

Buccal Mucosa As A Route For Systemic Drug Delivery: A Review

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ABSTRACT: Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable. It is the objective of this article to review buccal drug delivery by discussing the structure and environment of the oral mucosa and the experimental methods used in assessing buccal drug permeation/absorption. Buccal dosage forms will also be reviewed with an emphasis on bioadhesive polymeric based delivery systems.

I. INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, peroral 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 mucosae are

considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral 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.

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 LHRH (8, 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 (13-15), and the virtual lack of Langerhans cells (16) makes the oral mucosa tolerant to potential allergens. Furthermore, oral transmucosal drug delivery bypasses first pass effect and avoids pre-systemic elimination in the GI tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery.

Within the oral mucosal cavity, delivery of drugs is classified into three categories: (i) sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth, (ii) buccal delivery, which is drug administration through

the mucosal membranes lining the cheeks (buccal mucosa), and (iii) local delivery, which is drug delivery into the oral cavity.

II. OVERVIEW OF THE ORAL MUCOSA

A. 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. 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 (17). 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.

The turnover time for the buccal epithelium has been estimated at 5-6 days (18), 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 mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized (18). 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).

B. Permeability

The oral mucosae in general is a 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 (18). This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

It is 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 submucosal 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 (24). 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.

C. Environment

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some maybe attached to certain regions on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another (26). Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems (27). In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized mucus secreting cells like the goblet cells, however in the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva (26, 28). Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands (26, 28). At physiological pH the mucus network carries a negative charge (due to the sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer (17).

Another feature of the environment of the oral cavity is the presence of saliva produced by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals. It allows for the continuous mineralisation of the tooth enamel after eruption and helps in remineralisation of the enamel in the early stages of dental caries (29). Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus, and the degree of stimulation (26, 28). The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the pH. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

III. BUCCAL ROUTES OF DRUG ABSORPTION

There are two permeation pathways for passive drug transport across the oral mucosa: paracellular and transcellular routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.

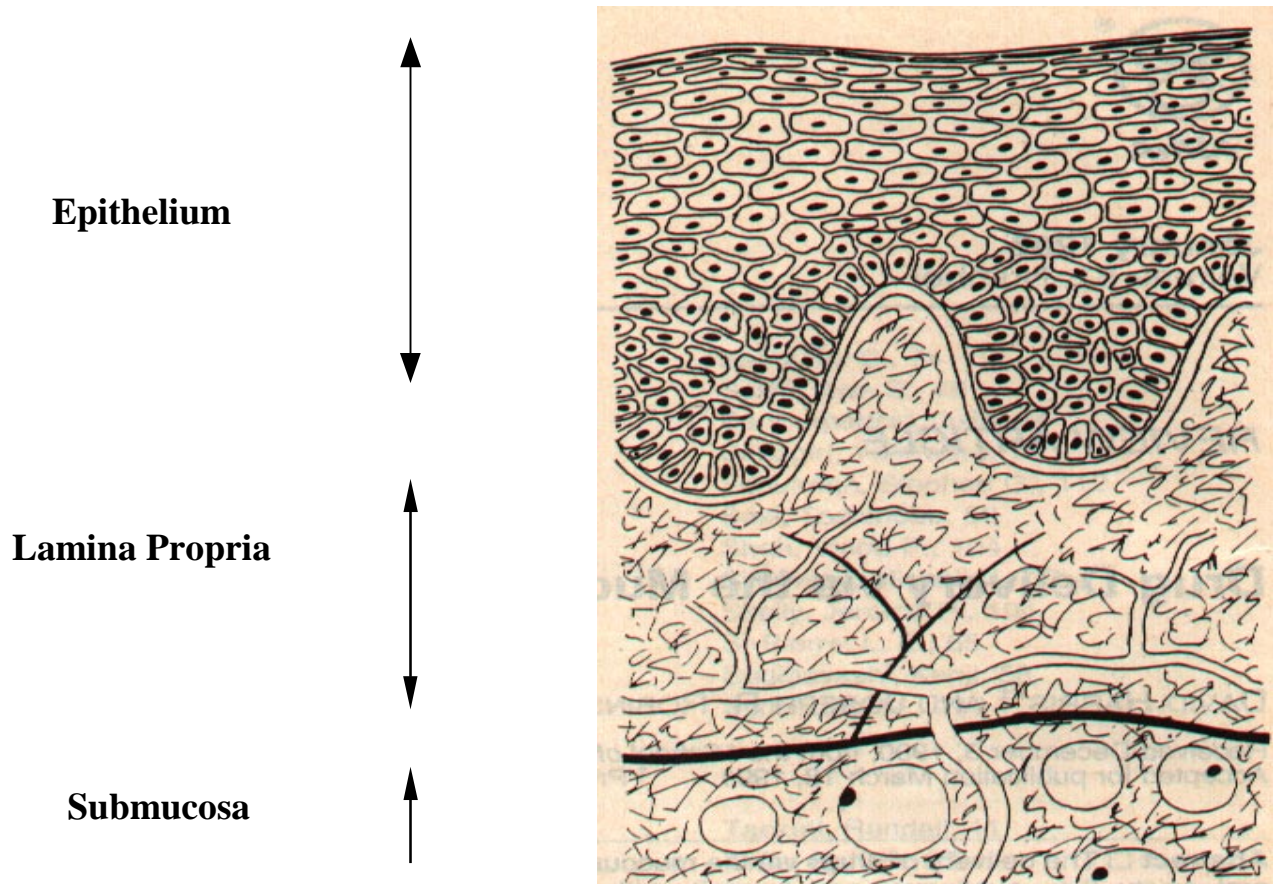


Figure 1. Structure of the oral mucosae. From reference (18) with permission.

IV. BUCCAL MUCOSA AS A SITE FOR DRUG DELIVERY

As stated above in section I, there are three different categories of drug delivery within the oral cavity (i.e., sublingual, buccal, and local drug delivery). Selecting one over another is mainly based on anatomical and permeability differences that exist among the various oral mucosal sites. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailabilities of many drugs, and is convenient, accessible, and generally well accepted (18). The sublingual route is by far the most widely studied of these routes. Sublingual dosage forms are of two different designs, those composed of rapidly

disintegrating tablets, and those consisting of soft gelatin capsules filled with liquid drug. Such systems create a very high drug concentration in the sublingual region before they are systemically absorbed across the mucosa. The buccal mucosa is considerably less permeable than the sublingual area, and is generally not able to provide the rapid absorption and good bioavailabilities seen with sublingual administration. Local delivery to tissues of the oral cavity has a number of applications, including the treatment of toothaches (30), periodontal disease (31, 32), bacterial and fungal infections (33), aphthous and dental stomatitis (34), and in facilitating tooth movement with prostaglandins (35).

Even though the sublingual mucosa is relatively more permeable than the buccal mucosa, it is not suitable for an oral transmucosal delivery system. The sublingual region lacks an expanse of smooth muscle or immobile mucosa and is constantly washed by a considerable amount of saliva making it difficult for device placement. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action making it appropriate for drugs with short delivery period requirements with infrequent dosing regimen. Due to two important differences between the sublingual mucosa and the buccal mucosa, the latter is a more preferred route for systemic transmucosal drug delivery (18, 23). First difference being in the permeability characteristics of the region, where the buccal mucosa is less permeable and is thus not able to give a rapid onset of absorption (i.e., more suitable for a sustained release formulation). Second being that, the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa which makes it a more desirable region for retentive systems used for oral transmucosal drug delivery. Thus the buccal mucosa is more fitted for sustained delivery applications, delivery of less permeable molecules, and perhaps peptide drugs.

Similar to any other mucosal membrane, the buccal mucosa as a site for drug delivery has limitations as well. One of the major disadvantages associated with buccal drug delivery is the low flux which results in low drug bioavailability. Various compounds have been investigated for their use as buccal penetration enhancers in order to increase the flux of drugs through the mucosa (Table 1). Since the buccal epithelium is similar in structure to other stratified epithelia of the body, enhancers used to improve drug permeation in other absorptive mucosae have been shown to work in improving buccal drug penetration (36). Drugs investigated for buccal delivery using various permeation/absorption enhancers range in both molecular weight and physicochemical properties. Small molecules such as butyric acid and butanol (37), ionizable low molecular weight drugs such as acyclovir (38, 39), propranolol (40), and salicylic acid (41), large molecular weight hydrophilic polymers such as dextrans (42), and a variety of peptides including octreotide (43), leutinizing hormone

releasing hormone (LHRH) (44), insulin (36), and α -interferon (45) have all been studied.

Table 1. List of compounds used as oral mucosal permeation enhancers

Permeation Enhancer	Reference(s)
23-lauryl ether	(48)
Aprotinin	(2)
Azone	(43, 51, 52)
Benzalkonium chloride	(53)
Cetylpyridinium chloride	(37, 53-55)
Cetyltrimethylammonium bromide	(53)
Cyclodextrin	(45)
Dextran sulfate	(48)
Lauric acid	(56)
Lauric acid/Propylene glycol	(36)
Lysophosphatidylcholine	(49)
Menthol	(56)
Methoxysalicylate	(48)
Methyloleate	(40)
Oleic acid	(40)
Phosphatidylcholine	(56)
Polyoxyethylene	(48)
Polysorbate 80	(37, 45, 54)
Sodium EDTA	(2, 43, 48)
Sodium glycocholate	(1, 36, 39, 43, 44, 46, 47, 49, 57)
Sodium glycodeoxycholate	(36, 41, 42, 44, 46-48)
Sodium lauryl sulfate	(2, 36, 37, 41, 45, 48, 53, 54)
Sodium salicylate	(2, 56)
Sodium taurocholate	(43-48, 54)
Sodium taurodeoxycholate	(46, 47, 49)
Sulfoxides	(36)
Various alkyl glycosides	(50)

A series of studies (42, 46, 47) on buccal permeation of buserelin and fluorescein isothiocyanate (FITC) labelled dextrans reported the enhancing effects of di- and tri-hydroxy bile salts on buccal penetration. Their results showed that in the presence of the bile salts, the permeability of porcine buccal mucosa to FITC increased by a 100-200 fold compared to FITC alone.

The mechanism of penetration enhancement of FITC-labelled dextrans by sodium glycocholate (SGC) was shown to be concentration dependent (47). Below 10 mM SGC, buccal permeation was increased by increasing the intercellular transport and at 10 mM and higher concentrations by opening up a transcellular route. Gandhi and Robinson (41) investigated the mechanisms of penetration enhancement of transbuccal delivery of salicylic acid. They used sodium deoxycholate and sodium lauryl sulfate as penetration enhancers, both of which were found to increase the permeability of salicylic acid across rabbit buccal mucosa. Their results also supported that the superficial layers and protein domain of the epithelium may be responsible for maintaining the barrier function of the buccal mucosa.

A number of research groups (1, 2, 36, 48-50) have studied the feasibility of buccal mucosal delivery of insulin using various enhancers in different animal models for in vivo studies. Aungst et al. (1, 2) who used sodium glycocholate, sodium lauryl sulfate, sodium salicylate, sodium EDTA (ethylenediamine tetraacetic acid), and aprotinin on rat buccal mucosa noticed an increase in insulin bioavailability from about 0.7% (without enhancer) to 26-27% in the presence of sodium glycocholate (5% w/v) and sodium lauryl sulfate (5% w/v). Similar results were obtained using dog as the animal model for the in vivo studies, where sodium deoxycholate and sodium glycocholate yielded the highest enhancement of buccal insulin absorption (36). These studies have all demonstrated the feasibility of buccal delivery of a rather large molecular weight peptide drug such as insulin.

V. EXPERIMENTAL METHODOLOGY FOR BUCCAL PERMEATION STUDIES

Before a buccal drug delivery system can be formulated, buccal absorption/permeation studies must be conducted to determine the feasibility of this route of administration for the candidate drug. These studies involve methods that would examine in vitro and/or in vivo buccal permeation profile and absorption kinetics of the drug.

A. In vitro Methods

At the present time, most of the *in vitro* studies examining drug transport across buccal mucosa have used buccal tissues from animal models. Animals are sacrificed immediately before the start of an experiment. Buccal mucosa with underlying connective tissue is surgically removed from the oral cavity, the connective tissue is then carefully removed and the buccal mucosal membrane is isolated. The membranes are then placed and stored in ice-cold (4°C) buffers (usually Krebs buffer) until mounted between side-by-side diffusion cells for the *in vitro* permeation experiments. The most significant questions concerning the use of animal tissues as *in vitro* models in this manner are the viability and the integrity of the dissected tissue. How well the dissected tissue is preserved is an important issue which will directly affect the results and conclusion of the studies. To date, there are no standard means by which the viability or the integrity of the dissected tissue can be assessed. Dowty et al. (58) studied tissue viability by using ATP levels in rabbit buccal mucosa. Using ATP levels as an indicator for tissue viability is not necessarily an accurate measure, however. Dowty et al. (58) reported a 50% drop in the tissue ATP concentration during the initial 6 hours of the experiment without a corresponding drop in tissue permeability. Despite certain gradual changes, the buccal tissue seems to remain viable for a rather long period of time. Therefore, a decrease in ATP levels does not assure a drop in permeability characteristics of the tissue. The most meaningful method to assess tissue viability is the actual permeation experiment itself, if the drug permeability does not change during the time course of the study under the specific experimental conditions of pH and temperature, then the tissue is considered viable.

Buccal cell cultures have also been suggested as useful in vitro models for buccal drug permeation and metabolism (25, 59-61). However, to utilize these culture cells for buccal drug transport, the number of differentiated cell layers and the lipid composition of the barrier layers must be well characterized and controlled. This has not yet been achieved with the buccal cell cultures used thus far.

B. In vivo Methods

In vivo methods were first originated by Beckett and Triggs (62) with the so-called buccal absorption test. Using this method, the kinetics of drug absorption were measured. The methodology involves the swirling of a 25 ml sample of the test solution for up to 15 minutes by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined in order to assess the amount of drug absorbed. The drawbacks of this method include salivary dilution of the drug, accidental swallowing of a portion of the sample solution, and the inability to localize the drug solution within a specific site (buccal, sublingual, or gingival) of the oral cavity. Various modifications of the buccal absorption test have been carried out (63-66) correcting for salivary dilution and accidental swallowing, but these modifications also suffer from the inability of site localization. A feasible approach to achieve absorption site localization is to retain the drug on the buccal mucosa using a bioadhesive system (67-69). Pharmacokinetic parameters such as bioavailability can then be calculated from the plasma concentration vs. time profile.

Other in vivo methods include those carried out using a small perfusion chamber attached to the upper lip of anesthetized dogs (70, 71). The perfusion chamber is attached to the tissue by cyanoacrylate cement. The drug solution is circulated through the device for a predetermined period of time and sample fractions are then collected from the perfusion chamber (to determine the amount of drug remaining in the chamber) and blood samples are drawn after 0 and 30 minutes (to determine amount of drug absorbed across the mucosa).

C. Experimental Animal Species

Aside from the specific methodology employed to study buccal drug absorption/permeation characteristics, special attention is warranted to the choice of experimental animal species for such experiments. For *in vivo* investigations, many researchers have used small animals including rats (1, 36, 37) and hamsters (51, 54, 72) for permeability

studies. However, such choices seriously limit the value of the data obtained since, unlike humans, most laboratory animals have an oral lining that is totally keratinized. The rat has a buccal mucosa with a very thick, keratinized surface layer. The rabbit is the only laboratory rodent that has non-keratinized mucosal lining similar to human tissue and has been extensively utilized in experimental studies (48, 55, 58, 73, 74). The difficulty in using rabbit oral mucosa, however, is the sudden transition to keratinized tissue at the mucosal margins making it hard to isolate the desired non-keratinized region (21). The oral mucosa of larger experimental animals that has been used for permeability and drug delivery studies include monkeys (75), dogs (34, 57, 65, 70), and pigs (42, 47, 76-80). Due to the difficulties associated with maintenance of monkeys, they are not very practical models for buccal drug delivery applications. Instead, dogs are much easier to maintain and considerably less expensive than monkeys and their buccal mucosa is non-keratinized and has a close similarity to that of the human buccal mucosa. Pigs also have non-keratinized buccal mucosa similar to that of human and their inexpensive handling and maintenance costs make them an equally attractive animal model for buccal drug delivery studies. In fact, the oral mucosa of pigs resembles that of human more closely than any other animal in terms of structure and composition (20, 81). However, for use in *in vivo* studies pigs are not as ideal as dogs due to their rapid growth which renders the animal handling rather difficult. Miniature breeds of pigs can be used but their high cost is a deterrent. For *in vitro* studies though, because of easy availability and low cost porcine tissue is more suited as compared to dog buccal tissue.

VI. BUCCAL DRUG DELIVERY SYSTEMS

Other than the low flux associated with buccal mucosal delivery, a major limitation of the buccal route of administration is the lack of dosage form retention at the site of absorption. Consequently, bioadhesive polymers have extensively been employed in buccal drug delivery systems. Bioadhesive polymers are defined as polymers that can adhere onto a biological substrate. The term mucoadhesion is applied

when the substrate is mucosal tissue (27). Polymers which can adhere to either hard or soft tissue have been used for many years in surgery and dentistry. Diverse classes of polymers have been investigated for their potential use as mucoadhesives. These include synthetic polymers such as monomeric α cyanoacrylat (82), polyacrylic acid (82), hydroxypropyl methylcellulose (17), and poly methacrylate derivatives (83) as well as naturally occurring polymers such as hyaluronic acid (84) and chitosan (85). Other synthetic polymers such as polyurethanes, epoxy resins, polystyrene, and natural-product cement have also been extensively investigated (86).

In general, dosage forms designed for buccal administration should not cause irritation and should be small and flexible enough to be accepted by the patient. These requirements can be met by using hydrogels. Hydrogels are hydrophilic matrices that are capable of swelling when placed in aqueous media

(87). Normally, hydrogels are crosslinked so that they would not dissolve in the medium and would only absorb water. When drugs are loaded into these hydrogels, as water is absorbed into the matrix, chain relaxation occurs and drug molecules are released through the spaces or channels within the hydrogel network. In a more broad meaning of the term, hydrogels would also include water-soluble matrices that are capable of swelling in aqueous media, these include natural gums and cellulose derivatives. These 'pseudo-hydrogels' swell infinitely and the component molecules dissolve from the surface of the matrix. Drug release would then occur through the spaces or channels within the network as well as through the dissolution and/or the disintegration of the matrix. The use of hydrogels as adhesive preparations for transmucosal drug delivery has acquired considerable attention in recent years. Table 2 summarizes the related research on mucoadhesive polymers and delivery systems.

Table 2- Related research on mucoadhesive polymers and delivery systems.

Bioadhesive Polymer(s) Studied	Investigation Objectives	Reference
HPC and CP	Preferred mucoadhesive strength on CP, HPC, and HPC-CP combination	(57)
HPC and CP	Measured Bioadhesive property using mouse peritoneal membrane	(88)
CP, HPC, PVP, CMC	Studied inter polymer complexation and its effects on bioadhesive strength	(89)
CP and HPMC	Formulation and evaluation of buccoadhesive controlled release delivery systems	(90)
HPC, HEC, PVP, and PVA	Tested mucosal adhesion on patches with two-ply laminates with an impermeable backing layer and hydrocolloid polymer layer	(91)
HPC and CP	Used HPC-CP powder mixture as peripheral base for strong adhesion and HPC-CP freeze dried mixture as core base	(30)
CP, PIP, and PIB	Used a two roll milling method to prepare a new bioadhesive patch formulation	(92)
Xanthum gum and Locust bean gum	Hydrogel formation by combination of natural gums	(93)
Chitosan, HPC, CMC, Pectin, Xantham gum, and Polycarbophil	Evaluate mucoadhesive properties by routinely measuring the detachment force form pig intestinal mucosa	(85)

Table 2- Related research on mucoadhesive polymers and delivery systems - continued

Bioadhesive Polymer(s) Studied	Investigation Objectives	Reference
Hyaluronic acid benzyl esters, Polycarbophil, and HPMC	Evaluate mucoadhesive properties	(84)
Hydroxyethylcellulose	Design and synthesis of a bilayer patch (polytef-disk) for thyroid gland diagnosis	(94)
Polycarbophil	Design of a unidirectional buccal patch for oral mucosal delivery of peptide drugs	(70)
Poly(acrylic acid) and Poly(methacrylic acid)	Synthesized and evaluated crosslinked polymers differing in charge densities and hydrophobicity	(82)
Number of Polymers including HPC, HPMC, CP, CMC.	Measurement of bioadhesive potential and to derive meaningful information on the structural requirement for bioadhesion	(86)
Poly(acrylic acid-co-acrylamide)	Adhesion strength to the gastric mucus layer as a function of crosslinking agent, degree of swelling, and carboxyl group density	(95)
Poly(acrylic acid)	Effects of PAA molecular weight and crosslinking concentration on swelling and drug release characteristics	(96)
Poly(acrylic acid-co-methyl methacrylate)	Effects of polymer structural features on mucoadhesion	(83, 97)
Poly(acrylic acid-co- butylacrylate)	Relationships between structure and adhesion for mucoadhesive polymers	(16)
HEMA copolymerized with Polymeg [®] (polytetramethylene glycol)	Bioadhesive buccal hydrogel for controlled release delivery of buprenorphine	(98)
Cydot [®] by 3M (bioadhesive polymeric blend of CP and PIB)	Patch system for buccal mucoadhesive drug delivery	(69, 99)
Formulation consisting of PVP, CP, and cetylpyridinium chloride (as stabilizer)	Device for oramucosal delivery of LHRH - device containing a fast release and a slow release layer	(44)
CMC, Carbopol 974P, Carbopol EX-55, Pectin (low viscosity), Chitosan chloride,	Mucoadhesive gels for intraoral delivery	(100)
CMC, CP, Polyethylene oxide, Polymethylvinylether/Maleic anhydride (PME/MA), and Tragacanth	Buccal mucoadhesive device for controlled release anticandidal device - CMC tablets yielded the highest adhesive force	(101)
HPMC and Polycarbophil (PC)	Buccal mucoadhesive tablets with optimum blend ratio of 80:20 PC to HPMC yielding the highest force of adhesion	(102)
PVP, Poly(acrylic acid)	Transmucosal controlled delivery of isosorbide dinitrate	(103, 104)

Table 2- Related research on mucoadhesive polymers and delivery systems - continued

Bioadhesive Polymer(s) Studied	Investigation Objectives	Reference
Poly(acrylic acid-co-poly ethyleneglycol) copolymer of acrylic acid and poly ethyleneglycol monomethyl-ether monomethacrylate	To enhance the mucoadhesive properties of PAA for buccal mucoadhesive drug delivery	(105-107)
Poly acrylic acid and poly ethylene glycol	To enhance mucoadhesive properties of PAA by interpolymer complexation through template polymerization	(108)
Drum dried waxy maize starch (DDWM), Carbopol 974P, and sodium stearyl fumarate	Bioadhesive erodible buccal tablet for progesterone delivery	(109)

Abbreviations: CP = Carbopol 934P, HPC = Hydroxy propyl cellulose, PVP = Poly(vinyl pyrrolidone), CMC = Sodium carboxymethyl cellulose, HPMC = Hydroxy propyl methyl cellulose, HEC = Hydroxy ethyl cellulose, PVA = Poly(vinyl alcohol), PIB = Poly(isobutylene), PIP = Poly(isoprene).

Nagai et al. (35) studied the applicability of hydroxypropyl cellulose (HPC) as a mucoadhesive agent, they found this high viscosity grade material to be a suitable adhesive for topical mucus membranes. They reported the combination of HPC and carbopol 934P (CP) to produce a preferable material for mucoadhesive dosage forms. They examined directly compressed tablets of these polymers by placing them on an agar gel bed. HPC tablets showed a slight adhesion but dissolved easily on the gel bed. On the other hand, CP tablets showed strong adhesion but the swollen CP tablets seemed too hard. The combination of HPC and CP provided the mucoadhesion and adequate softness to prepare the tablets. Satoh et al. (88) measured the bioadhesive property of tablets consisting of HPC and CP using mouse peritoneal membrane. The adhesive force of the HPC-CP tablet was affected by the mixing ratio of HPC and CP. The adhesion force showed a minimum value at the mixing ratio of 3:2 (HPC:CP) due to the formation of an interpolymer complex between HPC and CP in the acidic pH range.

Complex formation between CP and HPC seemed to suppress the interaction between molecules of hydrogel and the mucus membrane, and the adhesion

force was therefore most reduced at a mixture ratio of 1:4 (HPC/CP). Inter-polymer complexation and its effect on bioadhesive strength was also studied by Gupta et al. (89). They reported that CP shows strong complexation with poly(vinyl pyrrolidone) and hydroxypropyl cellulose, but very little with sodium carboxy methyl cellulose. The degree of complexation was higher at acidic pH and decreased with an increase in pH. Anlar et al. (90) reported on formulation and evaluation of buccoadhesive controlled release systems for the delivery of morphine sulfate. They prepared tablets by direct compression of carbomer and hydroxypropyl methyl cellulose (HPMC) and found the drug release behavior to be non-Fickian and also confirmed interpolymer complex formation between HPMC and carbomer in acidic pH medium.

Anders and Merkle (91), developed and evaluated adhesive patches for buccal administration, consisting of two-ply laminates of an impermeable backing layer and a hydrocolloid polymer layer containing the drug. The polymers used HPC, HEC, PVP, and PVA. The integrity of the laminate was based on adhesive bonds between the hydrocolloid layer and an agarose layer grafted to one side of the backing layer sheet. Their work showed that among the cellulose ethers studied

HEC and HPC possessed superior mucosal adhesion. Ishida et al. (30) utilized similar materials in a lidocaine delivery system for toothache. They used an HPC-CP powder mixture as a peripheral base aiming at strong adhesion, but an HPC-CP freeze-dried mixture was used as a core base. HPC and CP formed a complex during the freeze drying process, and this contributed to the ease of admixing by blockage of the functional group of CP. Guo (92) used a two roll milling method to prepare a new bioadhesive polymer patch formulation for controlled drug delivery consisting of CP, PIB, and PIP. It was found that the surface properties of buccal patches were not only dependent on the CP content but also dependent on the PIB:PIP ratio. The strongest peel strength was found on buccal patches with a CP:PIB:PIP ratio of 50:43.75:6.25.

Watanabe et al. (93) reported on hydrogels formed by the combination of natural gums, xantham gum, and locust bean gum, which are applicable in buccal delivery systems. Xantham gum is a natural gum obtained through fermentation of glucose by *Xanthomonas campestris*. Locust bean gum and xantham gum alone cannot form a hydrogel. However, when a mixture of these gums is dissolved in a neutral medium at 90°C and then cooled with ice for 30 min, a clear, strong hydrogel is formed. The mechanism of gel formation was reported to be the formation of a three dimensional network by interaction between the double helix structure of xantham gum and the straight molecular chain of locust bean gum. The gel strength of the hydrogels was affected by the mixing ratio of the gums, and the addition of sucrose improved the sustained release properties of the hydrogels. The hydrogel consisting of xantham gum and locust bean gum showed only a low mucoadhesion, but it can be applied to a buccal delivery system because of its safety, gel strength, sustained release properties and good feel in the mouth.

Anders et al. (94) designed a bilayer patch (polytef-disk) consisting of protirelin for thyroid gland diagnosis. The patch had a backing layer of teflon and mucoadhesive layer of protirelin dispersed in hydroxyethylcellulose. Veillard et al. (70) reported the use of a unidirectional buccal patch which consisted of

three layers: an impermeable backing layer, a rate limiting center membrane containing the drug, and a mucoadhesive layer containing bioadhesive polymer polycarbophil. The bioadhesive polymer swells, creating a flexible network through which diffusion of drug takes place. This patch was tested in dog buccal mucosa and was shown to remain in place for up to 17 hours without any obvious discomfort.

Ch'ng et al. (82) synthesized and evaluated a series of crosslinked, swellable polymers of acrylic acid and methacrylic acid, differing in charge densities and hydrophobicity. They found that an increase in the number of hydrophobic groups in the polymer structure reduced hydration whereas the density of the polymer was unaffected. Furthermore, polymers of acrylic acid loosely crosslinked (0.3 % w/w) with 3 different agents, divinyl glycol, 2,5-dimethyl-1,5-hexadiene, and divinyl benzene, showed the same degree of bioadhesion while poly(methacrylic acid) crosslinked with divinyl benzene showed reduced bioadhesion. The small percent of crosslinking agent, irrespective of physicochemical properties, did not contribute substantially to bioadhesion, whereas the starting monomer had a large effect. The effect of pH on the bioadhesion of poly(acrylic acid) crosslinked with divinyl glycol was also studied at constant temperature, ionic strength, and osmolality. It was found that the polymer showed maximum adhesion at pH 5 and 6 and a minimum at pH 7.

Park and Robinson (86) examined a large number of polymers as to their bioadhesive potential and to derive meaningful information on the structural requirements for bioadhesion. They concluded that charged carboxylated polyanions are good potential bioadhesives for drug delivery. To understand the role of the carboxyl groups in mucoadhesion, acrylic acid-acrylamide random copolymers [P(AA-co-AM)] were synthesized (95) and the adhesion strength of the crosslinked polymers to the gastric mucus layer as a function of pH, initial concentration of the crosslinking agent, degree of swelling, and carboxyl group density were examined. From the study on mucoadhesion of various P(AA-co-AM), it was found that at least 80% of the vinyl groups of the polymer must possess carboxyl groups in the protonated form.

The dependence of mucoadhesion on pH and carboxyl-group density suggests that mucoadhesion occurs through hydrogen bonding. In addition, the density of the crosslinking agent significantly affects mucoadhesion. As the density of the crosslinking agent is lowered, the mucoadhesive strength increases, although the density of carboxyl groups in the test surface area is reduced. It was concluded that for mucoadhesion to occur, polymers must have functional groups that are able to form hydrogen bonds above the critical concentration (80% for vinyl polymers), and the polymer chains should be flexible enough to form as many hydrogen bonds as possible. Similar results were achieved by Garcia-Gonzalez et al. (96) who evaluated the effects of poly(acrylic acid) (PAA) molecular weight and the concentration of crosslinking agent (sucrose) on swelling and drug (metoclopramide) release characteristics of PAA (carbopol) hydrogels. They reported that both factors and the interaction term had significant effects on hydrogel swelling and drug release. In particular, they found that increased sucrose concentration (high crosslinking density) led to reduced swelling and reduced drug release efficiency.

Leung and Robinson (83, 97) studied the contribution of anionic polymer structural features to mucoadhesion using 0.2% crosslinked copolymers of acrylic acid and methyl methacrylate. Their results showed that the expanded nature of both the interacting mucus and polymer networks influences the strength of mucoadhesion. They concluded that mucoadhesive polymer with the desired mucoadhesive strength can be designed by controlling the percentage of charged groups and the corresponding openness of the network.

Bodde et al. (16) investigated relationships between structure and adhesion for mucoadhesive polymers. Their study was based on an assumption that bioadhesion should possess two properties: (i) optimal polarity to make sure the polymer is "wetted" by the mucus, and (ii) optimal fluidity to allow for the mutual adsorption and interpenetration of polymer and mucus to take place. They studied acrylic polymer films, designed for buccal drug delivery. The films were made either through mixing or copolymerization of poly(butyl acrylate) and poly(acrylic acid). In both

cases satisfactory mucoadhesion was found within a range of compositions optimized for surface polarity and the fluidity of the polymer film.

In an attempt to enhance the intrinsic mucoadhesive properties of poly(acrylic acid), Shojaei and Li (105-107) designed and formulated a series of novel copolymers of acrylic acid and poly ethyleneglycol monomethylether monomethacrylate [P(AA-co-PEG)]. The addition of PEG into the polymer increased the potential for hydrogen bond formation, since the lone pair electrons of oxygen in the repeat unit ($\text{CH}_2\text{CH}_2\text{O}$) of PEG served as hydrogen bond acceptors (107). The surface properties of PAA for mucoadhesion were also improved by the PEG incorporation (107). Using these copolymers, a patch device was prepared for buccal acyclovir delivery and the feasibility of such delivery was proven in vitro with the incorporation of sodium glycocholate as the permeation enhancer (39).

Using copolymeric hydrogel discs of HEMA (monomer) and Polymeg[®] (macromer) a buccal mucoadhesive device for controlled release of buprenorphine was developed (98). The hydrogel containing a monomer:macromer ratio of 80:20 (w/w) yielded the best result both in terms of adhesion and drug release. The device was applied for a 3 hour application time and steady state levels were maintained for the time of application. Formulation of another buccal delivery system was reported by DeGrande et al. (69, 99) from the 3M company. The buccal patch device (Cydot; 3M Pharmaceutical, St. Paul, MN) consists of a flexible mucoadhesive matrix composed of a blend of poly(acrylic acid) (Carbopol 934P; B.F. Goodrich, Cleveland, OH) and poly(isobutylene) (Vistanex; Exxon Chemical Company, Houston, TX). The patch device is unidirectional with a polyurethane backing layer. The patch is intended for application to the upper gum and in vivo studies in human subjects have revealed effective bioadhesive characteristics for 12 hours of application (69). Several investigators have reported on the development of TmTs (transmucosal therapeutic systems) devices with a field-shaped bilayer design consisting of fast-release and sustained-release layers (44, 103, 104). The fast release layer contains PVP as the bioadhesive component and is

designed to adhere to the buccal mucosa and the sustained release layer consists of a mixture of PVP and poly(acrylic acid) and is intended to adhere to the gingival mucosa (103). Most recently, a TmTs formulation was reported for the buccal delivery of LHRH (lutinizing hormone releasing hormone) (44) with results indicating the feasibility of controlled release transmucosal delivery of the peptide drug.

VI. CONCLUSION

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

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