Systemic Drug Delivery via the Buccal Mucosal Route

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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 is permeable to many pharmacologically active agents. The objective of this article is to review buccal drug delivery by discussing the structure and environment of the oral mucosa and highlighting the experimental methods used in the assessment of buccal drug permeation and absorption. The review also assesses the current status of buccal permeation enhancers as well as buccal drug delivery systems.

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Among the various routes of drug delivery, the oral route is perhaps the most preferred by patients and clinicians alike. However, peroral administration of drugs has disadvantages, such as hepatic first-pass metabolism and enzymatic degradation within the gastrointestinal (GI) tract, that prohibit oral administration of certain classes of drugs, especially peptides and proteins. Consequently, other absorptive mucosa 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 cavities) offer distinct advantages over peroral administration for systemic effect. These advantages include possible bypass of first-pass effects and avoidance of presystemic elimination within the GI tract. Many research groups (1–3) have investigated the nasal cavity as a site for systemic drug delivery, and the route already has reached commercial status with several drugs, including leutinizing hormone-releasing hormone (LHRH), cyanocobalamin, azelastine hydrochloride, desmopressin acetate, and calcitonin (4–5). However, the potential irritation and the irreversible damage to the ciliary action of the nasal cavity from chronic application of nasal dosage forms make the nasal cavity less attractive for drug delivery. Also, the large intrasubject and intersubject variability in mucus secretion in the nasal mucosa could be a significant factor affecting drug absorption from this site. Even though the rectal, vaginal, and ocular mucosa offer certain advantages, the poor patient acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration.

Similar to the nasal route, the oral cavity as a site for drug delivery also has reached commercial status with several drugs, including nitroglycerin as sublingual tablets for angina and fentanyl as a transmucosal buccal device (Actiq, Abbott Laboratories, Abbott Park, IL) for breakthrough cancer pain (6). Furthermore, oral transmucosal drug delivery bypasses first-pass effects in the GI tract and liver and avoids GI side effects. Unlike the nasal cavity, however, drug delivery via the oral cavity is highly acceptable by patients. The mucosa is relatively permeable, has a rich blood supply, is robust, and shows short recovery times after stress or damage (7). Within the oral cavity the two common regions for drug delivery are the sublingual mucosa (area beneath the tongue) and the buccal mucosa (inner lining of the cheeks). Selecting one over the other is mainly based on anatomical and permeability properties of the vari-

Table I: Compounds used as oral mucosal permeation enhancers.

Permeation Enhancer	References
23-lauryl ether	(41)
Aprotinin	(65)
Azone	(38, 61, 89)
Benzalkonium chloride	(90)
Cetylpyridinium chloride	(37, 39, 42, 90)
Cetyltrimethylammonium bromide	(90)
Cyclodextrin	(63)
Dextran sulfate	(41)
Lauric acid	(91)
Lauric acid/propylene glycol	(36)
Lysophosphatidylcholine	(66)
Menthol	(91, 92)
Methoxysalicylate	(41)
Methyl oleate	(59)
Oleic acid	(59)
Phosphatidylcholine	(91)
Polyoxyethylene	(41)
Polysorbate 80	(37, 39, 63)
Sodium EDTA	(50, 61, 65)
Sodium glycocholate	(1, 36, 47, 50, 61, 62, 64, 66, 83)
Sodium glycodeoxycholate	36, 41, 48, 50, 60, 62, 64)
Sodium lauryl sulfate	(36, 37, 39, 41, 60, 63, 65, 90)
Sodium salicylate	(65, 91)
Sodium taurocholate	(39, 41, 50, 61–64)
Sodium taurodeoxycholate	(50, 64, 66)
Sulfoxides	(36)
Various alkyl glycosides	(67)

ous oral mucosal sites, the desired residence time, and the desired effects of the drug.

Buccal mucosa as a site for drug delivery

There are two permeation pathways for passive drug transport across the oral mucosa: paracellular and transcellular routes. Permeants may traverse these two routes simultaneously, but one route usually is more effective than the other, depending on the physicochemical properties of the diffusant. Because the intercellular spaces are less lipophilic in character than the cell membrane, hydrophilic compounds have higher solubilities in this environment. The cell membrane, however, is highly lipophilic in nature, and hydrophilic solutes have great difficulty permeating the cell membrane because of a low partition coefficient. Therefore, the intercellular spaces pose the major barrier to passive permeation of lipophilic compounds, and the cell membrane acts as the major transport barrier for hydrophilic compounds. Because 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.

Three different categories of drug delivery fall within the oral cavity: sublingual, buccal, and local. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailabilities of many drugs, and is convenient, accessible, and generally well accepted (8). The sublingual route is by far the most widely studied of these routes. Sublingual dosage forms are most often one of two 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 (9), periodontal disease (10,11), bacterial and fungal infections (12), and aphthous and dental stomatitis (13), and in facilitating tooth movement with prostaglandins (14). Even though the sublingual mucosa is relatively more permeable than the buccal mucosa, it is not suitable for a retentive oral transmucosal delivery system. The sublingual region lacks an expanse of smooth and immobile mucosa and is constantly washed by a considerable amount of saliva, making device placement difficult. Because of the high permeability and the rich blood supply, transport via the sublingual route results in a rapid onset of action, making it appropriate for highly permeable drugs with short delivery period requirements and an infrequent dosing regimen. However, the preferred site for retentive oral transmucosal delivery systems and for sustained- and controlled-release delivery devices is the buccal mucosa (8,15), mainly because of the differences in permeability characteristics between the two regions and the buccal mucosa's expanse of smooth and relatively immobile mucosa.

Methodology for buccal permeation studies

Before a buccal drug delivery system can be formulated, buccal absorption and 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 in vivo buccal permeation profile and absorption kinetics of the drug.

In vitro methods. At the present time, most of the in vitro studies examining drug transport across buccal mucosa use buccal tissues from animal models. Animals are sacrificed immediately before the start of an experiment. Buccal mucosa with underlying connective tissue is excised from the oral cavity, the connective tissue is surgically removed, and the buccal mucosal membrane is isolated. The membranes are then stored in ice-cold (4 °C) buffers (usually Krebs buffer) until they are 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 directly affects the results and conclusion of the studies.

To date, we have no standard means by which the viability or the integrity of the dissected tissue can be assessed. Dowty et al. studied tissue viability by using ATP levels in rabbit buccal mucosa (16). They reported a 50% drop in the tissue ATP concentration during the initial six 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 ensure a drop in permeability characteristics of the tissue. Tissue integrity is also commonly monitored by the use of permeation markers such as ^{14}C-mannitol, a hydrophilic marker for the paracellular route, and ^{3}H-testosterone, a lipophilic marker for the transcellular route or by monitoring the transepithelial electrical resistance (mostly applicable to buccal cell culture models). However, the most meaningful method for assessing tissue viability or integrity 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 to have maintained its integrity.

Buccal cell cultures also have been suggested as useful in vitro models for buccal drug permeation and metabolism (17–20). To use these cell cultures for buccal drug transport experiments, the number of differentiated cell layers and the lipid composition of the barrier layers must be well characterized and controlled. In a series of systematic studies, Jacobsen et al. and Nielsen et al. reported on the use of a human buccal cell line, TR146, grown on filters as a model for buccal permeation experiments (21–25). This model cell culture has been well characterized in terms of morphology, barrier properties, and cell differentiation and shown to be a promising screening tool to study passive transport of various model compounds across buccal epithelium.

In vivo methods. In vivo methods were first originated by Beckett and Triggs with the so-called buccal absorption test (26). Using this method, they measured the kinetics of drug absorption. The methodology involves the swirling of a 25-mL sample of the test solution for as long as 15 min in the mouth by human volunteers, followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined 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 tested, corrected for salivary dilution and accidental swallowing, but these modifications also suffer from the inability of site localization (27–30). A feasible approach to achieve absorption site localization is to retain the drug on the buccal mucosa using a bioadhesive system (31–33). Pharmacokinetic parameters such as bioavailability then can be calculated from the profile of plasma concentration versus time. Other in vivo methods include those carried out via a small perfusion chamber attached to the upper lip of anesthetized dogs (34,35). 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. Sample fractions then are collected from the perfusion chamber to determine the amount of drug remaining in the chamber, and blood samples are drawn after 0 and 30 min to determine the amount of drug absorbed across the mucosa.

Experimental animal species. Aside from the specific methodology used to study buccal drug absorption and 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 (38-40) for permeability studies. However, such choices seriously limit the value of the data obtained because, 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 nonkeratinized mucosal lining similar to human tissue and it has been used extensively in experimental studies (16,37,41–43). The difficulty in using rabbit oral mucosa, however, is the sudden transition to keratinized tissue at the mucosal margins, making it difficult to isolate the desired nonkeratinized region (44). The oral mucosa of larger experimental animals that has been used for permeability and drug delivery studies include monkeys (45), dogs (29,34,46,47), and pigs (48–54). The difficulties associated with the maintenance of monkeys render them impractical models for buccal drug delivery applications. Instead, dogs are much easier to maintain and considerably less expensive than monkeys, and their buccal mucosa is nonkeratinized and is similar to that of the human buccal mucosa. Pigs also have nonkeratinized buccal mucosa similar to that of humans, 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 humans more closely than any other animal in terms of structure and composition (55,56). However, for use in in vivo studies, pigs are not as near-ideal as dogs because of their rapid growth, which renders animal handling rather difficult. Miniature breeds of pigs can be used but their high cost is a deterrent. For in vitro studies, however, because of easy availability and low-cost, porcine tissue is more suited to this use than is dog buccal tissue.

Buccal permeation enhancement

One of the major disadvantages associated with buccal drug delivery is the low flux of drugs across the mucosal epithelium, which results in low drug bioavailability. Various compounds have been investigated for their use as buccal penetration and absorption enhancers to increase the flux of drugs through the mucosa (see Table I). Because the buccal epithelium is similar in structure to other stratified epithelia of the body, enhancers used to improve drug permeation in other absorptive mucosa have been shown to improve buccal drug penetration (36). Drugs investigated for buccal delivery using various permeation and absorption enhancers vary over a wide range of molecular weight and physicochemical properties. Small molecules such as butyric acid and butanol (37); ionizable low molecular weight drugs such as acyclovir (57,58), propranolol (59), and salicylic acid (60); large molecular weight hydrophilic polymers such as dextrans (48); and a variety of peptides, including octreotide (61), LHRH (62), insulin (1), and α-interferon (63) have been studied.

A series of studies on the buccal permeation of buserelin and fluorescein isothiocyanate labeled dextrans (FITC-D) reported the enhancing effects of di- and tri-hydroxy bile salts on buccal penetration (48,50,64) . Results from these studies showed that in the presence of the bile salts, the permeability of porcine buccal mucosa to FITC-D increased by 100 – 200-fold compared

Table II: Related research on mucoadhesive buccal delivery systems.

Bioadhesive Material(s) Studied	Investigation Objectives and References
HPC and CP	Preferred mucoadhesive strength on CP, HPC, and HPC-CP combination (47)
HPC and CP	Measured bioadhesive property using mouse peritoneal membrane (93)
CP, HPC, PVP, CMC	Studied interpolymer complexation and its effects on bioadhesive strength (94)
CP and HPMC	Formulation and evaluation of buccoadhesive controlled-release delivery systems (76)
HPC, HEC, PVP, and PVA	Tested mucosal adhesion on patches with two-ply laminates with an impermeable backing layer and hydrocolloid polymer layer (77)
HPC and CP	Used HPC-CP powder mixture as peripheral base for strong adhesion and HPC-CP freeze-dried mixture as core base (9)
CP, PIP, and PIB	Used a two-roll milling method to prepare a new bioadhesive buccal patch formulation (78)
Xanthum gum and locust bean gum	Hydrogel formation by combination of natural gums (95)
Chitosan, HPC, CMC, pectin, xanthum gum, and polycarbophil	Evaluate mucoadhesive properties by routinely measuring the detachment force from pig intestinal mucosa (73)
Hydroxyethylcellulose	Design and synthesis of a bilayer patch (polytef-disk) for thyroid gland diagnosis (79)
Polycarbophil	Design of a unidirectional buccal patch for oral mucosal delivery of peptide drugs (34)
HEMA copolymerized with Polymeg (polytetramethylene glycol)	Bioadhesive buccal hydrogel for controlled-release delivery of bupren orphine (84)
Cydot by 3M (bioadhesive polymeric blend of CP and PIB)	Patch system for buccal mucoadhesive drug delivery (33, 85)
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 (62)
CMC, Carbopol 974P, Carbopol EX-55, pectin (low viscosity), chitosan chloride	Mucoadhesive gels for intraoral delivery (96)
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 (97)
HPMC and polycarbophil (PC)	Buccal mucoadhesive tablets with optimum blend ratio of 80:20 PC to HPMC yielding the highest force of adhesion (98)
PVP, poly(acrylic acid)	Transmucosal controlled delivery of isosorbide dinitrate (86,87)
Poly(acrylic acid-co-poly ethyleneglycol) copolymer of acrylic acid and poly-ethyleneglycol monomethyl-ether mono-methacryalte	To enhance the mucoadhesive properties of PAA for buccal mucoadhesive delivery of acyclovir (80-82)
Drum-dried waxy maize starch, Carbopol 974P, and sodium stearylfumarate	Bioadhesive erodible buccal tablet for progesterone delivery (99)
Natural oligosaccharide gum, hakea	Evaluation of mucoadhesive buccal tablets for sustained release of salmon calcitonin (sCT) (88)
Poly(acrylic acid-co-ethylhexyl acrylate), P(AA-co-EHA)	Evaluation of P(AA-co-EHA) films for buccal mucoadhesive drug delivery (100)

Abbreviations: CP = Carbopol, HPC = hydroxypropyl cellulose, PVP = poly(vinyl pyrrolidone), CMC = sodium carboxymethyl cellulose, HPMC = hydroxypropyl methylcellulose, HEC = hydroxyethyl cellulose, PVA = poly(vinyl alcohol), PIB = poly(isobutylene), PIP = poly(isoprene).

with FITC-D alone. The mechanism of penetration enhancement of FITC-D by sodium glycocholate (SGC) was shown to be concentration dependent (50). 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 investigated the mechanisms of penetration enhancement of transbuccal delivery of salicylic acid (60). They used sodium deoxycholate and sodium lauryl sulfate as penetration enhancers and found that both enhancers can 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 have studied the feasibility of buccal mucosal delivery of insulin using various enhancers in different animal models for in vivo studies (1,36,41,65–67). Aungst et al. used sodium glycocholate, sodium lauryl sulfate, sodium salicylate,

sodium ethylenediamine tetraacetic acid (EDTA), and aprotinin on rat buccal mucosa and reported 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) (1,65). Similar results were obtained from in vivo studies using dog as the animal model, in which sodium deoxycholate and sodium glycocholate yielded the highest enhancement of buccal insulin absorption (36). These studies all have demonstrated the feasibility of buccal delivery of a rather large molecular weight peptide drug such as insulin.

Buccal drug delivery systems

Bioadhesive polymers have been used extensively in buccal drug delivery systems to provide dosage form retention. *Bioadhesive polymers* are defined as polymers that can adhere to a biological substrate. The term *mucoadhesion* is applied when the substrate is mucosal tissue (68). Diverse classes of polymers have been investigated for their potential use as mucoadhesives. These include synthetic polymers such as monomeric α cyanoacrylate (69), polyacrylic acid (69), hydroxypropyl methylcellulose (70), and polymethacrylate derivatives (71) as well as naturally occurring polymers such as hyaluronic acid (72) and chitosan (73). Other synthetic polymers such as polyurethanes, epoxy resins, polystyrene, and natural-product cement also have been extensively investigated (74).

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 (75). Normally, hydrogels are cross-linked so that they will not dissolve in the medium and will absorb only water. When drugs are loaded into these hydrogels, as water is absorbed into the matrix, polymer chain relaxation occurs and drug molecules are released through the spaces or channels within the hydrogel network. In a broader meaning of the term, hydrogels also would include water-soluble matrices that are capable of swelling in aqueous media; these include natural gums and cellulose derivatives. Upon immersion in water, these pseudo-hydrogels swell infinitely and the component molecules dissolve from the surface of the matrix. Drug is released by diffusion through the gel layer or channels within the network as well as by exposure through matrix erosion. The use of hydrogels or pseudo-hydrogels as adhesive preparations for transmucosal drug delivery has acquired considerable attention in recent years. Table II summarizes the related research on buccal mucoadhesive delivery systems.

Nagai et al. studied the applicability of hydroxypropyl cellulose (HPC) as a mucoadhesive agent and found it to be a high-viscosity material and a suitable adhesive for topical mucus membranes (14). Anlar et al. reported on formulation and evaluation of buccoadhesive controlled-release systems for the delivery of morphine sulfate (76). They prepared tablets by direct compression of Carbopol 910 and hydroxypropyl methylcellulose (HPMC) and found drug-release behavior to be non-Fickian, also confirming interpolymer complex formation between HPMC and Carbopol (CP) in acidic pH medium. Anders and Merkle (77) 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 were HPC, hydroxyethyl cellulose (HEC), poly(vinyl pyrrolidone) (PVP), and poly(vinyl alcohol). 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. used similar materials in a lidocaine delivery system for toothache (9). Guo used a two-roll milling method to prepare a new bioadhesive polymer patch formulation for controlled drug delivery consisting of Carbopol 934P, poly(isobutylene) (PIB), and poly(isoprene) (PIP) (78). Results showed 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.

Anders et al. designed a bilayer patch containing protirelin for thyroid gland diagnosis (79). The patch had a backing layer of PTFE and mucoadhesive layer of protirelin dispersed in hydroxyethylcellulose. Veillard et al. reported the use of a unidirectional buccal patch that consisted of three layers: an impermeable backing layer, a rate-limiting center membrane containing the drug, and a polycarbophil-based mucoadhesive layer (34). 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 as long as 17 h without causing any obvious discomfort.

In an attempt to enhance the intrinsic mucoadhesive properties of poly(acrylic acid), a series of novel copolymers of acrylic acid and poly ethyleneglycol monomethylether monomethacrylate (P[AA-co-PEG]) have been designed and formulated (80–82). The addition of PEG into the polymer increased the potential for hydrogen bond formation because the lone pair of electrons of oxygen in the repeat unit (CH_2CH_2O) of PEG served as hydrogen bond acceptors (82). The PEG incorporation also improved the surface properties of PAA for mucoadhesion (82). Using these copolymers, Shojaei et al. prepared a patch device for buccal acyclovir delivery, and the feasibility of such delivery was proven in vitro with the incorporation of sodium glycocholate as the permeation enhancer (83).

Cassidy et al. developed a buccal mucoadhesive device for the controlled release of buprenorphine using copolymeric hydrogel discs of HEMA monomer and Polymeg macromer (84). 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-h period, and steady-state levels were maintained for the time of application. Formulation of another buccal delivery system was reported by the 3M company (33,85). The buccal patch device (Cydot, 3M Pharmaceuticals, St. Paul, MN) consists of a flexible mucoadhesive matrix composed of a blend of poly(acrylic acid) (Carbopol 934P, BF 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. In vivo studies in

human subjects have revealed effective bioadhesive characteristics for 12 hours of application (33).

Several investigators have reported on the development of transmucosal therapeutic systems (TmTs), devices with a field-shaped bilayer design consisting of fast-release and sustained-release layers (62,86,87). The fast-release layer contains PVP as the bioadhesive component and is designed to adhere to the buccal mucosa. The sustained-release layer consists of a mixture of PVP and poly(acrylic acid) and is intended to adhere to the gingival mucosa (86). A TmTs formulation was reported for the buccal delivery of LHRH with results indicating the feasibility of controlled-release transmucosal delivery of the peptide drug (62).

Most recently, Alur et al. (88) reported on the in vitro and in vivo evaluation of mucoadhesive tablets consisting of a novel natural oligosaccharide gum (hakea) as a mucoadhesive material. They studied the suitability of the natural gum for sustained-release mucoadhesive buccal delivery of salmon calcitonin (sCT). Their results showed that the natural gum could sustain the release of sCT for more than 400 min while possessing strong mucoadhesive characteristics (88). The apparent bioavailability of sCT in New Zealand albino rabbits was reported as 37% and 16% for buccal tablets with 12 and 32 mg hakea, respectively (88).

Conclusion

The buccal mucosa offers several advantages for controlled drug delivery. The mucosa is well supplied with both vascular and lymphatic drainage; first-pass metabolism in the liver and presystemic elimination in the GI tract are avoided. The area is well suited for a retentive device and appears to be acceptable to patients. With the proper formulation and dosage form design, the permeability and the local environment of the mucosa can be controlled and manipulated to accommodate drug permeation. Buccal drug delivery is a promising area for systemic delivery of orally inefficient drugs as well as an attractive alternative for noninvasive delivery of potent peptide and perhaps protein drug molecules. However, the need for safe and effective buccal permeation and absorption enhancers is a crucial component for a promising future in the area of buccal drug delivery.

References

1. B.J. Aungst, "Comparison of Nasal, Rectal, Buccal, Sublingual and Intramuscular Insulin Efficacy and the Effects of a Bile Salt Absorption Promoter," *J. Pharmacol. Exp. Ther.* 244 (1), 23–27 (1988).
2. Z. Shao and A.K. Mitra, "Nasal Membrane and Intracellular Protein and Enzyme Release by Bile Salts and Bile Salt–Fatty Acid Mixed Micelles: Correlation with Facilitated Drug Transport," *Pharm. Res.* 9 (9) (1992).
3. A.P. Soyani and Y.W. Chien, "Systemic Delivery of Peptides and Proteins across Absorptive Mucosae," *Crit. Rev. Ther. Drug Carrier Sys.* 13 (1–2), 85–184 (1996).
4. T. Shimamoto, "Pharmaceutical Aspects. Nasal and Depot Formulations of Leuprolide," *J. Androl.* 8 (1), S14–S16 (1987).
5. R. Dal Negra et al., "Calcitonin Nasal Spray in Patients with Chronic Asthma: a Double-blind Crossover Study vs Placebo," *Int. J. Clin. Pharmacol. Ther. Toxicol.* 29 (4), 144–146 (1991).
6. J. Streisand et al., "Absorption and Bioavailability of Oral TransMucosal Fentanyl Citrate," *Anesthesiology* 75, 223–229 (1991).
7. C.A. Squier, "The Permeability of Oral Mucosa," *Crit. Rev. Oral Biol. Med.* 2 (1), 13–32 (1991).
8. D. Harris and J.R. Robinson, "Drug Delivery via the Mucous Membranes of the Oral Cavity," *J. Pharm. Sci.* 81 (1), 1–10 (1992).
9. M. Ishida et al., "Mucosal Dosage Form of Lidocaine for Toothache Using Hydroxypropyl Cellulose and Carbopol," *Chem. Pharm. Bull.* 30, 980–984 (1982).
10. A.E.M. Collins et al., "Evaluation of a Controlled Release Compact Containing Tetracycline Hydrochloride Bonded to Tooth for the Treatment of Periodontal Disease," *Int. J. Pharm.* 51, 103–114 (1989).
11. R. Elkayam et al., "Sustained Release Device Containing minocycline for Local Treatment of Periodontal Disease," *J. Controlled Release* 7, 231–236 (1988).
12. L. Samaranayake and M. Ferguson, "Delivery of Antifungal Agents to the Oral Cavity," *Adv. Drug Del. Dev.* 13, 161–179 (1994).
13. T. Nagai, "Adhesive Topical Drug Delivery System," *J. Controlled Release* 2, 121–134 (1985).
14. T. Nagai and Y. Machida, "Mucosal Adhesive Dosage Forms," *Pharm. Int.* 196–200 (August, 1985).
15. R.B. Gandhi and J.R. Robinson, "Oral Cavity as a Site for Bioadhesive Drug Delivery," *Adv. Drug Del. Rev.* 13, 43–74 (1994).
16. M.E. Dowty et al., "Transport of Thyrotropin Releasing Hormone in Rabbit Buccal Mucosa In Vitro," *Pharm. Res.* 9 (9), 1113–1122 (1992).
17. L.A. Tabak et al., Role of Salivary Mucins in the Protection of the Oral Cavity," *J. Oral Pathol.* 11, 1–17 (1982).
18. M.R. Tavakoli-Saberi and K.L. Audus, "Cultured Buccal Epithelium: an In Vitro Model Derived from the Hamster Pouch for Studying Drug Transport and Metabolism," *Pharm. Res.* 6, 160–162 (1989).
19. M.R. Tavakoli-Saberi et al., "Aminopeptidase Activity in Human Buccal Epithelium and Primary Cultures of Hamster Buccal Epithelium," *Pharm. Res.* 6, S-197 (1989).
20. H.R. Leipold and E. Quadros, "Nicotine Permeation through Buccal Cultures," *Proc. Int. Symp. Contr. Rel. Bioact. Mater.* 20, 242–243 (1993).
21. J. Jacobsen et al., "TR146 Cells Grown on Filters as a Model for Human Buccal Epithelium: I. Morphology, Growth Properties, and Permeability," *Int. J. Pharm.* 125, 165–184 (1995).
22. J. Jacobsen et al., "TR146 Cells as a Model for Human Buccal Epithelium: II. Optimisation and Use of a Cellular Sensitivity MTS/PMS assay," *Int. J. Pharm.* 141, 217–225 (1996).
23. J. Jacobsen et al., "Filter-Grown TR146 Cells as an In Vitro Model of Human Buccal Epithelial Permeability," *Eur. J. Oral Sci.* 107, 138–146 (1999).
24. H.M. Nielsen and M.R. Rassing, "TR146 Cells Grown on Filters as a Model of Human Buccal Epithelium: III. Permeability Enhancement by Different pH Values, Different Osmolality Values, and Bile Salts," *Int. J. Pharm.* 185, 215–225(1999).
25. H.M. Nielsen et al., "TR146 Cells Grown on Filters as a Model of Human Buccal Epithelium: Permeability of Fluorescein Isothiocyanate-Labelled DexTrans in the Presence of Sodium Glycocholate." *J. Controlled Release* 60, 223–233 (1999).
26. A.H. Beckett and E.J. Triggs, "Buccal Absorption of Basic Drugs and Its Application as an In Vivo Model of Passive Drug Transfer through Lipid Membranes," *J. Pharm. Pharmacol.* 19 (Suppl.), 31S–41S (1967).
27. W. Schurmann and P. Turner, "Membrane Model of the Human Oral Mucosa as Derived from Buccal Absorption Performance and Physicochemical Properties of the Beta-Blocking Drugs Atenolol and Propranolol," *J. Pharm. Pharmacol.* 30, 137–147 (1978).
28. I.G. Tucker, "A Method to Study the Kinetics of Oral Mucosal Drug Absorption from Solutions," *J. Pharm. Pharmacol.* 40, 679–683 (1988).
29. C.L. Barsuhn et al., "Human Buccal Absorption of Flubriprofen," *Clin. Pharmacol. Ther.* 44, 225–231 (1988).
30. I. Gonzalez-Younes et al., "Absorption of Flubriprofen through Human Buccal Mucosa," *J. Pharm. Sci.* 80, 820–823 (1991).
31. L. Benes et al., "Plasma Melatonin (M) and Sulfatoxymelatonin (aMT6s) Kinetics after Transmucosal Administration to Humans," in *Melatonin and the Pineal Gland — From Basic Science to Clinical Application,* Y. Touitou et al., Eds. (Elsevier Science Publishers B.V., Amsterdam, 1993), pp. 347–350.

32. R.L.McQuinn et al., "Sustained Oral Mucosal Delivery in Human Volunteers of Buprenorphine from Thin Non-eroding Mucoadhesive Polymeric Disks," *J. Controlled Release* 34, 243–250 (1995).
33. L. Benes et al., "Transmucosal, Oral Controlled-Release, Transdermal Drug Administration in Human Subjects: A Crossover Study with Melatonin," *J. Pharm. Sci.* 86 (10), 1115–1119 (1997).
34. M.M. Veillard et al., "Preliminary Studies of Oral Mucosal Delivery of Peptide Drugs," *J. Controlled Release* 6, 123–131 (1987).
35. H. Yamahara and V.H. Lee, "Drug Metabolism in the Oral Cavity," *Adv. Drug Del. Rev.* 12, 25–39 (1993).
36. B.J. Aungst and N.J. Rogers, "Comparison of the Effects of Various Transmucosal Absorption Promoters on Buccal Insulin Delivery," *Int. J. Pharm.* 53, 227–235 (1989).
37. I.A. Siegel and H.P. Gordon, "Surfactant-Induced Increase of Permeability of Rat Oral Mucosa to Non-electolytes In Vivo," *Arch. Oral Biol.* 30 (1), 43–47 (1985).
38. Y. Kurosaki et al., "Enhanced Permeability of Keratinized Oral Mucosa to Salicylic Acid with 1-Dodecylacycloheptan-2-one (Azone). In Vitro Studies in Hamster Cheek Pouch," *Int. J. Pharm.* 49, 47–55 (1989).
39. Y. Kurosaki et al., "Effects of Surfactants on the Absorption of Salicylic Acid from Hamster Cheek Pouch as a Model of Keratinized Oral Mucosa," *Int. J. Pharm.* 47, 13–19 (1988).
40. M. Tanaka et al., "Absorption of Salicylic through the Oral Mucous Membrane of Hamster Cheek Pouch," *Chem. Pharm. Bull.* 28 (4), 1056–1061 (1980).
41. C.K. Oh and W.A. Ritschel, "Biopharmaceutic Aspects of Buccal Absorption of Insulin," *Meth. Find Exp. Clin. Pharmacol.* 12 (3), 205–212 (1990).
42. I.A. Siegel et al., "Mechanisms of Non-electrolyte Penetration across Dog and Rabbit Oral Mucosa In Vitro," *Arch. Oral Biol.* 26, 357–361 (1981).
43. M.E. Dowty et al., "Enzyme Characterization Studies on the Rate-Limiting Barrier in Rabbit Buccal Mucosa," *Int. J. Pharm.* 88, 293–302 (1992).
44. C.A. Squier and P.W. Wertz, "Structure and Function of the Oral Mucosa and Implications for Drug Delivery," in *Oral Mucosal Drug Delivery,* M.J. Rathbone, Ed. (Marcel Dekker, New York, Vol. 74, 1996), pp. 1–26.
45. M. Mehta et al., "In Vitro Penetration of Tritium-Labelled Water (THO) and [3H]PbTx-3 (a red tide toxin) through Monkey Buccal Mucosa and Skin," *Toxicol. Lett.* 55, 185–194 (1991).
46. V. Kataja and A. Yap, "Combination of Cisplatin and Interferon-α2a (Roferon-A) in Patients with Non-Small Cell Lung Cancer (NSCLC). An Open Phase II Multicenter Study," *Eur. J. Cancer* 31A, 35–40 (1995).
47. M. Ishida et al., "New Mucosal Dosage Form of Insulin," *Chem. Pharm. Bull.* 29 (3), 810–816 (1981).
48. A.J. Hoogstraate et al., "Buccal Delivery of Fluorescein Isothiocyanate-Dextran 4400 and the Peptide Drug Buserelin with Glycodeoxycholate as an Absorption Enhancer in Pigs," *J. Controlled Release* 41, 77–84 (1996).
49. C.A. Lesch et al., "The Permeability of Human Oral Mucosa and Skin to Water," *J. Dent. Res.* 68, 1345–1349 (1989).
50. A.J. Hoogstraate et al., "Effects of Bile Salts on Transport Rates and Routes of FTIC-Labelled Compounds across Porcine Buccal Epithelium In Vitro. *J. Controlled Release* 40, 211–221 (1996).
51. E. Quadros et al., "Buccal and Colonic Absorption of CGS 16617, A Novel ACE Inhibitor," *J. Controlled Release* 19, 77–86 (1991).
52. C.A. Squier and B.K. Hall, "The Permeability of Skin and Oral Mucosa to Water and Horseradish Peroxidase as Related to the Thickness of the Permeability Barrier," *J. Invest. Dermatol.* 84 (176–179) (1985).
53. A.J. Hoogstraate et al., "Diffusion Rates and Transport Pathways of FITC-Labelled Model Compounds through Buccal Epithelium," *Proc. Int. Symp. Contr. Rel. Bioact. Mater.* 20, 234–235 (1993).
54. A.J. Hoogstraate et al. "Diffusion Rates and Transport Pathways of FITC-Labelled Model Compounds through Buccal Epithelium," *Pharm. Res.* 9, S-188 (1992).
55. C.A. Squier et al., "Lipid Content and Water Permeability of Skin and Oral Mucosa," *J. Invest. Dermatol.* 96 (1), 123–126 (1991).
56. P. Collins et al., "Comparative Study of Porcine Oral Epithelium. *J. Dent. Res.* 60(A), 543 (1981).
57. A.H. Shojaei and X. Li, "In Vitro Permeation of Acyclovir through Porcine Buccal Mucosa," *Proc. Int. Symp. Contr. Rel. Bioact. Mater.* (Vol. 23) (Controlled Release Society, 1996) pp. 507–508.
58. A.H. Shojaei and X. Li, "Determination of Transport Route of Acyclovir across Buccal Mucosa," in *Proc. Int. Symp. Contr. Rel. Bioact. Mater.* (Vol. 24) (Controlled Release Society, 1997) pp. 427–428.
59. A.M. Manganaro and P.W. Wertz, "The Effects of Permeabilizers on the In Vitro Penetration of Propranolol through Porcine Buccal Epithelium. *Mil. Med.* 161 (11), 669–672 (1996).
60. R. Gandhi and J. Robinson, "Mechanisms of Penetration Enhancement for TransBuccal Delivery of Salicylic Acid," *Int. J. Pharm.* 85, 129–140 (1992).
61. G.J.M. Wolany et al., "Buccal Absorption of Sandostatin (octreotide) in Conscious Beagle Dogs," *Proc. Int. Symp. Contr. Rel. Bioact. Mat.* 17, 224–225 (1990).
62. S. Nakane et al., "Oramucosal Delivery of LHRH: Pharmacokinetic Studies of Controlled and Enhanced Transmucosal Permeation," *Pharm. Dev. Technol.* 20 (3), 251–259 (1996).
63. A. Steward et al., "The Effect of Enhancers on the Buccal Absorption of Hybrid (BDBB) Alpha-Interferon," *Int. J. Pharm.* 104, 145–149 (1994).
64. S. Senel et al., "Enhancement of In Vitro Permeability of Porcine Buccal Mucosa by Bile Salts: Kinetic and Histological Studies," *J. Contr. Rel.* 32, 45–56 (1994).
65. B.J. Aungst and N.J. Rogers, "Site Dependence of Absorption-Promoting Actions of Laureth-9, Na Salicylate, Na2EDTA, and Aprotinin on Rectal, Nasal, and Buccal Insulin Delivery," *Pharm. Res.* 5 (5), 305–308 (1988).
66. J. Zhang et al., "An In Vivo Dog Model for Studying Recovery Kinetics of the Buccal Mucosa Permeation Barrier after Exposure to Permeation Enhancers: Apparent Evidence of Effective Enhancement without Tissue Damage," *Int. J. Pharm.* 101, 15–22 (1994).
67. B.J. Aungst, "Site Dependence and Structure-Effect Relationships for Alkylglycosides as TransMucosal Absorption Promoters for Insulin," *Int. J. Pharm.* 105, 219–225 (1994).
68. N.A. Peppas and P.A. Buri, "Surface, Interfacial and Molecular Aspects of Polymer Bioadhesion on Soft Tissues," *J. Contr. Rel.* 2, 257–275 (1985).
69. H.S. Ch'ng et al., "Bioadhesive Polymers as Platforms for Oral Controlled Drug Delivery II: Synthesis and Evaluation of Some Swelling, Water-Insoluble Bioadhesive Polymers," *J. Pharm. Sci.* 74 (4), 399–405 (1985).
70. R.E. Gandhi and J.R. Robinson, "Bioadhesion in Drug Delivery," *Indian J. Pharm. Sci.* 50 (May/June), 145–152 (1988).
71. S.S. Leung and J.R. Robinson, "Polymer Structure Features Contributing to Mucoadhesion: II," *J. Contr. Rel.* 12, 187–194 (1990).
72. Y.D. Sanzgiri et al., "Evaluation of Mucoadhesive Properties of Hyaluronic Acid Benzyl Esters," *Int. J. Pharm.* 107, 91–97 (1994).
73. C.M. Lehr et al., "In Vitro Evaluation of Mucoadhesive Properties of Chitosan and Some Other Natural Polymers," *Int. J. Pharm.* 78, 43–48 (1992).
74. K. Park and J.R. Robinson, "Bioadhesive Polymers as Platforms for Oral Controlled Drug Delivery: Method to Study Bioadhesion," *Int. J. Pharm.* 19, 107–127 (1984).
75. T. Nagai and Y. Machida, "Buccal Delivery Systems Using Hydrogels," *Adv. Drug Del. Rev.* 11, 179–191 (1993).
76. S. Anlar et al., "Formulation and In Vitro–In Vivo Evaluation of Buccoadhesive Morphine Sulfate Tablets," *Pharm. Res.* 11 (2), 231–236 (1994).
77. R. Anders and H. Merkle, "Evaluation of Laminated Mucoadhesive Patches for Buccal Drug Delivery," *Int. J. Pharm.* 49, 231–240 (1989).
78. J.-H. Guo, "Investigating the Surface Properties and Bioadhesion of Buccal Patches," *J. Pharm. Pharmacol.* 46, 647–650 (1994).
79. R. Anders et al., "Buccal Absorption of Protirelin: An Effective Way to Stimulate Thyrotropin and Prolactin," *J. Pharm. Sci.* 72, 1481–1483 (1983).

80. A.H. Shojaei and X. Li, "Novel Copolymers of Acrylic Acid and Polyethylene Glycol Monomethylether Monomethacrylate for Buccal Mucoadhesion: Preparation and Surface Characterization," *Pharm. Res.* 12 (S1) (9), S210 (1995).
81. X. Li and A.H. Shojaei, "Novel Copolymers of Acrylic Acid and Polyethylene Glycol Monomethylether Monomethacrylate for Buccoadhesion: In Vitro Assessment of Buccoadhesion and Analysis of Surface Free Energy," *Proc. Int. Symp. Contr. Rel. Bioact. Mater.* 23, 165–166 (1996).
82. A.H. Shojaei and X. Li, "Mechanisms of Buccal Mucoadhesion of Novel Copolymers of Acrylic Acid and Polyethylene Glycol Monomethylether Monomethacrylate," *J. Contr. Rel.* 47 (2), 151–161 (1997).
83. A.H. Shojaei et al., "TransBuccal Delivery of Acyclovir (I): In Vitro Determination of Routes of Buccal Transport," *Pharm. Res.* 15 (8), 1182–1188 (1998).
84. J.P. Cassidy et al., "Controlled Buccal Delivery of Buprenorphine," *J. Contr. Rel.* 25, 21–29 (1993).
85. G. De Grande et al., "Specialized Oral Mucosal Drug Delivery Systems: Patches, in *Oral Mucosal Drug Delivery* (Vol. 74), M.J. Rathbone, Ed. (Marcel Dekker, New York, 1996), pp. 285–318.
86. K. Yukimatsu et al., "Development of a Transmucosal Controlled-Release Device for Systemic of Antianginal Drugs Pharmacokinetics and Pharmacodynamics," *Drug Dev. Ind. Pharm.* 20 (4), 503–534 (1994).
87. Y. Nozaki et al., "Transmucosal Controlled Systemic Delivery of Isosorbide Dinitrate: In Vivo/In Vitro Correlation," *J. Contr. Rel.* 43, 105–114 (1997).
88. H.H. Alur et al., "Evaluation of a Novel, Natural Oligosaccharide Gum as a Sustained-Release and Mucoadhesive Component of Calcitonin Buccal Tablets," *J. Pharm. Sci.* 88 (12), 1313–1319 (1999).
89. Y. Kurosaki et al., "Enhancing Effect of 1-Dodecylazacycloheptan-2-one (Azone) on the Absorption of Salicyclic Acid from Keratinized Oral Mucosa and the Duration of Enhancement In Vivo," *Int. J. Pharm.* 51, 47–54 (1989).
90. I.A. Siegel and H.P. Gordon, "Effects of Surfactants on the Permeability of Canine Oral Mucosa In Vitro," *Toxicol. Lett.* 26, 153–157. (1985).
91. A. Coutel-Egros et al., "Combined Effects of pH, Cosolvent and Penetration Enhancers on the In Vitro Buccal Absorption of Propranolol through Excised Hamster Cheek Pouch," *Int. J. Pharm.* 84, 117–128 (1992).
92. A.H. Shojaei et al., "Transbuccal Permeation of a Nucleoside Analog, Dideoxycytidine: Effects of Menthol as a Permeation Enhancer," *Int. J. Pharm.* 192 (2), 139–146 (1999).
93. K. Satoh et al., "Factors Affecting the Bioadhesive Property of Tablets Consisting of Hydroxypropyl Cellulose and Carboxyvinyl Polymer," *Chem. Pharm. Bull.* 37, 1366–1368 (1989).
94. A. Gupta et al., "Interpolymer Complexation and Its Effect on Bioadhesion Strength and Dissolution Characteristics of Buccal Drug Delivery Systems," *Drug Dev. Ind. Pharm.* 20 (3), 315–325 (1994).
95. K. Watanabe et al., "Drug Release Behaviors from Hydrogel Prepared with Water Soluble Dietary Fibers," *J. Pharm. Sci. Technol. Jpn.* 51, 29–35 (1991).
96. T. Nguyen-Xuan et al., "Mucoadhesive Semisolid Formulations for Intraoral Use Containing Sucralfate," *Eur. J. Pharm. Biopharm.* 43 (2), 133–137 (1996).
97. M. Nair and Y.W. Chien, "Development of Anticandidal Delivery Systems: (II) Mucoadhesive Devices for Prolonged Drug Delivery in the Oral Cavity," *Drug Dev. Ind. Pharm.* 22 (3), 243–253 (1996).
98. B. Taylan et al., "Design and Evaluation of Sustained-Release and Buccal Adhesive Propranolol Hydrochloride Tablets," *J. Contr. Rel.* 38, 11–20 (1996).
99. J. Voorspoels et al., "Buccal Absorption of Progesterone in the Dog," *Proc. Int. Symp. Contr. Rel. Bioact. Mater.* 24, 185–186 (1997).
100. A.H. Shojaei, et al., "Evaluation of Poly(acrylic acid-co-ethylhexyl acrylate) Films for Mucoadhesive Transbuccal Drug Delivery: Factors Affecting the Force of Mucoadhesion," *J. Contr. Rel.* 67 (2/3), 223–232 (2000). **PT**