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AN OVERVIEW OF BUCCAL MUCOSA AS A SITE FOR DRUG DELIVERY

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ABSTRACT

The oral mucosae in general are 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. 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. More over buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer the drug to patients who cannot be dosed orally to prevent accidental swallowing.

Keywords: Pre-systemic elimination, non-invasive delivery, permeability.

1. 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.

I. 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].

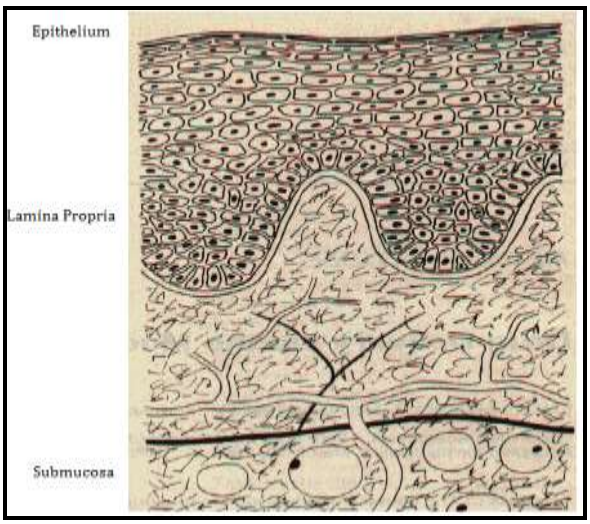

Figure 1: Structure of the oral mucosae [18].

B. Permeability

The oral mucosae in general are 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 200µm 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.

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II. 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.

III. 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 [26-30], 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 [11], large molecular weight hydrophilic polymers such as dextrans [12], and a variety of peptides including octreotide [23], leutinizing hormone releasing hormone (LHRH) [24], insulin [36], and a-interferon [25] have all been studied.

A series of studies [12-22] 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 [27]. 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 [21] 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.

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Table 1: List of compounds used as oral mucosal permeation enhancers [25-34]

Permeation Enhancer
23-lauryl ether
Aprotinin
Azone
Benzalkonium chloride
Cetylpyridinium chloride
Cetyltrimethylammonium bromide
Cyclodextrin
Dextran sulfate
Lauric acid
Lauric acid/Propylene glycol
Lysophosphatidylcholine
Menthol
Methoxysalicylate
Methyloleate
Oleic acid
Phosphatidylcholine
Polyoxyethylene
Polysorbate 80
Sodium EDTA
Sodium glycocholate
Sodium glycodeoxycholate
Sodium lauryl sulfate
Sodium salicylate
Sodium taurocholate
Sodium taurodeoxycholate
Sulfoxides
Various alkyl glycosides

The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal drug delivery involves administration of desired drug through buccal mucosal membrane lining the oral cavity. The mucosal lining of oral cavity offers some distinct advantages. The buccal mucosa is highly vascularized and more accessible for the administration and removal of dosage form. However, advantages of buccal route include rapid cellular recovery and achievement of a localized site on the smooth surface of buccal mucosa. Moreover a significant reduction in dose can be achieved.

CONCLUSION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration problems such as high first pass metabolism, drug degradation in harsh gastro intestinal environment can be circumvented by administering a drug via buccal route. More over buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity.

It is also possible to administer the drug to patients who cannot be dosed orally to prevent accidental swallowing.

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