity.
4. It should allow easy incorporation of the drug and offer non hindrance to its release.
5. The polymer must not decompose on storage or during shelf-life of the dosage form.
6. The polymer cost should not be high.

Different generation of buccoadhesives:[11]

Table 2: List of Various Mucoadhesive Polymers

Synthetic polymers	Natural polymers
Cellulose derivatives Methylcellulose, Ethylcellulose, Hydroxylpropyl cellulose, Hydroxypropyl methyl Cellulose, Sodium Carboxy methylcellulose.	Tragacanth Sodium alginate Karaya gum Guar gum Xanthan gum Lectin Soluble starch Gelatin Pectin Chitosan
Poly acrylic acid Poly hydroxymethyl Methylacrylate. Poly ethylene oxide Poly vinyl pyrrolidone Poly (vinyl alcohol)	

First generation buccoadhesive polymers:

The most widely investigated group of buccoadhesive is hydrophilic macromolecules containing numerous hydrogen bond forming groups, so called first generation' buccoadhesive polymers.

First generation buccoadhesive polymers present significant formulation challenges, being hydrophilic, with limited solubility in other solvents while forming high viscosity, often pH sensitive, aqueous solution at low concentrations.

These are non-specific traditional type of buccoadhesive Polymers and divided into three main sub-sets.

They are namely-

- Anionic polymer
- Cationic polymer
- Non-ionic polymer

Among these three sub types anionic and cationic polymers shows greatest buccoadhesive strength.

Anionic polymers:

- These are having high buccoadhesive functionality and low toxicity. Therefore, these are most widely used buccoadhesive polymers in the pharmaceutical formulations.
- These are having negative charge at pH values exceeding the pK_a of the polymer due to the presence of carboxyl and sulphate functional groups.
- Examples: poly (-acrylic acid) (PAA), sodium carboxy methyl cellulose (NaCMC).
- Due to the formation of strong hydrogen bonding interactions with mucin. both PAA and NaCMC possess excellent buccoadhesive characteristics
- Polycarbophil is insoluble in aqueous media, permitting high level of entanglement within the mucus layer and it increases the mass 100 times in aqueous media at neutral pH.
- One clear difference between Carbomer and Polycarbophil is the level of cross-linking and the cross-linking agent itself.
- Carbomers are cross-linked with allyl sucrose or allyl pentaerythriotol, whereas Polycarbophil polymers are cross-linked with di vinyl glycol.
- Both compounds have the same acrylic backbone but vary in their cross- link density that is often tailored to suit pharmaceutical or cosmetic performance.

Cationic polymers:

- These are also used in the formulation of buccoadhesive dosage forms and the main cationic polymer is chitosan.
- Chitosan is a cationic polysaccharide, produced by the deacetylation of chitin.
- Chitosan is gaining increasing importance due to its good biodegradability, biocompatibility and Nontoxic nature. and it has been reported to bind via ionic interactions between primary amino functional groups and the sialic acid and sulphonic acid substructures of mucus.
- The main benefit of using Chitosan within pharmaceutical applications has been the ease with which various chemical groups may be added, in particular to the C-2

position allowing for the formation of novel polymers with added functionality. Using such modifications, the properties of Chitosan may be tailored to suit the requirements of specific pharmaceutical-technological challenges.

Second generation buccoadhesive polymers:

These are novel promising strategy to improve the buccoadhesive properties of the formulations. They have the following advantages:

1. More site specific hence called cytoadhesives.
2. Are least effected by mucus turnover rates.
3. Site specific drug delivery

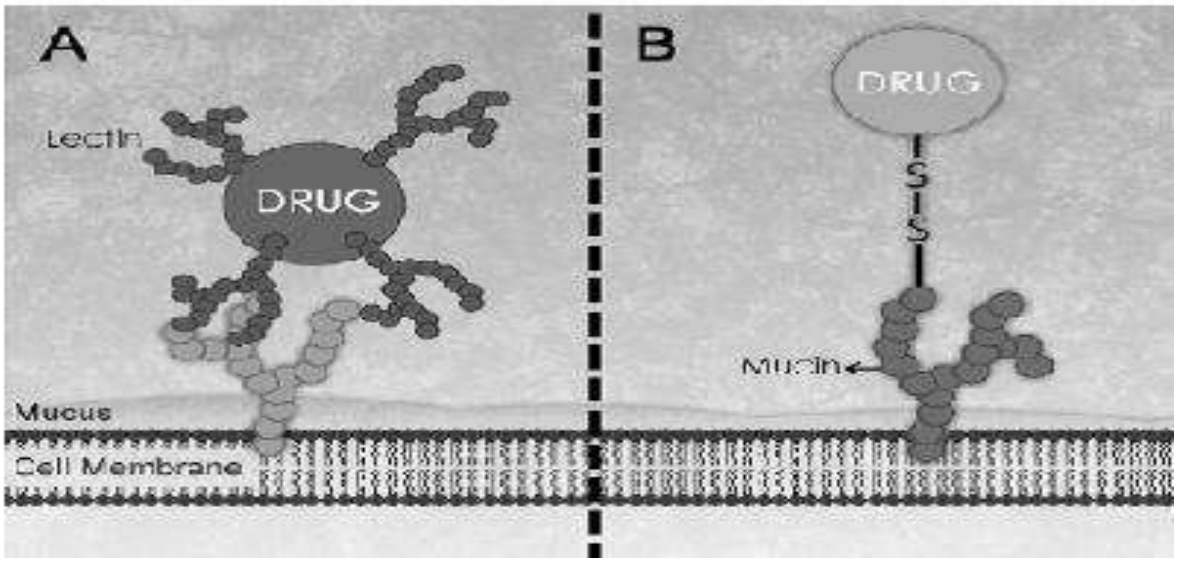

Figure 5: Mechanism of buccoadhesion (A) Lectins (B) Thiomers

Lectins:

- These are defined as proteins or glycoprotein capable of specific recognition of and reversible binding to carbohydrate moieties of complex glycol-conjugates, without altering the covalent structure of any of the recognized glycosyl ligands.
- After initial mucosal cell-binding, lectins can either remain on the cell surface or the case of receptor-mediated adhesion possibly become internalized via a process of endocytosis.
- Lectin-based platform could not only allow targeted specific attachment but additionally offer a method of controlled drug delivery of macromolecular pharmaceutical via active cell-mediated drug uptake .

Thiolated polymers:

- These are Thiomers which are obtained from hydrophilic polymers such as polyacrylates,

Chitosan or deacetylated gellan gum.

- Formation of covalent bonds with cysteine-rich sub domain of the mucus gel layer, due to the presence of thiol groups leading to enhanced residence time and improved bioavailability.

Table 3: List of Thiomers used in buccoadhesion

Polymer	Improvement in Mucoadhesive Potential
Chitosan–iminothiolane	250 times improved than standard value
Poly(acrylic acid)–cysteine	100 times improved
Poly(acrylic acid)–homocysteine	20 times improved
Chitosan–thioglycolic acid	10 times improved
Poly(methacrylic acid)–cysteine	Better cohesive and adhesive
Sodium CMC–cysteine	Better adhesive
Alginate–cysteine	4 times improved

BUCCAL MUCOADHESIVE DOSAGE FORMS

Buccal mucoadhesive dosage forms can be classified into three types based on their geometry.[18]

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

Type II: It is a device in which 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 into the oral cavity.

Type III: It is a unidirectional drug release device, from which loss of drug 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. (Figure.6)

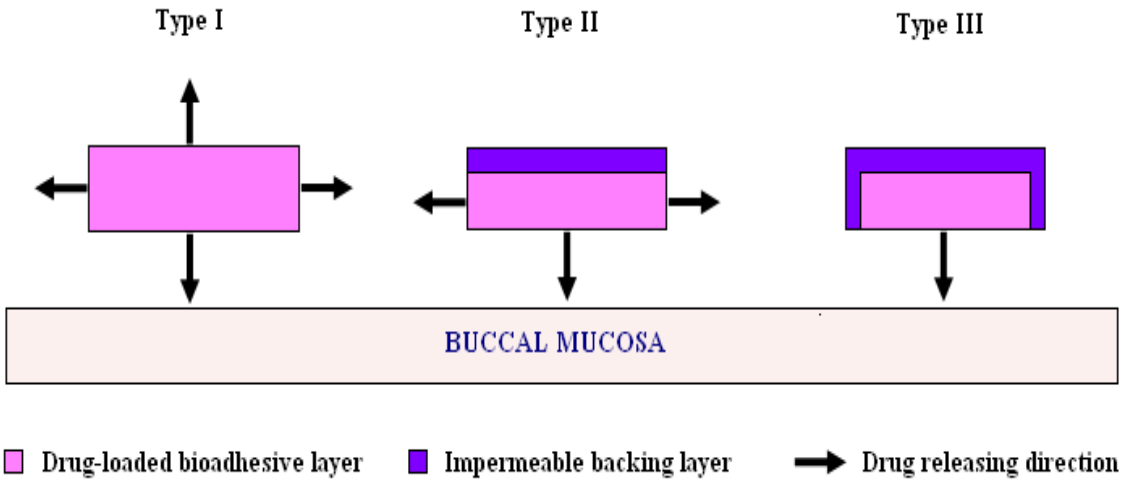

Figure 6: Design of buccal mucoadhesive dosage forms

The different types of Buccoadhesive dosage forms are:

Buccal tablets: [11]

- Buccal tablets are small, oval, and flat, with a diameter of approximately 5-8mm.
- Unlike conventional tablets, buccoadhesive tablets allow for speaking and drinking 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 the lip and the gum.
- Successive tablets can be applied to alternate sides of the mouth.

Buccal patches and films:

- Because of their comfort and flexibility, patches and films may be preferred over adhesive tablets.
- 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.
- An impermeable backing layer may also be applied to control the direction of drug release to prevent drug loss, and minimize deformation and disintegration of the device during the application period.
- Patches and films are more preferred in the case of local delivery for oral diseases, protection of the wound surface and help to reduce pain and treat the disease more effectively.
- Two methods used to prepare adhesive patches include solvent casting and direct milling.[19]
- 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 homogenously mixed and compressed to the desired thickness, and patches of predetermined size and shape are then cut or punched out.[20]

Buccal gels and ointment:[11]

- 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 gel at the site of application has been overcome by using buccoadhesive formulations.
- Certain bioadhesive polymers, e.g. poloxamers 407, sodium carboxy methyl cellulose, 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.

Chewing gum:

- Medicated Chewing Gum is a novel drug delivery system containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa.[21]
- Although medicated chewing gums pose difficulties in regulating the dose administered, they still have some advantages as drug delivery devices, particularly in the treatment of disease in the oral cavity and in nicotine replacement therapy.
- Some commercial products 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.
- However, chewing gum slowly generates a steady plasma level of nicotine rather than a sharp peak as experienced when smoking.
- Possible swallowing of significant amount of nicotine during chewing may lead to decreased effectiveness of the chewing gum due to first-pass metabolism and gastrointestinal discomfort.
- It is a major challenge to optimize the dose-response relationship of nicotine administered in a chewing gum.[11]

Hydrogels:[11]

- Hydrogels are also a promising dosage form, which are formed polymers that are hydrated in an aqueous environment and physically entrap drug molecules for subsequent slow release by diffusion or erosion.

- Buccoadhesive hydrogel are able to interact with the mucus and attach mucosal surface, resulting in a prolonged residence time of buccoadhesive drug release device in a body.
- These dosage forms provide an extended retention time, sufficient drug penetration, as well as high efficacy and patient acceptability.
- Normally, hydrogel are cross linked so that they would not dissolve in the medium and absorb water.
- When drugs are loaded into these hydrogel, as water is absorbed into matrix, chain relaxation occurs and drug molecules are released through the spaces or channels within the hydrogel network.
- Drug release would then occur through the spaces or channels within the network as well as through the dissolution and/or the disintegration of the matrix.
- The use of hydrogel as adhesive preparation for buccoadhesive drug delivery has acquired appreciable attention in recent years.

Powders:

- These are a mixture of bioadhesive polymers and the drug and are sprayed onto the buccal mucosa.[3]
- Example : Hydroxypropyl cellulose and beclomethasone in powder form when sprayed on to the oral mucosa of rats, a significant increase in the residence time relative to an oral solution is seen, and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hours.[22]

Microparticles: [23]

- Have more advantages than tablet.
- The physical properties of microspheres enable to make them closely contact with a large mucosal surface.
- They can also be delivered to less accessible sites like GI tract and nasal cavity and they cause less local irritation at the site of adhesion but the due to their short residence time at site of absorption the success of these microspheres is limited.

Lozenges: [24]

- Lozenges are used as topically within mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals.
- In lozenges multiple daily dosing is required because the release of drug in oral cavity is initially high and then rapidly decline to the subtherapeutic levels.

Sprays:[2]

- Buccoadhesive sprays are gaining popularity over other dosage forms because of comfort, flexibility, high surface area and availability of drug in solution form.
- The fentanyl Oralet ™ is the first FDA-approved (1996) formulation developed 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.

METHODS USED TO STUDY BIOADHESION: [10]

In vitro/Ex vivo methods:

Methods based on measurement of tensile strength:

These methods measure the force required to break the adhesive bond between a model membrane and the test polymers. The instruments usually employed are modified balances or tensile testers. In this method, the force required to separate the bioadhesive sample from freshly excised rabbit stomach tissue was determined using a modified tensiometer. A section of the tissue, having the mucus side exposed, was secured on a weighed glass vial placed in a beaker containing USP simulated gastric fluid. Another section of the same tissue was placed over a rubber stopper again with the mucus side exposed and secured with a vial cap and a small quantity of polymer was placed between the two mucosal tissues. The force was used to detach the polymer from the tissue was then recorded. The results of the study provided important information regarding the effects of hydrophobicity, charge density and experimental conditions such as pH, ionic strength, mucolytic agents and applied pressure on bioadhesion.

Figure 7: Bioadhesion test using the texture analyzer

Methods based on measurement of shear strength:

The shear stress measures the force that causes the bioadhesive to slide with respect to the mucus layer in a direction parallel to their plane to contact. An example is the Wilhelmy plate method uses a glass plate suspended from a microbalance which is dipped in a temperature controlled mucus sample and the force required to pull the plate out of the solution is determined under constant experimental conditions.

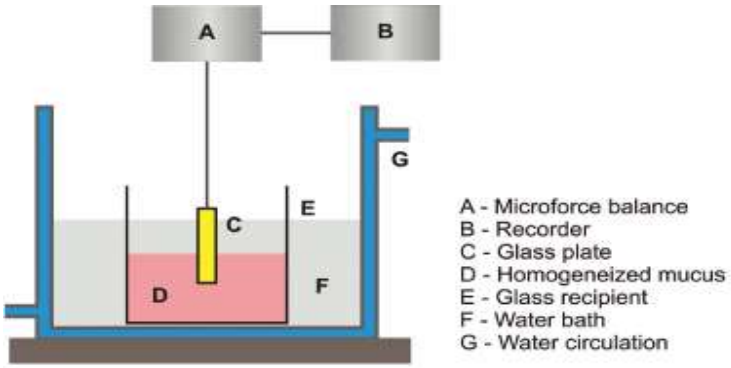

Figure 8: Apparatus to Determine Mucoadhesion in vitro using Wilhelmy Plate Method.

OTHER IN VITRO METHODS:

1. Adhesion weight method:

In this method a test system where suspensions of ion-exchange resin particles flowed over the inner mucosal surface of a section of guinea-pig intestine and the weight of the adherent particles determined. Although the method was of limited value due to poor data reproducibility resulting from fairly rapid degeneration and biological variations of the tissue ,it was possible for them to determine the effect of particle size and charge on the adhesion after five minutes contact with everted intestine.

2. Fluorescent probe method:

In this method the membrane lipid bilayer and membrane proteins were labelled with pyrene and fluorescein isothiocyanate, respectively .The cells were then mixed with candidate bioadhesives and the changes in fluorescence spectra were monitored. This gave a direct indication of polymer binding and its influence on polymer adhesion.

3. Flow channel method:

A flow channel method that utilized a thin channel made of glass and filled with 2% w/w aqueous solution of bovine submaxillary mucin, thermostated at 37°C was passed through the glass channel. A particle of a bioadhesive polymer was placed on the mucin gel and its static and dynamic behavior was monitored at frequent intervals using a camera.

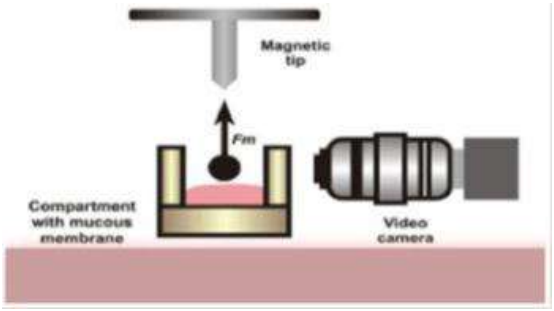

Figure 9: Flow Channel Method

4. Mechanical spectroscopic method:

This method used to investigate the interaction between glycoprotein gels and polyacrylic acid and the effect of pH and polymer chain length on this.

5. Falling liquid film method:

In this method, small intestine segments from rats were placed at an inclination of a tygon tube flute. The adhesion of particles to this surface was monitored by passing the particle suspension over the surface.

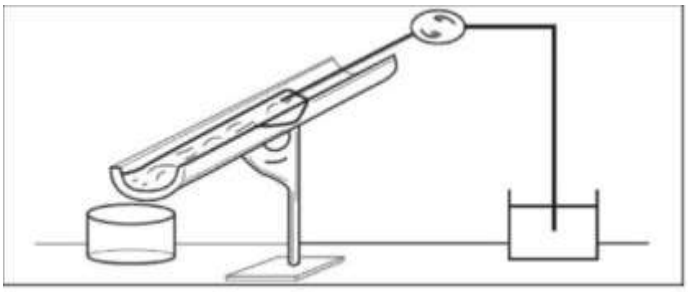

Figure 10: Falling Liquid Film Method

6. Colloidal gold staining method:

The technique employed red colloidal gold particles which were stabilized by the adsorbed mucin molecules (mucin-gold conjugates). Upon interaction with mucin-gold conjugates, bioadhesive hydrogels developed a red colour on the surface. Therefore, the interaction between them could easily be quantified either by the measurement of the intensity of the red colour on the hydrogel surface or by the measurement of the decrease in the concentration of the conjugates from the absorbance changes at 525 nm.

7. Viscometric method:

A simple viscometric method was used to quantify mucin–polymer bioadhesive bond strength. Viscosities of 15 %w/v porcine gastric mucin dispersion in 0.1N HCl (pH 1) or 0.1N acetate buffer (pH 5.5) were measured with a Brookfield viscometer in the absence or presence of selected neutral, anionic, and cationic polymers. Viscosity components and the forces of bioadhesion were

calculated.

8. Thumb test:

It is a simple test method which can be used to identify mucoadhesive. The adhesiveness is quantitatively measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time. It is most likely that any mucoadhesive system is adhesive to fingers, since most mucoadhesive are non-specific and not mucin specific. Like mucin, the skin has many hydroxyl groups. Although the thumb test may not be conclusive, it provides important information on mucoadhesive potential.

9. Adhesion number:

With a mucoadhesive in the form of small particles, the adhesion number can be used as a parameter for mucoadhesion. The determination of adhesion strength for small particles would be difficult. The adhesion number is typically represented by the following equation:

Na = (N /No). 100

Where Na is the adhesion number

No = is the total number of applied particles

N = Number of particles attached to the substrate.

As the adhesion strength increases, the adhesion number also increases.

10. Electrical conductance:

The adhesion of Orabase, Carbopol, Cudispert, guar gum, and methyl cellulose to artificial biomembranes in artificial saliva was studied by using a modified rotational viscometer capable of measuring electrical conductance. This parameter, measured as a function of time, was found to be influenced by the sample, the artificial saliva and the artificial biomembranes. In the presence of adhesive material the conductance was comparatively low. As the adhesive was removed, the value increased to a final value corresponding to the conductance of the saliva, which indicated the absence of adhesion.

- **In Vivo Methods:**
  - Use of radioisotopes
  - Use of gamma scintigraphy
  - Use of pharmacoscintigraphy
  - Use of Electron paramagnetic resonance (EPR) oximetry
  - X-ray studies
  - Isolated loop technique

These techniques are less common due to time consuming, high cost and ethical factors. But these are important to assess the true mucoadhesive potential specially a case of oral mucoadhesive drug delivery. The GI transit time can be measured by using one of the many radio opaque markers like barium sulphate which is coated to the bioadhesive dosage form so as to assess the GI transit by means of X-ray inspection.

By means of gamma scintigraphy both the distribution and retention can be studied. In 1985 Chng et.al. Studied the transit of various 51 cr radio labeled polyacrylic acid beads through the rat GI tract. The beads were fed to the rats and at different time intervals after which the rats were sacrificed. The rats intestine was then systemically dissected into 20 equal parts and the amount of radiation in each part measured thus allowing, the transit overtime to be realized. The development of a noninvasive technique to determine the transit time of mucoadhesive polymers was done by Davis. The transit time could be imaged via labeling of the polymer with a gamma emitting nucleotide which was determined with the help of gamma scintigraphy.

RECENT AND FUTURE OF BUCCAL DRUG DELIVERY:[14,25]

- Buccal nitroglycerine, can use for acute therapy for an anginal attack as well as for chronic prophylaxis.
- Novel liquid aerosol formulations of insulin.
- Buccal drug delivery will provide a platform for the successful delivery of vaccines and antigens.

Table 4: List of brand name and company name: [19]

Active Substance	Brand	Company	Polymer used/Technology	Formulation
Prochorperaxine maleate	Buccastem	Reckitt Benckiser	Xanthan gum,Povidone	Tablet
Prochorperazine	Emezine	BDSI	Undisclosed	Tablet
Glyceryl trinitrate	Suscard	Forest lab	HPMC	Tablet
Fentanyl	Fentora	Cephalon Inc	Oravescent	Tablet
Fentanyl	Actiq	Cephalon Inc	Modified food starch	Tablet
Miconazole	Loramyc	Bioalliance pharma	Undisclosed	Tablet
Miconazole	Tibozole	Tibotec pharmaceutical	CP	Tablet
Miconazole	Daktarin	Janssen-Cilag	Undisclosed	Tablet
Testosterone	Striant	Columbia lab	HPMC,CP	Tablet
Triamcinolone acetonide	Aphtach	Teijin ltd	HPMC,PAA	Tablet
Hydrocortisone sodium succinate	Corlan pellets	UCB pharma	Acacia gum	Oromucosal pellets
Triamcinolone acetonide	Orabase	Conva tech	Pectin, Gelatin	Oral paste
Chlorhexidine digluconate	Corsodyl gel	Glaxosmithcline	HPMC	Oromucosal gel
Choline salicylate	Bonjela	Reckitt Benckiser	HPMC	Oromucosal gel

CP; Carbopol, HPMC; Hypromellose,PAA; Polyacrylic acid

CONCLUSION

The buccal mucosa offers several advantages over 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 possible and attractive alternative for non-invasive delivery of potent protein and peptide drug molecules. However, the need for effective and safe buccal permeation absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery.

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