



AN OVERVIEW ON MUCOADHESIVE DRUG DELIVERY SYSTEM

Sandeep S. Tate^{1*}, Ganesh V. Devkate¹, Sonali B. Deokate¹, Atul S. Bhujbal², Avinash P. Tupe³,
Dr. Rajendra N. Patil³

¹Department of Pharmaceutics, Shivnagar Vidya Prasarak Mandal's College of Pharmacy, Malegaon (BK), Baramati-413115, India.

²Department of Pharmacology, Shivnagar Vidya Prasarak Mandal's College of Pharmacy, Malegaon (BK), Baramati-413115, India.

³Department of Pharmaceutical Chemistry, Shivnagar Vidya Prasarak Mandal's College of Pharmacy, Malegaon (BK), Baramati-413115, India.

***Corresponding Author: Sandeep S. Tate**

Department of Pharmaceutics, Shivnagar Vidya Prasarak Mandal's College of Pharmacy, Malegaon (BK), Baramati-413115, India.

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ABSTRACT

Oral route is perhaps the most preferred to the patient and the clinician alike. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosa is considered as potential sites for drug administration. Trans mucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over per oral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug absorption.

KEYWORDS: Oral route, Trans mucosal routes, bypass of first pass.

INTRODUCTION

Buccal Delivery

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosa is considered as potential sites for drug administration. Trans mucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over per oral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of pre systemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug absorption.^[1]

The nasal cavity as a site for systemic drug delivery has been investigated by many research groups^[1-7] and the route has already reached commercial status with several drugs including LHRH8-9 and calcitonin.^[10-12] However, the potential irritation and the irreversible damage to the ciliary action of the nasal cavity from chronic application of nasal dosage forms, as well as the large intra- and

inter-subject variability in mucus secretion in the nasal mucosa, could significantly affect drug absorption from this site. Even though the rectal, vaginal, and ocular mucosae all offer certain advantages, the poor patient acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration. The oral cavity, on the other hand, is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage, and the virtual lack of Langerhans cells makes the oral mucosa tolerant to potential allergens. Furthermore, oral Trans mucosal drug delivery by passes first pass effect and avoid pre-systemic elimination in the GI tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery.^[13-15]

Within the oral mucosal cavity, delivery of drugs is classified into three categories.^[16]

Sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth. Buccal delivery, which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa). Local delivery, which is drug delivery into the oral cavity.

Overview of the Oral Mucosa

Structure

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (Figure 1). Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer.^[17] 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 travel from the basal layers to the superficial layers.^[17]

The turnover time for the buccal epithelium has been estimated at 5-6 days¹⁸, and this is probably representative of the oral mucosa as a whole. 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 mucosa of area subject to mechanical stress (the gingivae and hard palate) is keratinized similar to the epidermis. The mucosa of the soft palate, the sublingual, and the buccal regions, however, are not keratinized¹⁸. 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. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amounts of ceramide.^[19-21] 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.^[18-20]

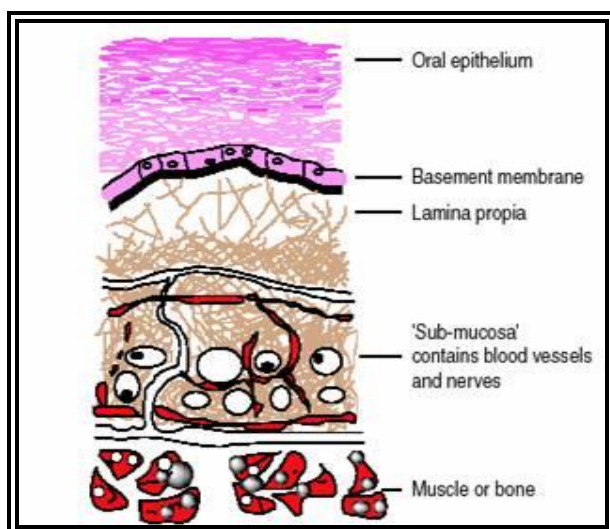


Figure 1:- Structure of the oral mucosa.

Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin.^[22] As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeabilities 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.^[18]

It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called 'membrane coating granules' (MCG).^[23] 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 200 μm of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase^[24] and lanthanum nitrate.^[25] When applied to the outer surface of the epithelium, these tracers penetrate only through outermost layer or two of cells. When applied to the sub mucosal surface, they permeate up to, but not into, the outermost cell layers of the epithelium. According to these results, it seems apparent that flattened surface cell layers present the main barrier to permeation, while the more isodiametric cell layers are relatively permeable. 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 obtained 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.^[19] The MCGs of keratinized epithelium are composed of lamellar lipid stacks, whereas the non-keratinized epithelium contains MCGs that are non-lamellar. The MCG lipids of keratinized epithelia include sphingomyelin, glucosylceramides, ceramides and other nonpolar lipids, however for non-keratinized epithelia, the major MCG lipid components are cholesterol esters, cholesterol, and glycosphingolipids.^[19] Aside from the MCGs, the basement membrane may present some resistance to permeation as well, however the outer epithelium is still considered to be the rate limiting step to mucosal penetration. The structure of the basement membrane is not dense enough to exclude even relatively large molecules.^[24-25]

Mucoadhesion/bioadhesion

Definition

In 1986, Longer and Robinson defined the term bioadhesion as the attachment of a synthetic or natural macromolecule to mucus and/or an epithelial surface^[26]. The general definition of adherence of a polymeric material to biological surfaces (bioadhesive) or to the mucosal tissue (mucoadhesive) still holds.^[27]

Factors affecting mucoadhesion in the oral cavity

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

Polymer-related factors

Molecular weight. In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above 1, 00,000.^[28] 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, has been shown by Tiwari *et al.*^[29]

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.^[30] 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.^[31]

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.^[32] 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.^[33]

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.^[32] 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.^[34]

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.^[33] It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium.^[35] Additionally, some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties.^[36]

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.^[33] 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 a 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 polyvinylpyrrolidone or poly (vinyl alcohol) as film-forming polymers did not further enhance the mucoadhesive properties of the polymer.^[48] On the contrary, it decreased the desired strength of mucoadhesion.^[37]

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.^[32] However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bioadhesion occurs.^[33]

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 pH of the microenvironment surrounding the mucoadhesive polymer can alter the ionization state and, therefore, the adhesion properties of a polymer. Mucin turnover rate is another environmental factor.^[38]

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^[39] and 12–24 h in humans.^[40]

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.^[41]

Buccal mucoadhesive dosage forms

Buccal mucoadhesive dosage forms can be categorized into three types (Figure 2) 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.

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.^[42]

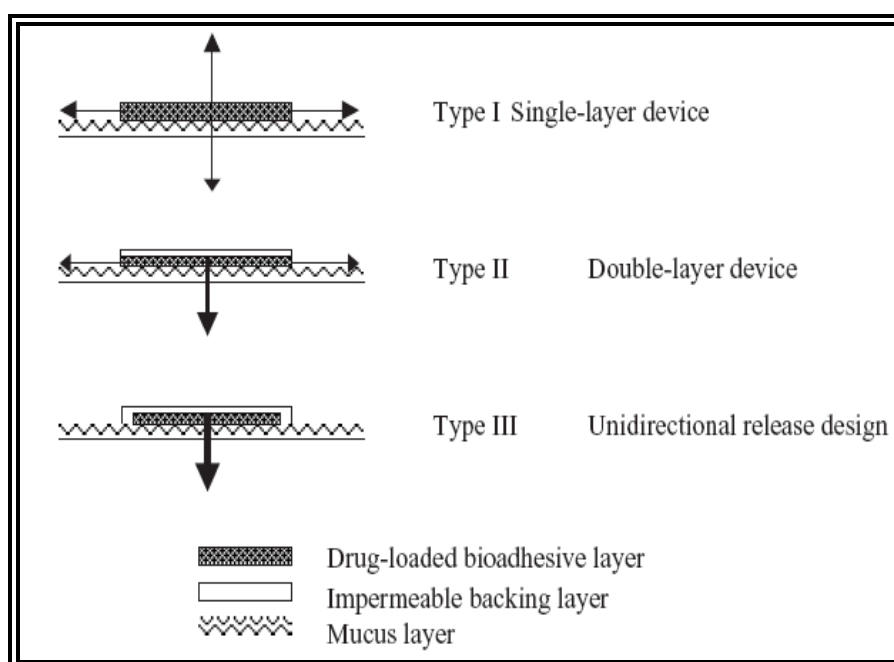


Figure 2:- Schematic representations of types of buccal mucoadhesive dosage forms.

Pharmaceutical Aspects

Solubility Modifiers

Despite the increased bioavailability of hepatically metabolized drugs by buccal delivery, poor solubility of drug in saliva may impede drug release from its device for uptake by buccal mucosa. Solubilization of a poorly water-soluble drug by complexing with cyclodextrin and delivering via the buccal mucosa is advantageous in increasing drug absorption and bioavailability. Buccal tablets of danazol-sulfobutylether 7b-cyclodextrin complex were prepared using different polymers and were evaluated for bioadhesion, *in vitro* release, and bioavailability in female beagle dogs.^[43]

The buccal-administered danazol-sulfobutylether b-cyclodextrin complex and the danazol sulfobutylether b-cyclodextrin poly-carbophil tablets had absolute bioavailabilities of 64% and 25%, respectively, which are significantly greater than 1.8% observed for the commercial formulation Danocrine. The increased bioavailability was attributed to the enhanced solubility due to complexation and the avoidance of extensive hepatic metabolism upon buccal administration. Imidazole antimycotics (e.g., miconazole, econazole, and clotrimazole) are extensively used in the local treatment of fungal infections in the oral cavity. Due to their low water solubility and high lipophilicity, they were released

extremely slowly from the lipophilic chewing gum base. Formulating hydroxypropyl- β -cyclodextrin inclusion complex of these antimycotics into chewing gums was found to increase the drug release from the chewing gums.^[44]

Penetration Enhancers

Buccal penetration enhancers are capable of decreasing penetration barrier of the buccal mucosa by increasing cell membrane fluidity, extracting the structural intercellular and/or intracellular lipids, altering cellular proteins, or altering mucus structure and rheology.^[45]

Penetration enhancement may be only drug specific at a certain application site. This is particular to the buccal membrane since it is non keratinized and the intercellular lipids are less structured compared to the skin stratum corneum. The buccal mucosa is multilayered without tight junctions and effective penetration enhancers for transdermal and/or intestinal drug delivery may not have similar effects on buccal drug delivery. Currently, the most commonly investigated penetration enhancers include bile salts, fatty acids, and sodium lauryl sulfate. It is well known that bile salts play an important role as physiological surfactants in the absorption of lipids and lipid- soluble vitamins. Bile salts have been extensively employed to enhance the absorption of drugs through various epithelia including buccal membranes.^[46-47] These compounds are believed to act by extraction of membrane protein or lipids, membrane fluidization, and reverse micellization in the membrane. They also have inhibitory effects on mucosal membrane peptidases.^[45]

It is generally considered that buccal mucosal damage caused by bile salts would be reversible and less serious due to the nature of buccal mucosa, but long-term safety studies have not been documented. Purified oleic acid was reported to modify the barrier property of buccal mucosa, and thus led to remarkable and continuous hypoglycemia effect after buccal delivery of insulin from Pluronic gel48. Cod-liver oil extract, which is a mixture of 16 types of unsaturated and saturated acids, showed enhancement effect on ergotamine tartrate through buccal mucosa of guinea pigs.^[49]

The promoting action presented a synergistic mode of its various components. Sodium lauryl sulfate has been reported to increase the buccal delivery of several drugs when included in various dosage forms. However, sodium lauryl sulfate was reported to cause marked irritation to the buccal epithelium. Chitosan exhibits several favorable properties such as biodegradability, biocompatibility, bioadhesion and antifungal/antimicrobial properties and attracts considerable interest in buccal delivery of antimicrobial agents.^[45-50]

Chitosan was also observed to have a significant enhancing effect on permeation of drugs across the buccal mucosa. Two compounds, hydrocortisone and

transforming growth factor beta, were formulated in gel forms and applied on the surface of porcine buccal mucosa *in vitro*.^[51]

Fluxes of both compounds were increased, and higher concentration of hydrocortisone was observed in the upper epithelial layer for chitosan gels compared to those for phosphate buffer solutions. There was less penetration of hydrocortisone into the deeper tissue layers, whereas the hydrophilic peptide appeared in the deeper layer. This effect may be related to both the direct fluidizing effect on the organized intercellular lipid lamellae and bioadhesive nature of chitosan. Glyceryl monooleate is a polar and sparingly water-soluble lipid and can form lyotropic liquid crystalline phases in the presence of water. Its cubic and lamellar liquid crystalline phases have bioadhesive properties, and the cubic phase also shows protective action against enzymatic degradation of peptide drugs and improved chemical stability of compounds containing amide groups.^[51]

Buccal permeation of [D-Ala², D-Leu⁵] enkephalin is enhanced by a co transport mechanism of lipid and peptide. It is a promising drug carrier for the buccal delivery of peptide drugs as well as a penetration enhancer. Irritation and toxicity are always concerns with penetration enhancers, although the oral mucosa is more resistant to damage than other mucosal membranes.

To date, the information available on buccal absorption enhancement is much less than that for transdermal enhancement. The relationships among structure, irritation, and enhancement effect of the enhancer have not been clearly elucidated. Very few penetration enhancers are available for buccal delivery systems, and penetration enhancers are not used in marketed buccal delivery systems owing to the lack of a satisfactory profile with respect to irritation and effectiveness. Current research is focused on developing a penetration enhancer^[45]. Specifically for buccal drug delivery but without membrane toxicity. Developments in polymer science and nanotechnology might provide the potential to design a novel nontraditional penetration enhancer with transient, localized actions and minimal, recoverable disruption to buccal membrane.^[51]

Bioadhesives

The buccal regions are very suitable for a bioadhesive system because of a smooth, relatively immobile surface and accessibility. The major advantages of bioadhesive systems are the increased residence time of drug device in the oral cavity and localization of drugs in a particular region. The bioadhesion process has been explained by electronic, adsorption, wetting, diffusion, and fracture theories.^[52]

The interaction between the mucus and bioadhesive polymers is a result of physical entanglement and secondary bonding, mainly hydrogen bonding and van

der Waals attractions. These forces are related to the chemical structure of the polymers. The functional groups available on the surface of polymer conformation favoring bioadhesion include hydroxyls, carboxyls, amines, and amides. The bioadhesive polymer must have a critical molecular weight and an adequate length to allow chain interpenetration^[52].

Anionic polymers are usually preferred due to negatively charged mucin at physiological pH. Physical properties such as the rate of hydration and rheological properties of the polymeric formulations have a major impact on their bioadhesion and consequently, their eventual duration of retention.^[53]

Adhesion occurs shortly after the beginning of hydration and swelling, but the bonds formed are not very strong. Excessive hydration may result in formation of slippery, non adhesive mucilage, thus decreasing adhesive strength or even loss of adhesion. This is also probably a result of dilution of functional groups available for adhesive interactions at the interface between the bioadhesive systems and the mucus. Adhesive strength is maximal at a certain degree of hydration. Polymers with bioadhesive properties include biopolymers (e.g., chitosan and sodium alginate) and synthetic polymers (e.g., cellulose derivatives, polyacrylic polymers, polyvinylpyrrolidone, and polyvinyl alcohol). The above-mentioned nonspecific bioadhesives can be considered as first-generation bioadhesives. The duration of bioadhesion is largely determined by the fast turnover of mucus layer. Factors such as saliva secretion, food intake, local pH, and compositions of delivery systems also strongly affect bioadhesion. Lectins are proteins/glycoproteins that possess high specific affinity for carbohydrates. Recently, lectin based second-generation bioadhesives have attracted considerable interest for oral drug delivery.^[54]

The specific bioadhesion is also termed cytoadhesion and is a highly specific interaction between adhesives and cell surfaces comparable to a receptor-ligand or ligand-antigen interaction. Unfortunately, reports of specific bioadhesion in buccal delivery are very limited. It was observed that lectin binding on human buccal cells occurred within 20 s and appeared not to be detached by saliva flushing.^[55]

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