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REVIEW

Buccal Delivery Systems

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ABSTRACT

The oral cavity is an attractive site for drug delivery due to ease of administration and avoidance of possible drug degradation in gastrointestinal tract and first-pass metabolism. Buccal drug delivery specifically refers to the delivery of drugs within/through buccal mucosa to affect local/systemic pharmacological actions. This review briefly describes advantages and limitations of buccal drug delivery, anatomical structure of oral mucosa, and methodology in evaluating buccal drug delivery system, focusing on physiology, pharmacology, pathology, and formulation design in line with recent developments in buccal delivery systems.

Key Words: Buccal delivery; Bioadhesion; Penetration enhancer; Enzyme inhibitor; Formulation design.

INTRODUCTION

The oral cavity is an attractive site for drug delivery due to ease of administration and avoidance of possible drug degradation in the gastrointestinal tract and first-pass metabolism. There are four potential regions for drug delivery in the oral cavity, namely buccal, sublingual, palatal, and gingival. Buccal drug delivery specifically refers to the delivery of drugs within/through the buccal mucosa to affect local/systemic pharmacological actions. Buccal-delivered drugs may be used for treatment of diseases in the oral cavity or for systemic use.[1] However, inherent limitations, including short residence time, small absorption area, and barrier property of the buccal mucosa, are challenges to buccal drug delivery.

Oral mucosal and bioadhesive drug delivery systems have been well documented.[1,2] This article will briefly describe advantages and limitations of buccal drug delivery, anatomical structure of oral mucosa, and methodology in evaluating buccal drug delivery systems, focusing on physiology, methodology, and formulation design in line with recent developments in buccal delivery systems.

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ANATOMY AND BIOCHEMISTRY OF ORAL MUCOSA

Oral mucosa is lined with an epithelium supported by a connective tissue termed lamina propria and separated from the epithelium by a basal membrane. The epithelium of oral mucosa is stratified with regional variation in terms of structure and function.[1] Three types of oral mucosa are referred to as masticatory, lining, and specialized mucosa. The epithelium of masticatory mucosa in gingival and hard palate regions is keratinized and further subdivided into four layers, namely, keratinized, granular, prickle-cell, and basal layers. The nonkeratinized epithelium of lining mucosa covers the remaining regions, except the dorsal surface of the tongue and is made up of superficial, intermediate, prickle-cell, and basal layers. Specialized mucosa in the dorsum of the tongue consists of both keratinized and nonkeratinized mucosa. The physiological structure of buccal mucosa is illustrated in Fig. 1. Small vessels and capillaries that open to the internal jugular vein distribute within the lamina propria, thus avoiding the hepatic first-pass clearance of buccal-delivered drugs. Blood flow in the oral mucosa is generally faster and richer than that in the skin.[1,3] The nonkeratinized buccal mucosa was reported to have approximately a thickness of 500–600 μm and surface area of 50.2 cm^2.[1]

Membrane-coating granules are small lipid organelles in the prickle-cell layer.[1] The intercellular lipids discharged from membrane-coating granules are responsible for the epithelial cohesion and formation of the superficial permeability barrier in the epithelium.[3] This main penetration barrier exists in the outermost quarter to one-third of the epithelium. The keratinized epithelia contain more neutral lipids that are associated with the barrier function, while nonkeratinized epithelia contain more polar lipids.[4] The loosely packed intercellular lipids and the presence of large amounts of phospholipids in nonkeratinized, even in keratinized mucosa, account for the overall higher permeability of the oral mucosa than that of the skin stratum corneum.[5] The nonkeratinized mucosa is more permeable than the keratinized mucosa, forming the major administration site in the oral cavity. The oral mucosal membranes do not have tight junctions as seen in intestinal membranes.[1]

The secretion of saliva from salivary glands features regional, individual, and time variations.[1] The buccal region contains minor salivary glands. The mucus layer covers the oral mucosal surface and serves to lubricate and protect as well as to act as a wetting agent. Mucin is a group of glycoproteins composed of oligosaccharide side chains attached to a protein core. Three-quarters of the protein core are heavily glycosylated and impart a gel-like characteristic to mucus. The remaining nonglycosylated groups are involved in cross-linking via disulfide bonds among mucin molecules.[4] Mucus is negatively charged at physiological saliva pH of 5.8–7.4 because of the presence of sialic acids ($pKa = 2.6$) and ester sulfates at the terminals of some pendant oligosaccharide side chains.[4]

GENERAL CONSIDERATIONS IN FORMULATION DESIGN

Physiological Aspects

The buccal mucosa has a very limited area for application of the buccal delivery system, thus limiting device size and drug load. The actual area for drug absorption depends on the size of the dosage form. Generally, a device with the size of 1–3 cm^2 and a daily dose of 25 mg or less would be preferred for buccal delivery.[4,6] The maximal duration of buccal drug delivery is approximately 4–6 h, as meal

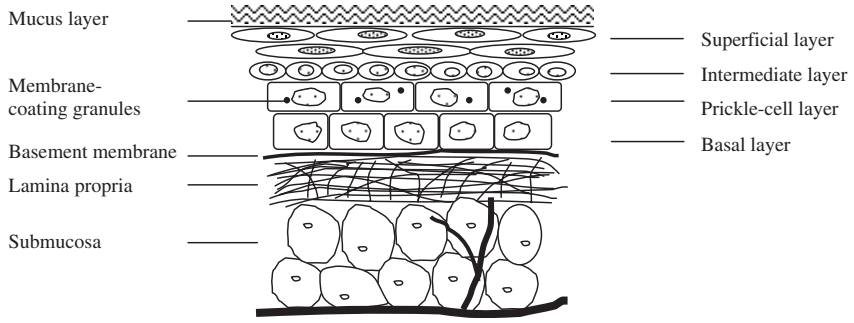

Figure 1. Schematic representation of physiological structure of buccal layer.

intake and/or drinking may require the removal of the delivery device.[6] Faster turnover of buccal mucosal epithelium (3–8 days) relative to the skin (about 30 days) may affect drug absorption by continually changing permeability characteristics.[3]

The epithelial layer is not uniformly hydrophobic and has two possible drug penetration routes, the transcellular route and the paracellular route (Fig. 2). The lipophilic drugs penetrate mainly through the more lipophilic transcellular route, while the less lipophilic paracellular route, characterized by loosely packed polar intercellular lipids, is the principle route for hydrophilic drugs.[1] Both routes coexist for all drugs, but the route with the least penetration resistance is usually preferred over the other, depending on the physicochemical properties of the drugs. However, smaller paracellular route area limits the penetration of hydrophilic drugs, whereas lipophilic drugs usually have high penetration rates through transcellular routes. This indicates that chemical modification of drug lipophilicity may increase drug penetration through buccal mucosa via the transcellular route. The permeability of ionizable drugs across buccal mucosa follows the pH-partitioning theory characteristic of passive diffusion.[3] Increasing nonionized fraction of ionizable drugs could favor drug penetration through the transcellular route. Control of pH is critical for successful buccal delivery of ionizable drugs. Lidocaine is a weak, basic drug with a pKa value of 7.9. The decrease in dissolution pH increased the ionic fraction of the drug and thus its apparent solubility, but decreased its permeability through buccal mucosa.[7] This accounted for the insignificant relationship between the penetration rate through buccal mucosa and release rate of the drug from film into artificial saliva but significant relationship between the penetration rate and the release rate of nonionized drug. Nicotine is a diacidic base with pKa values of approximate 3 and 8. Nonionized nicotine permeated mainly via the transcellular pathway while the mono- and di-protonized molecules permeated via the paracellular pathway.[8] Variation in saliva pH influenced the serum levels of nicotine after administration of nicotine chewing gum.[9]

The secretion of saliva is affected by disease and various stimuli.[1] An acidic excipient can stimulate the secretion of saliva, which is an important consideration in selecting formulation excipients. Saliva has a weak buffering capacity to maintain pH value within local regions. Saliva contains no proteases but moderate levels of esterases, carbohydrases, and phophatases,[5] which may degrade certain drugs. Although saliva secretion facilitates the dissolution of drug, involuntary swallowing of saliva can result in drug loss from the site of absorption. Also, the nonuniform distribution of drugs within saliva on release from delivery systems implies that some areas of the oral cavity might not receive therapeutic levels of drugs,[10] which is thus an important concern in the development of a locally administered buccal drug delivery system. The mucus layer with the thickness in the range from 1 to 400 μm forms a physical barrier to drug permeation through buccal mucosa[3] but can be advantageous for bioadhesive preparations. Short turnover time of mucus layer is detrimental to achieve long-term bioadhesion and sustained drug release.[11] Drugs can interact with mucin through electrostatic attractions (e.g., tetracycline), hydrogen bonding (e.g., urea), or hydrophobic interaction (e.g., testosterone) and prevent their transport through the epithelia.[11]

Pathological Aspects

Diseases can make the epithelium thicker (hyperplastic) or thinner (atrophic) than normal or even lost (ulcerated). These alter the barrier property of the mucosa[1] and thus increase the permeability of the mucosa, which will tend to facilitate local delivery of drugs for treatment of mucosal diseases. However, this complicates the application of bioadhesive delivery devices for retention and controlled release of drugs. The marked changes at the mucosal surface may include increased desquamation or sloughing, a

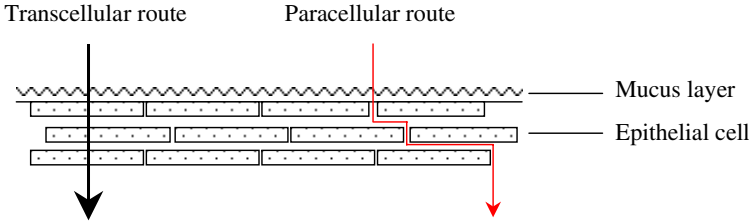

Figure 2. Schematic representation of penetration routes in buccal drug delivery.

factor which is detrimental to maintaining bioadhesion.[1] Diseases are also likely to influence the mucus secretion and properties,[11] thus affecting the drug transport and bioadhesive properties. Cancer patients often develop oral candidosis and a substantial decrease in salivary flow after irradiation treatment. The bioadhesive buccal tablet containing miconazole has been shown to be effective in treatment of infections, but its efficacy was substantially influenced by low saliva secretion.[12] It is important to understand the nature of mucus under relevant disease conditions before designing effective buccal delivery systems when the mucus layer affects the drug transport to the mucosal surface.

Pharmacological Aspects

The intended application and target site of drug affect the selection of dosage form. For treatment of oral disease, the residence time and local concentration of the drug in the mucosa are important considerations. For a systemic effect, the amount of drug transported across the mucosa into the circulatory system is a determinant of dosage forms. A diagnostic agent can be delivered to assist the diagnosis of oral mucosal cancer. 5-Aminolevulinic acid and its esters in the form of rinse have been used in photodynamic diagnosis and photodynamic therapy.[13] L-Cysteine was slowly released from buccal tablets for removing carcinogenic acetaldehyde, the first metabolite of ethanol, from saliva and thus prevented it from interacting with cellular proteins.[14] Despite the type of dosage forms, the drug must be released from the dosage form and taken up by the oral mucosa, which can be optimized by a suitable formulation design.

Despite the possible gastrointestinal and hepatic degradation, buccal delivery confers many advantages for delivering peptide/protein and other drugs that encounter degradation after oral administration.[15] Several peptides, including thyrotropin-releasing hormone, insulin, octreotide, leuprolide, and oxytocin have been delivered via the buccal route.[3] However, the relative bioavailabilities of these peptides by the buccal route were still low (0.1–5.0%) due to the inherent permeation barrier and enzymatic barrier of buccal mucosa,[15] and incorporation of penetration enhancers and/or enzyme inhibitors was needed. In contrast, rapid and extensive absorption of small lipophilic drugs (e.g., buprenorphine, testosterone, atipamezole, fentanyl, butophanol, melatonin, and nifedipine) through the well-vascularized buccal mucosa is possible, and the relative bioavailabilities of these drugs were relatively high.[15] Besides the physicochemical parameters such as solubility, permeability, and stability of drugs, organoleptic properties of drug or delivery device are important considerations for buccal administration. A bad tasting drug or rough textured device will result in poor patient compliance or acceptance. Drugs with the potential of changing the physiological condition of the oral cavity may not be suitable for buccal delivery.

Pharmaceutical Aspects

Factors influencing drug release and penetration within/through buccal mucosa will affect the therapeutic efficacy and should be considered in the formulation design. As the dosage form is to be resident in a highly developed taste-sensing organ, careful considerations for organoleptic factors are needed. Excipients enhancing palatial properties are often required to improve acceptability of dosage form or masking less desirable properties of the bioactive constituent. Some additives can be incorporated to improve drug release pattern and absorption.

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.[3] Penetration enhancement may be only drug specific at a certain application site. This is particular to the buccal membrane since it is nonkeratinized 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.[16,17] These compounds are believed to act by extraction

of membrane protein or lipids, membrane fluidization, and reverse micellization in the membrane.[3] They also have inhibitory effects on mucosal membrane peptidases.[3] 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,[3] 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 gel.[18] 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.[19] 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.[3,6,20] However, sodium lauryl sulfate was reported to cause marked irritation to the buccal epithelium.[3]

Chitosan exhibits several favorable properties such as biodegradability, biocompatibility, bioadhesion, and antifungal/antimicrobial properties, and attracts considerable interest in buccal delivery of antimicrobial agents.[21] Chitosan was also observed to have a significant enhancing effect on permeation of drugs across the buccal mucosa.[22] Two compounds, hydrocortisone and transforming growth factor beta, were formulated in gel forms and applied on the surface of porcine buccal mucosa in vitro.[22] 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.

Glycryl 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.[23] Buccal permeation of [D-Ala^2, D-Leu^5]enkephalin is enhanced by a cotransport 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.[3,4] 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,[3,5] 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 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.[5]

Enzyme Inhibitors

Among mucosal routes, the buccal mucosa has relatively low enzymatic activity, and drug inactivation is neither rapid nor extensive.[6] However, enzymes in saliva and buccal mucosa can still degrade drugs, particularly peptide/protein drugs. Several proteolytic enzymes were found in buccal epithelium.[3] Coadministration of enzyme inhibitors increases protein drug absorption. Enzyme inhibitors such as aprotinin, bestatin, puromycin, and bile salts stabilize protein drugs by affecting activity of proteolytic enzymes, altering the conformation of the peptide drug or forming micelles, and/or rendering the drug less accessible to enzymatic degradation.[3,6] Unfortunately, the relevant contribution of cytosolic, membrane-bound, and intercellular peptidase activities to degradation of buccal delivered peptide drugs remains uncertain and inconsistent. The peptidase activity of the cytosol and membrane cannot be distinguished using commonly used tissue homogenate technique.[3] Particularly, as peptide/protein drugs are transported through the paracellular route, the cytosolic peptidases may be inaccessible for the drugs during their permeation. Peptidase activity on the surface of the porcine buccal mucosa was investigated.[24] Aminopeptidases appeared to represent a major metabolic barrier to the buccal delivery of peptide drugs, and the absence of endopeptidase and carboxypeptidase is advantageous for the buccal delivery of peptide drugs. Esterase activity is

important with respect to buccal delivery of ester drugs or prodrugs.[25]

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.[2] 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.[2] 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.[26] 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, nonadhesive 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.[11] 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.[27] 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.[2] 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.[28] Studies with a radiolabeled technique indicated existence of significant lectin binding to buccal cells.[29] The limited observations are already encouraging further investigatious of specific bioadhesion for buccal delivery. It seems possible to enhance drug delivery by anchoring the delivery device to the buccal epithelial cell with lectin-based specific bioadhesives.

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 7β-cyclodextrin complex were prepared using different polymers and were evaluated for bioadhesion, in vitro release, and bioavailability in female beagle dogs.[30] The buccal-administered danazol-sulfobutylether 7β-cyclodextrin complex and the danazol-sulfobutylether 7β-cyclodextrin polycarbophil tablets had absolute bioavailabilities of 64% and 25%, respectively, which are significantly greater than 1.8% observed for the commerical 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 chlotrimazole) 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.[31]

DOSAGE FORMS FOR BUCCAL DRUG DELIVERY

Dosage forms such as mouthwashes, erodible/chewable buccal tablets, and chewing gums allow only a short period of release, and reproducibility of drug absorption is poor. Application of bioadhesive semisolid gels creates considerable technical problems. Bioadhesive buccal films/patches and tablets are the less developed type of dosage forms. These bioadhesive buccal films/patches and tablets were usually fabricated in different geometry, as shown in Fig. 3. Type I is a single-layer device, from which drug can be released multidirectionally. Type II device has a impermeable backing layer on top of the drug-loaded bioadhesive layer, and drug loss into oral cavity can be greatly decreased. Type III is a unidirectional release device, from which drug loss will be avoided and drug can penetrate only via the buccal mucosa.

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 diseases in the oral cavity and in nicotine replacement therapy. Some commercial products are available in the market. Caffeine chewing gum, Stay Alert®, was developed recently for alleviation of sleepiness.[32] 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.[8] However, chewing gum slowly generates a steady plasma level of nicotine rather than a sharp peak as experienced when smoking. Possible swallowing of considerable 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.[8]

Hydrogel-based bioadhesive tablets can adhere to the buccal mucosa, and the drug is released upon hydration of the device, forming a hydrogel. The device should be fabricated so that the swelling rate of bioadhesive polymer is optimized to ensure a prolonged period of bioadhesion as well as a controlled or sustained drug release. Single-layer buccal tablets of testosterone have a low bioavailability due to the lack of an impermeable backing layer on the tablet, causing a significant amount of the total dose to be swallowed.[33] Tablets of triamcinolone acetonide (Aftach®), developed for local treatment of aphthous ulcers, consist of a bioadhesive hydroxypropyl cellulose/polyacrylic acid layer and a lactose nonadhesive backing layer.[34] Nifedipine/propranolol hydrochloride double-layer tablets for systemic delivery with prolonged drug release and adequate adhesiveness were developed.[35] Nicotine replacement therapy requires a fast release of nicotine followed by a prolonged release of nicotine for maximal efficacy. A bilayer buccal adhesive nicotine tablet provided a drug release pattern combining fast release and prolonged release profiles and resulted in

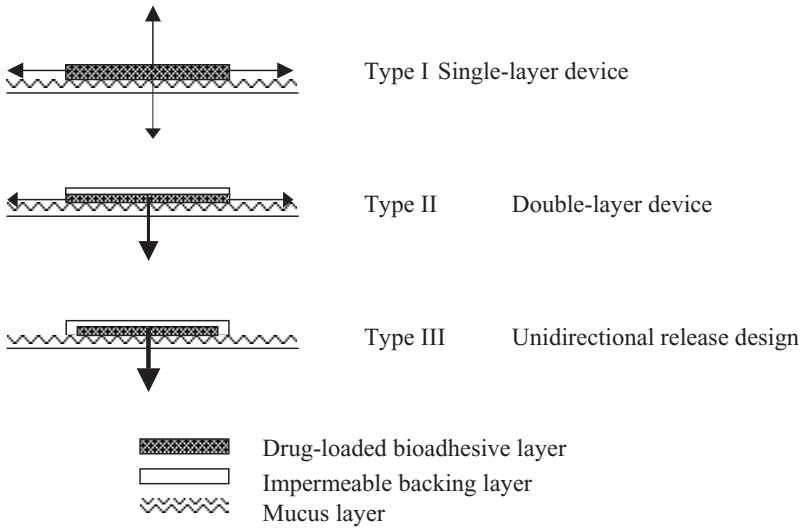

Figure 3. Schematic representation of buccal dosage form design.

improved smoking cessation rates.[36] A problem associated with the double-layer tablet was separation of the two layers. This may be overcome by modifying the device so that there is a gradient in hydrophilicity from one side to the other.[37]

Bioadhesive tablets are usually prepared by direct compression. Drugs can also first be formulated in certain forms (e.g., microspheres) for achieving some desirable properties before direct compression to produce tablets. Chitosan was considered as a promising drug carrier for the buccal delivery of antimicrobial agents owing to its bioadhesive and antimicrobial properties as well as penetration enhancing effect.[21,22] Chlorhexidine-chitosan microsphere-based buccal tablets have shown enhanced antimicrobial activity and prolonged drug release in the oral cavity.[38] Recent invention can overcome the problem associated with application of semisolid dosage forms onto buccal mucosa. The bioadhesive tablet system of cationic ergotamine tartrate for treatment of migraine consisted of a reservoir of drug suspended in semisolid pharmaceutical bases in the central cavity and an adhesive region around the drug reservoir.[19] This buccal delivery device has shown better drug absorption than homogenous polyvinyl alcohol hydrogel and oral capsules. Nevertheless, the disadvantage of bioadhesive tablets is lack of physical flexibility and poor patient compliance for long-term and repeated use.

Flexible adhesive films and laminated patches are used as buccal delivery systems. These require (a) a bioadhesive to facilitate intimate contact with the mucosa and increase residence time, (b) a vehicle that releases the drug at an appropriate rate, and (c) additives such as penetration enhancers and/or enzyme inhibitors. An adhesive hydroxypropyl cellulose film containing lidocaine was studied for dental analgesia.[7] Bioadhesive chitosan film of chlorhexidine gluconate showed characteristics of increased residence time of drug and prolonged antimicrobial action.[39] A novel bilayer bioadhesive film of testosterone is composed of a pH-sensitive bioadhesive layer containing polycarbophil/Eudragit S-100 and a pharmaceutical wax as the impermeable backing layer.[15] The adhesion time of these films to rabbit buccal pouch was affected by the ratio of these two polymers. The presence of the wax-backing layer greatly enhanced the adhesion time of the bioadhesive layer and bioavailability by retarding the diffusion of saliva into the drug layer and drug loss into mouth. These bilayer bioadhesive buccal patches containing plasmid DNA were also explored for mucosal immunization in rabbits.[40] The antigenspecific IgG titer with buccal films is comparable to that of subcutaneous protein injection, indicating that buccal immunization with these films is feasible.

Bioadhesive films/patches are commonly manufactured by solvent casting methods using adhesive coating machines, which involve dissolving a drug in a casting solution, casting film, and drying and laminating with a backing layer or a release liner. The processing technology is quite similar to pressure-sensitive adhesive-based patch manufacturing. Very recently, a hot-melt extrusion method was reported to fabricate hot-melt extruded films for buccal delivery, which overcomes the disadvantages associated with a solvent casting method such as environmental concerns, long processing times, and high costs.[41]

METHODOLOGY IN EVALUATION OF BUCCAL DELIVERY SYSTEMS

Drug Release from Dosage Forms

Drug release tests are currently carried out according to the official pharmacopoeias. They require a large volume of dissolution medium and are operated under sink or pseudo-sink conditions. However, the initial fast release of some buccal dosage forms cannot be measured with the existing methods. These methods do not simulate the conditions prevailing for buccal administration where low liquid environment exists and a nonsink condition is more appropriate for a poorly permeable drug. Furthermore, new phenomena may be encountered in small liquid volumes, which would not be seen in in vitro dissolution tests with a large amount of liquid. Hence, in vitro dissolution tests for buccal delivery systems should be performed in small volumes of dissolution medium. A new method capable of determining the release of drugs from tablets in low liquid surroundings was recently reported.[42] This method is based on the measurement of the alternating ionic current through a cell containing the dissolution medium and the substance to be dissolved. The tablets studied should not contain salt or any other conducting substances, and the measurements are performed in a salty solution of known composition. When a tablet is introduced into the salty solution and absorption of liquid occurs, the decrease in the number of charge in the liquid surrounding is recorded and correlated to the absorbed liquid volume. Similarly, provided the drug is charged, its release increases the number of ions in the liquid surrounding

the tablet, and hence the measured current. It was found that the liquid absorption time depended on the initial liquid volume while liquid absorption and drug release were well separated in time as significant release occurred after the absorption had ended. This method provided reliable data with good time resolution, especially for a short time period.

Continuous mastication is needed for drug release from medicated chewing gum since the insoluble gum matrix acts as a solid phase barrier during the whole chew-out process. No standard method is available for quantification of drug release from chewing gum. Chew-out studies have been carried out, in which volunteers chew a gum for a period of time and the release is represented by the drug amount remaining in the gum. This method is obviously very difficult to standardize. An apparatus for in vitro drug release testing of medicated chewing gums was described and reported to provide mastication action on chewing gum as well as an adequate agitation of release medium.[43]

In Vitro and In Vivo Studies

Similar to an in vitro permeation study in transdermal drug delivery, different types of diffusion cells with certain modifications are suitable to conduct permeation studies, except that the buccal mucosa dissected from model animals are used as diffusion barriers for buccal delivery. Despite the careful endeavor in tissue preparation to maintain viability and integrity of oral mucosa, the loss of mucus layer on the surface of the oral mucosal membrane is unavoidable since the mucus network is extremely sensitive to environmental changes.[11] It is very difficult to design meaningful, well-controlled, reproducible experiments to exactly mimic drug delivery through the mucus layer and underlying mucosa in vivo. A TR146 cell culture has been proposed as a model of human buccal epithelia in terms of physical permeation and biochemical barriers.[8,25] In vivo studies are conducted in model animals. Buccal mucosa of rabbit is routinely used besides dog, pig, and monkey due to its similarity to human buccal mucosa in terms of keratinization.

Toxicity and Irritation Studies

Evaluation of toxicity and irritation should be concerned with mucosal tissue irritation, extent of damage to mucosal cells, and their rate of recovery. Irritation is very subjective and is usually rated by the trained examiner. Membrane damage to the mucosal cells can be examined histologically. The rate of recovery is generally inversely related to the extent of membrane damage. Due to the buccal mucosa's ability for rapid recovery, the toxicological issue with respect to penetration enhancers may not be as significant as with other mucosal membranes.[3]

Bioadhesion Measurement

Methods available for measuring bioadhesion are limited, and method selection depends on applicability, reproducibility, and useful information provided. It is unnecessary to compare the absolute values obtained from different methods and is more meaningful to examine the relative bioadhesive performance using each technique. In addition, some factors, including saliva secretion, mastication, and mucus turnover that can markedly affect the adhesion strength and duration of adhesion in vivo are not present in in vitro testing.

Duration of Bioadhesion

The duration of bioadhesion in vivo can be measured by using gamma scintigraphy,[44] electron paramagnetic resonance,[45] or transit studies with fluorescent-coupled dosage forms.[46] The measurement of residence time of adhesive at the application site provides quantitative information on in situ/in vivo bioadhesive properties.

Rheological Measurement

Bioadhesion, an interaction between polymer used and mucin, can be indirectly inferred by changes in viscosity and other rheological properties. These measurements give certain information on the behavior of the polymer chain structures, particularly in terms of the rigidity, elasticity, and deformability of the systems. These indirectly indicate the desirable properties of the bioadhesives such as strong hydrogen bonding groups, strong anionic charges, high molecular weight, sufficient chain flexibility, and surface energy properties favoring spreading. The testing conditions need to be carefully controlled for good reproducibility. However, these methods cannot give direct information about what actually occurs at the interface[2] but provide greater predictability

in screening potential bioadhesive polymers when formulating buccal delivery systems.

Tensile Test

The tensile test is based on the measurement of detachment force of the polymer layer from the mucus substrate. Detachment force and adhesion work are indicative of bioadhesion strength. The testing conditions are rather critical, and operation variables should be optimized and well-controlled in order to obtain reliable and reproducible results. Such tests cannot easily distinguish between bioadhesive and cohesive forces.

Other Methods

A direct-staining method was established to evaluate the bioadhesion of polymeric aqueous dispersion on buccal cells both in vitro and in vivo by employing Alcian blue to bind to anionic polymers and Eosin to bind to the amine groups in polymers.[47] Unbound dye was removed by washing with 0.25 M sucrose. The extent of polymer adhesion was quantified by measuring the relative staining intensity of control and polymer-treated cells by image analysis. This method is only suitable for assessing the liquid dosage forms, which are widely employed to enhance oral hygiene and to treat local disease conditions of the mouth such as oral candidiasis and dental caries.

A lectin-binding inhibition technique involving an avidin–biotin complex and a colormetric detection system was developed to investigate the binding of bioadhesive polymers to buccal epithelial cells without having to alter their physicochemical properties by the addition of ''marker'' entities.[48] The lectin from *Canavalia ensiformis* (Concanavalin A) has been shown to bind to sugar groups present on the surface of buccal cells.[49] Therefore, if polymers bind to buccal cells, they would mask the surface glycoconjugates, thus reducing or inhibiting *Canavalia ensiformis* lectin binding.

Atomic force microscopy was used to determine the bioadhesion of polymer onto the buccal cell surfaces.[50] Changes in surface topography were indicative of the presence of polymer bound onto buccal cell surfaces. Unbound cells showed relatively smooth surface characteristics with many small craterlike pits and indentations spread over cell surfaces, while polymer-bound cells lost the crater and indentation characteristics and gained a higher surface roughness.

FUTURE PERSPECTIVES

Nonspecific bioadhesive dosage forms have been extensively accepted in buccal delivery, but the intrinsic rapid turnover of mucus layer and sensitivity to environmental factors limit retention of bioadhesion. The increasing interest in lectin-based specific bioadhesion provides an opportunity for developing cytoadhesive dosage forms.

The delivery of peptide/protein drugs to the human body via the nonparenteral route still remains a big challenge. Buccal delivery is a promising alternative. The inherent complexity of the oral cavity dictates the difficulties in developing an appropriate dosage form for buccal delivery. Difficulties in accurate evaluation of buccal delivery dosage forms also limit its development. Advances in experimental methodology and computational methodology will be helpful to shorten the processing time from formulation design to clinical use.

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