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Mucosa as a route for systemic drug delivery

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ABSTRACT

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. 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 relatively permeable. The objective of this article is to review mucosa as a route for drug delivery by discussing the structure and environment of the oral mucosa and materials used for oral permeation enhancers.

Keywords: Mucosa, Buccal delivery, Permeation enhancers.

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INTRODUCTION

The mucosa is considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vagina, ocular and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages includes possible bypass of the first pass effect, avoidance of presystemic elimination of gastro intestinal 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 (Aungst, 1988, Aungst and Rogers 1988, Lee, 1990, Tengamunuay, 1990, Shao, 1992, Shao, 1994 and Soyani, 1996), and the route has already reached commercial status with several drugs including calcitonin((Dal Negra et al., 1991 and Ploskar, 1996). However, the potential irritation and irreversible damage to the ciliary action application of nasal dosage forms, as well as the large intra and inter subject variability in mucus secretion in the nasal mucosa could significantly effect drug absorption from this site. Even through the rectal, vaginal and ocular mucosa 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 (Rathbone, 1991 and De Vries et al., 1991), and the virtual lack of langerhans cells makes the oral mucosa tolerant to potential allergies. Furthermore, oral transmucosal drug delivery bye pass first pass effect and avoids pre-systemic elimination in the gastro intestinal tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery (Lee 1990). 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 mucosal membrane lining the cheeks (buccal mucosa) and,
iii). Local delivery which is drug delivery into the oral cavity.

Overview of oral mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a laminar 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 miotically active basal layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium (Gandhi, 1988). 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 (Harris, 1988), 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 500-800µm, while the mucosal thickness of the hard and soft plates, 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 the areas of subject to mechanical stress (the gingivae and hard plate) are keratinized similar to the epidermis. The mucosae of the soft plate, the sublingual and the buccal regions, however are not keratinized. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. The epithelia are relatively impermeable to the water. In contrast, non-keratinised epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amount of ceramide. They also contain small amount of neutral but polar lipids, mainly cholesterol sulphate and glucosyl ceramides. These epithelia have been found to be considerable more permeable to watch than keratinzed epithelia (Wertz, 1991).

Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater that that of the skin (Aungst, 1989). 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 mucosa. In general the permeabilities of the oral mucosa decrease in order of sublingual greater than buccal and buccal greater than palatal. This rank order is passed on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosae being relatively thin and non-keratinizes, 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) (Gandhi, 1994). When cells go through differentiation, membrane coating granules 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. The barrier exists in the outer most 200µm of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase and lanthum nitrate (Squier, 1984 and Hill, 1979). When applied to the outer surface of the epithelium, these tracers penetrate only through the outermost layer or two of cells when applied to the submucosal surface they permeate upto, but not into the outer most cell layer of the epithelium. Accordingly to these results, it seems apparent that flattened surface cells present the main barrier to permeation, while the more isodiametric cell layers are relatively permeable to both keratinized and nonkeratinized

epithelia, keratinization by itself is not expected to play a significant role in the barrier function. The components of the MCG's in keratinized and non-keratinized epithelia are different, however the MCG's of keratinized epithelium are composed of lamellar lipid stacks, whereas the non-keratinised epithelia include sphingomyelin, glucosylceramides, ceramides and other nonpolar lipids however for non-keratinized epithelia, the major MCG's lipid component are glycophingolipids (Bodde, 1990). Aside from the present some resistance to permeation as well, however the outer epithelium still considered to be the rate limiting step to mucosal penetration. The structure of the basement membrane is not dense enough to exclude relatively large molecules.

Environment

The cells of the oral epithelia are surrounded by an inter cellular ground substance mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be force of association or some may be attached to certain regimes on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as lubricant, allowing cells to move relative to one another (Tabak, 1982). Align the same lines the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems. In stratified squamous epithelia found elsewhere in the body, mucus is secreted by the major and minor salivary glands as a part of saliva. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands (Rathbone, 1994). At physiological pH the mucus network carries a negative charge (due to sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH mucus can form a strong cohesive gel structure that will bind to the epithelial cell surface as gelatinous layer (Gandhi, 1988). The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high 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 in this water rich environment of the oral cavity.

Buccal route of oral 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, lipophillic compounds would have low solubilities in this environment. The cell membrane, however is rather lipophillic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophillic compound 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 routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.

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Buccal mucosa as a site of drug delivery

There are different categories of drug delivery within the oral cavity (i.e sublingual, buccal, local drug delivery) selecting one over another is mainly based on anatomical and permeability difference that exist among the various oral mucosal sites. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailabilities of many drugs, and it is convenient, accessible and generally well accepted (Harris, 1988). The sublingual routes is by far the most widely studies of these routes. Sublingual dosage forms are of two different designs, those composed of rapidly disintegrating tablets and those consisting of soft gelatin capsular filled with liquid drug. Such system creates a very high concentration in the sublingual region before they are systematically absorbed across the mucosa. The buccal mucosa is consisting 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 both aches, periodontal disease, bacterial and fungal infections, aphthous and dental stomatitis and in facilitating tooth movements with prostoglandins (Nagai, 1985 and Nagai, 1993).

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 rapid onset of action making it appropriate for drugs with short delivery period requirements with infrequent dosage 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[13, 16]. First difference being in the permeability characteristic 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 for retention systems used for oral transmucosal drug delivery. Thus the buccal mucosa more appropriate for sustained delivery applications, delivery of less permeable molecular, 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 used as buccal penetration enhancers in order to increase the flux of drugs through the mucosa (shown in 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 absorption mucosa have been shown to work in improving buccal drug penetration (Gandhi, 1992).

Studies undertaken as buccal as a route of drug delivery

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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, ionizable low molecular weight drugs such as acyclovir, propranolol and sailicylic acid, large molecular weight hydrophilic polymers such as dextrans and a variety of peptides including octreotide, leutinizing hormone releasing harmone (LHRH), insulin and a interferon have all been studied.

A series of studies on buccal permeation of burselin and fluorescein isothiocynate (FITC) (Gandhi, 1992 and Hoostraate etal., 1996), labeled dextrans reported the enhancing effects of dihydroxy and trihydroxy bile salts on buccal permeation. Their results showed that in the presence of 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 labeled dextrans by sodium glycocholate (SGA) was shown to be concentration dependent. Below 10 mm sodium glycocholate, buccal permeation was increased by increasing the intercellular transport and at 10mm and higher concentrations by opening up a transcellular route.

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

23-lauryl ether (Oh, 1990)	Lauric acid (Gandhi, 1992)	Sodium EDTA (Aungst, 1988)
Aprotinin(Aungst, 1988)	Lysophosphatidylcholine (Manganaro, 1996)	Sodium glycocholate (Aungst, 1988)
Azone (Kurosaki et al., 1988)	Menthol(Zhang et al., 1994)	Sodium glycodeoxycholate (Shojaei, 1996)
Benzalkonium chloride (Siegel, 1985)	Methoxysalicylate(Shojaei, 1996)	Sodium lauryl sulfate (Aungst, 1988)
Cetylpyridinium chloride (Kurosaki et al., 1988)	Methyloleate (Manganaro, 1996)	Sodium salicylate (Aungst, 1988)
Cetyltrimethylammonium bromide (Steward, 1994)	Oleic acid (Senel et al., 1994)	Sodium taurocholate(Shojaei, 1996)
Cyclodextrin (Coutel etal., 1992)	Phosphatidylcholine(Zhang et al., 1994)	Sodium taurodeoxycholate (Manganaro, 1996)
Dextran sulfate(Shojaei, 1996)	Polyoxyethylene (Shojaei, 1996)	Sulfoxides (Gandhi, 1992)
Lauric acid(Zhang et al., 1994)	Polyoxyethylene(Shojaei, 1996)	Various alkyl glycosides (Aungst, 1994)

Related research on muco –adhension polymers and delivery systems were done using various bioadhesion polymers and with respect to invistigation objectives given in Table-2

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Table 2. Related research on mucoadhesive polymers and delivery systems

Bioadhesive polimer(s) Studied	Investigation Objectives
HPC and CP	Preferred mucoadhesive strength on CP, HPC and HPC-CP combination (Satoh etal., 1989)
HPC and CP	Measured Bioadhesive property using mouse peritoneal membrane (Ishida etal., 1981)
CP, HPC, PVP and CMC	Studied inter polymer complexation and its effects on bioadhesive strength (Gupta, 1994)
CP and HPMC	Formulation and evaluation of buccoadhesive controlled release delivery systems (Anlar etal, 1994)
HPC, HEC, PVP and PVA	Tested mucosal adhesion on patches with two –ply laminates with an impermeable backing layer and hydrocolloid polymer layer (Anders, 1989)
HPC and CP	Used HPC-CP powder as peripheral base for strong adhesion and HPC-CP freeze dried mixture as core base (Ishida, 1982)
CP, PIP and PIB	Used a tow roll milling method to prepare a new bioadhesive patch formulation (Guo, 1994)
Xanthan gum and Locust bean gum	Hydrogel formation by combination of natural gums (Watanbe etal., 1991)
Chitosan, HPC, CMC, Pectin, Xanthan and Polycarbophil	Evaluated mucoadhesive properties by routinely measuring the detachment force from pig intestinal mucosa (Lehr, 1992)
Hyaluronic acid, Benzyl esters, Polycarbophil and HPMC	Evaluate mucoadhesive properties (Sanzgiri etal., 1994)
Hydroxyethylcellulose	Design and synthesis of a bilayer patch (polyef-disk) for thyroid gland diagnosis (Anders, 1983)
Polycarbophil	Design of a unidirectional buccal patch for oral mucosal delivery of peptide drugs (Veillard, 1987)
Poly(acrylic acid and Poly (methacrylic acid)	Synthesized and evaluated crosslinked polymers differing in charge densities and hydrophobicity (Ch'ng, 1985)
Number of Polymers including HPC, HPMC, CP, CMC	Measurement of bioadhesive potential ad derive meaningful information on the structural requirement for bioadhesion (Park, 1984)
Poly(acrylic acid-co-acrylamide)	Adhesion strength to the gastric mucus layer as a function of cross linking agent, degree of swelling, and carboxyl group density (Park, 1987)
Poly(acrylic acid)	Effects of PAA molecular weight and crosslinking concentration on swelling and drug release characteristics (Garcia etal., 1993)
Poly(acrylic acid-co-methyl methaacrylate)	Effects of polymer structural features on mucoadhesion (Leung, 1988)
Poly(acrylic acid-co-butylacrylate)	Relationships between structure and adhesion for mucoadhesive polymers (Squier, 1991)
HEMA copolymerized with Polymeg® (Polytetramethylene glycol)	Bioadhesive buccal hydrogel for controlled release delivery of buprenorphine (Cassidy, 1993)
Cydot® by 3M (biopolymeric blend of CP and PIB)	Patch system for buccal mucoadhesive drug delivery (De Grande etal., 1996)
Formulation consisting of PVP, CP and Cetylpyridinium chloride (as stabilizer)	Device for oral mucosal delivery of LHRH-device containing a fast release and slow release layer(Nakane,

	1996)
CMC, Carbopol 974P, Carbopol EX-%%, Pectin (low viscosity), Chitosan chloride	Mucoadhesive gels for intraoral delivery (Nguyen etal., 1996)
CMC, CP, Polyethylene oxide, Polymethyl vinyl ester/Maleic anhydride (PME/MA) and Tragacanth	Buccal mucoadhesive device for controlled release anticandidal device – CMCtablets yielded the highest adhesive force (Nair, 1996)
HPMC and Polycarbophil (PC)	Buccal mucoadhesive tablets with optimum blend ratio of 80:20 PC to HPMC yielding the highest force of adhesion (Taylan et al., 1996)
PVP, Poly(acrylic acid)	Transmucosal controlled delivery of isosorbide dinitrate (Yukimatsu, 1994)
Poly(acrylic acid-co-poly ethylene glycol) copolymer of acrylic acid and poly ethylene glycol, monomethylether monomethacrylate	To enhance the mucoadhesive properties of PAA for buccal mucoadhesive drug delivery (Shojaei, 1995)
Poly acrylic acid and poly ethylene glycol	To enhance mucoadhesive properties of PAA by interpolymer complexation through template polymerization (Choi et al., 1997)
Drum dried waxy maize starch (DDWM), Carbopol 974P and sodium stearyl fumarate	Bioadhesive erodible buccal tablet for progesterone delivery (Voorspoels, 1997)

CP-Carbopol 934P, HPC-Hydroxy propyl cellulose, PVP-Poly(vinyl pyrolidone), CMC-Sodium carboxy methyl cellulose, HPMC_Hydroxy propyl methyl cellulose, HEC-Hydroxy ethyl cellulose, PVA- Poly(vinyl alcohol), PIB-Poly(isobutylene) and PIP-Poly(isoprene).

CONCLUSION

The buccal mucosa offers several advantages for controlled drug delivery for extended period 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 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 delivery is a promising area for continued research with the aim of systemic delivery at orally inefficient drugs as well as feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. However, the need for safe and effective buccal permeation and absorption enhancers would be a crucial component for a prospective future in the area of buccal drug delivery system.

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