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An Overview on Bioadhesive Buccal Drug Delivery System

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Abstract:

Buccal delivery is defined as drug administration by mucosal cells that fill the cheeks (buccal mucosa). A future challenge for pharmacologists is to improve the effective non-parental delivery of solid proteins and peptides to the system's distribution. Based on our current understanding of the chemical and physical properties of the absorption and body composition of many biotechnologically produced drugs, they cannot be successfully transmitted through a standard oral route. Because after oral administration many drugs are given pre-systemic exposure to the liver, which often leads to a significant lack of significant interaction between membrane of the absorptiom and bioavailability availability

Introduction:

Significant interest from the past year has been shown in the formulation of bio adherence scale forms of the novel mucosal delivery of drugs trying to overcome limitations here. The term 'bio adhesive' refers to substances that bind to a biological substrate, such as mucosal membranes. The attachment of the adhesive drug delivery devices to the mucosal membrane leads to an increase in the gradient concentration of the drug in the absorption site and thus improves the availability of drugs delivered systematically[1]. In addition, bio adhesion measurement forms have been used to identify local disturbances in the mucosal surface (e.g. oral ulcers) to reduce the total required dose and to reduce the side effects that can be caused by drug administration. The absorption of the drug into the oral mucosa is mainly by non-permeable circulation in the lipoid membrane. Chemicals with a differential coefficient in the range of 40- 2000 and pK2-10 are considered suitable to enter the buccal mucosa. Buccal-regulated chemicals include steroids, barbiturates, papain, and trypsin etc. The drug can be injected into the oral cavity through the oral mucosa either through the lower or buccal larynx. The absorption of therapeutic chemicals from these routes overcomes premature drug damage within the intestinal tract and active drug loss due to early approval of hepatic metabolism which may be associated with the oral administration route[2]. Rapid absorption from these routes is often seen as a result of narrowing of the mucous membranes and rich blood supply. After ingestion, the drug is transmitted through a deep vein of the tongue or facial vein which then progresses to normal circulation through the jugular vein, by transferring the liver and thus protecting the drug from initial exposure. Since language drug use disrupts eating, drinking and taking this route, which is generally considered unsuitable for long-term treatment, Baccal drug administration can also be supplemented with saliva polymers without minor language problems.

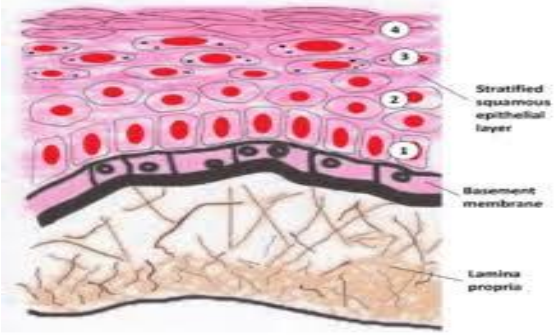
Within the mucosal oral cavity, drug delivery can be divided into three stages:

• Bilingual delivery: What is the systemic delivery of drugs through oral mucosal cells?

• Buccal delivery, which is drug administration by mucosal cells that fill the cheeks (buccal mucosal).
• Local delivery, which brings drugs into the oral cavity[3].

Structure of oral mucosa:

The oral mucosa can be divided into two common regions, the external vestibule and the oral cavity. The vestibule is attached to the outside by the lips and cheeks and inside the upper and lower tooth layers. The oral cavity is located inside the dental cavity framed at the top by strong and soft circles and at the bottom of the tongue and under the mouth. The oral mucosa contains the outer layer of the squamous squamous epithelium, below which lies the lower membrane, and below this, too, there is a suitable lamina and sub mucosa[4,5].



The oral mucosa can be divided into five main areas in the oral cavity:
• Lower lip (under tongue)
• Buccal mucosa (cheeks)
Amber (gingiva)
• Palatal mucosa
• The inner side of the lips.

a) Epithelial Lining:

Epithelial membranes provide a protective layer between the oral environment and deep tissue. It contains the epithelium that is the core of cells that are tightly bound together to form different layers in the maturation process from the deeper layers to the surface. The upper layer of the hard lip and tongue forms keratin to produce a firm, non-abrasive epithelial surface that is resistant to abrasion, but the epithelium of the cheek, lower lip and soft palate is not keratinized and makes it easier to deliver[6]. The size of the oral epithelium which is the most keratinized part between the sites as shown in the table provided below:

Table 1: Average epithelial thickness of oral mucosa

Tissue	Structure	Epithelial thickness (micrometer)	Blood flow ($ml.min^{-1}$, cm^{-2})
Buccal	Non-keratinised	500-600	2.40
Sublingual	Non-keratinised	100-200	0.97
Gingival	Keratinized	200	1.47
Palatal	keratinised	250	0.89

b) Basement Membrane and Connective Tissues:

The subcutaneous layer is a continuous layer of extracellular material, forming a boundary between the basic layer of the epithelium and the connective tissue of the lamina propria and sub-mucosa. It creates a barrier to cell transfer and to other large molecules across the mucosa. Below the lining lies the lamina propria a continuous sheet of collagen-containing connective tissue, stretch fibers, and cellular components in an aqueous soil. It also carries blood capillaries and nerve fibers that work in that mucosa[7].

c) Secretions:

Fluid from the oral mucosa, mucus and saliva helps to keep the area moist. This hydration improves membrane permeability of the drug. The main secretion is provided by three pairs of glands, namely, parotid (lower and front of the ear), sub-maxillary (lower jaw) and lower glands (below the tongue)[8]. Mucus has the following common formulations:

Drug detection using buccal mucosa:

There are two drug delivery pathways through the squamous stratified epithelium of the oral mucosa of the mucosa Tran (intracellular, passing through the cell) and Para cell (intercellular, passing through the cell).

Enlargement throughout the buccal mucosa has been reported mainly by Para's cellular

route through lipids of cells produced by granules covering membranes[9] (fig. 2).

The Para cellular And Trans cellular Routes of Transport Have Been Designated to The Buccal Mucosa

Barriers to penetration across buccal mucosa: Obstacles such as saliva, mucus, lining membranes, underlying membranes etc., Delay the rate and intensity of drug absorption through the buccal mucosa. A major barrier to penetration lies in the very outer part of one-third of the epithelium. Coating Granules or Cored Granules: In non-keratinized epithelia, the collection of lipids and cytokeratin's in keratinocytes is less pronounced and morphology changes are much less severe than in keratinized epithelia[10]. Mature cells on the outer part of the non-keratinized epithelia become larger and flatter the nuclei and other organelles and cytokeratin's do not bind to form fibrous bundles as seen in the keratinizing membrane. As cells reach the upper third of the epithelium, membrane-covering granules are visible in the upper part of the cells and appear to interact with plasma membranes to release their contents into the particle space. The membrane granules are found in non-keratinizing non-keratinizing epithelial cells[11], bound to the membrane and measuring approximately 0.2 μm in diameter. Such granules have been observed in other non-keratinized human epithelia, including the cervix and throat. However, current studies using ruthenium tetroxide as a post-fixative show that in addition to cored granules, a small portion of the granules in the non-keratinized epithelium contains lamellae, which may be a source of short-lived piles of lamellar lipids scattered throughout the intercellular spaces on the outer part of the epithelium. In contrast to the intercellular spaces of the stratum cornea, those of the upper layer of non-keratinizing epithelia contain beneficial electrons, which can represent non-lamellar phase lipid, with a few short spaces of lipid lamellae.

Basement Membrane: Although the upper layers of the oral epithelium represent a major barrier to the entry of foreign material, it is clear that the lower membrane also plays a role in reducing the passage of crossings between the epithelium and connective tissue. The same approach seems to work in the opposite direction. Charging of the basal lamina elements can reduce the level of lipophilic chemicals that can easily cross the upper epithelial barrier[12].

Mucus: The epithelial cells of the buccal mucosa surrounded by an underground substance called mucus in size vary from 40 μm to 300 μm .Or the underlying glands and small salivary glands provide only about 10% of them all saliva, when combined produces most of the mucus and is very important in maintaining a layer of mucin above the oral mucosa. It acts as a delivery vehicle that acts as a lubricant that allows cells to interact and is believed to play a major role in adherence to illicit drug delivery systems[13].

At buccal pH, the mucus can form a tightly packed gel structure that binds to the epithelial cell part as a gelatinous layer. Mucus molecules are able to combine to form polymers or a three-dimensional extended network. The by-products of mucus are produced, for example G, L, S, P and F mucus, forming a separate network of gels. Other substances such as ions, protein chains, and enzymes are also able to alter the interaction of mucus molecules and, as a result, their biophysical structures.

Mucus is composed mainly of Mucins and inorganic salts suspended in water. Mucins belong to the family of high-protein, high-

density oligosaccharide chains attached to the protein content. Three-quarters of the protein backbone has high glucose veins and transmits a gel-like substance to the mucus. Mucins' dense sugar coating gives them more water retention capacity and makes them more resistant to proteolysis, which is not essential for maintaining mucosal barriers.

Mucoadhesive polymers[14,15]:

Polymer is a common term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bond. The name is derived from the Greek words: polys meaning many parts and more meanings 26. Mucoadhesive is a synthetic or natural polymer that interacts with a layer of mucus covering the surface of the mucosal epithelial and large molecules that make up a large portion of tissue. The concept of Mucoadhesive has warned many researchers that it is possible that these polymers could be used to overcome physical barriers to long-term drug delivery27. The development of Orahesive followed, leading to the launch of the Orabase in 1959. Orabase was made of natural gums and represented the first intentionally made Mucoadhesive. The product of Orabase (Adcortyl in Orabase) provides local relief of oral ulcers in two ways: preventive function and anti-inflammatory activity (due to triamcinolone acetone).

Classification:

Generally, adhesive polymers can be classified as synthetic vs. natural, soluble in water vs. insoluble, and charged compared to uncharged polymers. Table 1 summarizes the Mucoadhesive polymoas used in the delivery of buccal drugs[16].

Mucoadhesive Polymers Used In Buccal Delivery

Polymers are widely used in dry or hydrated buccal dosage forms including polyacrylic acid (PAA), polyvinyl alcohol (PVA), sodium carboxyl methyl cellulose (NaCMC), hydroxyl propylmethyl cellulose (HPMC) , hydroxyl ethyl cellulose (HEC), hydroxy propyl cellulose (HPC) and sodium alginate[17].

A new generation of muco adhesive polymers (other than polymers that have been applied) can adhere directly to the surface of the cell, rather than adhere to a thin layer. They interact with the cell surface through specific receptors or covalent bonding instead of indirect processes, which are the characteristics of previous polymers. Examples of this are the incorporation of L-cysteine into thiolated polymers and target-targeted polymers. These polymers phase promise the delivery of a wide variety of new drug particles, especially macromolecules, and create new opportunities for greater drug interactions and improved targeted drug delivery[1].

Dissolved polymers or customized thiomers are a polymo of the Mucoadhesive base, showing the side chains with a pumpkin. These polymers are obtained by the incorporation of conjugated sulfidryl groups. Powdered polymers are a type of second generation Mucoadhesive polymer based on hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum. lists standard hydrophilic polymers that are thiolated with the following effect on Mucoadhesive bond strength. The presence of thiol groups allows the formation of covalent bonds with sub-cysteine-rich backgrounds of the mucus gel layer, which leads to increased duration and improved bioavailability. In recent years, lectins have been studied as special adhesives for the delivery of drugs to the oral cavity. Its clarity lies in the mechanism of mucoadhesion[18]: such substances are able to detect and bind certain residues of sugar to

the mucosal surface without altering the structure of the known ligand. Recently, lamellar and cubic liquid crystalline glycerol monooleate (GMO) phases showed Mucoadhesive properties and potential use as carriers for buccal drug delivery.

Mechanism of Mucoadhesion: The mechanism of adhesion of certain macro-molecules to the surface of a mucous tissue is not well understood yet. The Mucoadhesive must spread over the substrate to initiate close contact and hence increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a Mucoadhesive to be successful, the attraction forces must dominate. Each step can be facilitated by the nature of the dosage form and how it is administered[1].

Thus, the mechanism of mucoadhesion is generally divided in two steps:

The contact stage, and the consolida-tion stage The first stage or the contact stage is characterized by the contact between the Mucoadhesive and the mucous membrane, with spreading and swelling of the formu-lation, initiating its deep contact with the mucus layer. In the consolidation step, the Mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the Mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds[19].

The two Steps of the Mucoadhesion Process.

Theories of mucoadhesion:

Although the chemical and physical basis of muco-adhesion are not yet well understood, there are six classi-cal theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon.

Theories of Mucoadhesion

Penetration enhancers: Penetration enhancers are the substances, which increase the buccal mucosal membrane permeation rate. Although most penetration enhancers were originally designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers must be a priority in drug delivery. With the rapid development of biotechnology, more and more protein, peptide, and nucleotide drugs are becoming available, most of which have low membrane-absorption characteristics including[6.7]: A large size with high molecular weight, Domains of different hydrophobicity, Irregular shapes, and delicate structures easily inactivated. These drugs are unable to cross membrane barriers in therapeutic amounts and thus research into penetration enhancers becomes ever more important

Classification of Penetration Enhancers

A new promoter of the introduction of buccal delivery called lysalbinic acid has been studied using the hamster cheek mucosa as a simple animal model for the first test of sucking promoters. It has been shown that the combined administration of lysalbinic acid with low protein content (6–16 kDa), such as α-interferon and insulin, can significantly increase their absorption by buccal epithelium. Therefore, lysalbinic acid has been shown to increase the tendency of the hamster's oral cavity to peptide compounds with low to medium weight[20].

Mechanism of buccal permeation enhancers:

Provides an overview of some of the proposed mechanisms action of penetration enhancers.

Mucosal Penetration Enhancers and Mechanisms of Action

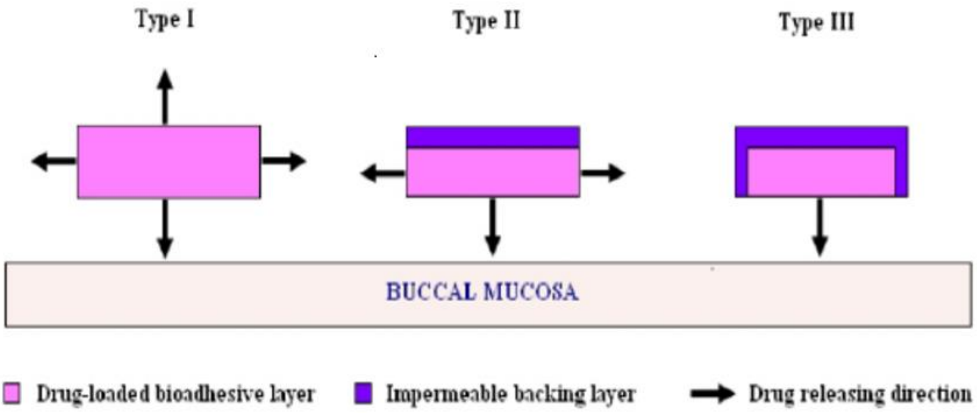
Enzyme Inhibitors: Co-administration of a drug with enzyme inhibitors is another

strategy to improve the absorption of buccal drugs, especially peptides. The enzyme inhibitors, such as decomposition, statin, puromycin and bile salts stabilize protein proteins in a variety of ways, including affecting enzymes, modifying peptides or proteins and / or making the drug less susceptible to degradation. -enzymatic.
It has been shown that some Mucoadhesive polymers can act as an enzyme inhibitor. The special significance of this finding lies in the distribution of therapeutic compounds that are more common in broadly enzymatic breakdown, such as proteins and polypeptide drugs. Research has shown that polymers, such as poly (acrylic acid), work in a competitive way with proteolysis enzymes.

This is due to their strong attachment to divalent metals (Ca2 +, Zn2 +). These cations are important cofactors of metalloproteinase, such as trypsin. Circular dichroic studies suggest that a decrease in Ca2 +, which mediates the presence of certain Mucoadhesive polymers, causes a second formation of trypsin, and initiates a different breakdown of the enzyme.
Buccal Weight Forms: Over the past few years, various dosage forms for the delivery of buccal drugs have been developed. List the active ingredients delivered by the buccal route

Buccal Mucoadhesive Dosage: 3 types

Buccal Mucoadhesive dosage forms can be categorized into three types based on their geometry illustrated in the following



Type I:
It is a single layer metal produced by a variety of drugs. This type of dosage form has a higher risk of drug loss due to swallowing.
Type II:
In this type a non-abrasive support layer is placed over the adhesive layer of the tree, forming a two-line device and preventing drug loss in the upper part of the dosage form in the oral cavity.
Type III:
This is a unidirectional discharge, in which the loss of the drug is minimal, because the drug is released only on the side closest to the buccal mucosa. This can be achieved by covering the entire face of the equilibrium form, with the exception of the one that meets the buccal mucosa.
Buccal scale forms can also be classified as “dam” or “matrix”. In the list of dams, the most abundant drug is present in a pool surrounded by a polymeric membrane, which controls the rate of drug release. In matrix-type systems, the drug is evenly distributed throughout the polymer matrix, and drug release is controlled by the expansion of the polymer network[21].

Buccal Mucoadhesive dosage forms should be made of various drugs. Several peptides, including thyrotrophic-releasing hormone (TRH), insulin, protirelin, buserelin and oxytocin, are delivered in the form of buccal, albeit low concentrations (0.1-5%) due to hydrophobicity their and the weight of the upper cells, and as natural fillings with enzymatic barriers to the buccal mucosa.

Buccal dosage forms can be used to treat both local and systemic conditions. A promising example of the Buccal Mucoadhesive formula for systematic use is the buccal delivery of salmon calcitonin (sCT) using a thin film compound containing 40 μg of sCT (200 IU).

An in vivo study of New Zealand white rabbits with white rabbits showed an equitable finding of 43.8 ± 10.9%, and the decrease in calcium calcium levels after sCT buccal treatment was similar to those observed with sCT. These results suggest that the effective therapeutic value of salmon calcitonin may be brought to a systematic distribution by the buccal mucosa. It summarizes the various buccal measurement forms described in books 5

Buccal Tablets:

Tablets have become the most widely investigated dosage form for the delivery of buccal drugs. Buccal tablets are small, table-shaped and oval-shaped and unlike conventional tablets that allow for drinking and speaking without much hassle. They become soft, adhere to the mucosa and are kept in shape until the damage and / or removal is complete[22].

List of Buccal Mucoadhesive tablets

Monolithic matrix tablets and two layers designed for the delivery of buccal drugs. provided a systematic representation of several types of matrix tablets. Bioadhesive tablets can be prepared using a variety of methods such as direct compression or wet granulation process. With the delivery of buccal drugs, pills placed in a buccal bag can be eliminated or eliminated; therefore, they should be constructed and pressed with sufficient pressure to provide a solid tablet. To make energy or achieve the unwanted release of a drug, unavoidable water-soluble substances, such as ethyl cellulose, hydrogenated castor oil, etc. buccal mucosa. If necessary, the drug can be applied to certain areas of the body, such as microspheres, before direct compression to obtain certain desirable properties, e.g. improved function and long-term drug release[21].

Buccal patches:

Buccal dots are defined as laminate containing an impermeable support layer, a layer of drug-containing pools that release the drug in a controlled manner, and a bio adhesive site for mucosal adhesion. Two methods, namely, solvent dispersion method and direct grinding are used to fix adhesive stains. In the case of solvent dispersion, the middle sheet in which the fist is inserted is fixed by spraying a solution of wood and polymers (s) on the supporting metal sheets. and subsequently allowing the solvent(s) to evaporate[22].

Schematic Representation of Different Matrix Tablets For Buccal Delivery. Arrows Indicate the Direction of Drug Release

In a straightforward grinding method, the composition of the compound is evenly mixed and pressed to the desired size, and pieces of pre-determined size and shape are cut or punched.

And to control the direction of drug withdrawal, to prevent drug losses, and to reduce the distortion and separation of the metal during application, can be applied by an inaccessible support layer.

Buccal films:

In more recent times, many Mucoadhesive dosage forms for the delivery of buccal drugs have been developed such as tablets, films, stains, discs, ointments and gels. However, buccal films are preferred over Mucoadhesive discs and tablets in terms of patient comfort and flexibility and ensure a more accurate dosage and longer duration compared to gels and ointments. Buccal films also reduce pain by protecting the wound area and thus increasing the effectiveness of the treatment. The proper buccal film should be flexible, stretchy, and soft but strong enough to withstand fractures due to pressure from the oral cavity. In addition, it should also have a good Mucoadhesive strength to be kept in the mouth for the required time[23].

Buccal gels and ointments:

These misolid dosage forms have the advantage of easy distribution throughout the oral mucosa. The problem of improper gel storage at the application site has been overcome by using a bio adhesive structure. Certain polymer adhesive bio for example, sodium carboxy methyl cellulose changes the phase from liquid to semisolid. These changes improve or improve viscosity, leading to continuous or controlled drug release[23].

New Drug Delivery Programs: New drug delivery systems use lipophilic gel, buccal spray and

phospholipid vesicles to deliver peptides via the buccal channel. The use of cubic and lamellar liquid crystalline layers of glycerol monooleate has been suggested as a buccal drug carrier for peptide drugs.

The development of the novel aerosol novel (Oralin, Generatex Biotechnology) 119 was recently launched, and is now in phase III clinical trials. This system allows the delivery of a direct dose of insulin with a metered dose inhaler in the form of fine drops directed at the mouth. The drug level in the mouth increases significantly compared to conventional technology. This oral aerosol injection is rapidly infused with buccal mucosal epithelium, and provides the levels of plasma insulin needed to control postprandial glucose uptake in diabetic patients. This novel, painless formulation, oral insulin formulation has many benefits including rapid absorption, easy (user-friendly) administration, direct dosage control (such as injection within a single unit) and drug delivery by bolus

The impaired phospholipid vesicles, transfersomes, were recently designed to deliver insulin into the buccal 120 cavity. They are similar in liposomes but different in function. Transmitters respond to external pressures with rapid conversion that requires low power. This high disability allows them to transport drugs across all epithelial barriers. To prepare these vesicles, surfactants, such as sodium cholate or sodium dehoxycholate are inserted into the vesicular membrane. The insulin treatment of rabbits exceeds that observed by traditional liposomes: compared with subcutaneous administration of insulin solution, the incidence of deformed vesicles was significantly higher than that of conventional vesicles.

Conclusion: Over the past few decades, research on buccal drug delivery has revealed significant growth and development. The transmucosal route is becoming increasingly popular because it has important benefits such as avoiding early liver transplantation and pre-termination of the intestinal tract. Buccal drug delivery has a good promise for the systematic delivery of non-oral medications as well as another possible and attractive alternative to the delivery of non-potent peptide and protein drug molecules.

Despite the benefits of drug delivery through the buccal mucosa, this route remains a major challenge, with major obstacles being a limited area of absorption and mucosa barriers. Strategies learned to overcome such barriers include the use of substances that include mucoadhesive, enzyme inhibitory and penetration enhancer and the formation of new substances, in addition to improving compliance patients prefer close and long-lasting contact of the drug with the suction mucosa.

New and unexpected challenges are expected in the use of mucoadhesives for the delivery of new medicines and in the search for appropriate mucoadhesives. Efforts should be made to develop in vitro and ex vivo models that allow one to visualize and compare different materials and constructions according to their ability to promote drug absorption through the buccal channel.

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