

Drug permeation enhancement via buccal route: possibilities and limitations

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Abstract

Over the last decade, there has been a particular interest in delivering drugs, especially peptides and proteins via the buccal route. It provides direct entry into the systemic circulation thus avoiding the hepatic first-pass effect and degradation in the gastrointestinal tract, ease of administration, and the ability to terminate delivery when required. However membrane permeation can be a limiting factor for many drugs administered via the buccal route, and the epithelium that lines the oral mucosa is a very effective barrier to the absorption of drugs. In order to deliver broader classes of drugs across the buccal mucosa, reversible methods of reducing the barrier potential of this tissue must be employed. This requisite has fostered the study of penetration enhancers that will safely alter the permeability restrictions of the buccal mucosa. It has been shown that buccal penetration can be improved by using various classes of transmucosal and transdermal penetration enhancers such as bile salts, surfactants, fatty acids and derivatives, chelators, cyclodextrins and chitosan. Among these chemicals used for the drug permeation enhancement, bile salts are most common. The first part of this paper focuses on work related to the elucidation of mechanisms of action of bile salts in buccal permeation enhancement of various drugs and mucosal irritation. In the second part, results showing the enhancing effect of chitosan on buccal permeation of hydrocortisone, a commonly used topical oral anti-inflammatory agent, and transforming growth factor beta (TGF- β), which is a bioactive peptide to which the oral mucosa is relatively impermeable is presented. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Buccal; Bile salts; Chitosan; TGF- β ; Hydrocortisone; Morphine; Penetration enhancement

1. Introduction

For many drugs, especially peptides and proteins, the buccal route offers many advantages over conventional routes of delivery with an improved bio-

availability due to the avoidance of degradation in the gastrointestinal tract and hepatic first-pass metabolism. Excellent accessibility, high patient acceptance and compliance, and robustness can be given as the attractive features of buccal mucosa [1]. How-

Abbreviations: EDTA, ethylenediamine tetraacetic acid; FITC, fluorescein isothiocyanate; GC, sodium glycocholate; GDC, sodium glycodeoxycholate; LPC, lysophosphatidylcholine; MPH, morphine hydrochloride; PBS, phosphate buffer solution; SC, sodium cholate; SDC, sodium deoxycholate; STDHF, sodium taurodihydrofusidate; TC, sodium taurocholate; TDC, sodium taurodeoxycholate; TmTs, transmucosal therapeutic system

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ever, the permeability barrier in the buccal mucosa still remains as a major limitation to delivery of drugs via this route. Therefore, new strategies are needed to be developed to enhance the drug permeation.

One generalized approach to overcome the barrier properties of the buccal mucosa for drugs is the incorporation of chemical compounds into the buccal drug delivery systems. Substances that help to promote drug permeation through the buccal epithelium are referred to as penetration enhancers, permeation promoters or absorption enhancers [2]. The chemicals used as penetration enhancers ideally should be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic [3]. In addition, the tissue should revert to its normal integrity and barrier properties upon removal of the chemical. Penetration enhancers can be divided into many categories according to their structure, mechanism of action, and the type of drugs whose permeation they enhance. Most of the compounds used as buccal mucosal penetration enhancers are the ones generally used to compromise barrier function. Table 1 provides an overview of some of the different chemical classes that have been used, with examples of materials and the proposed mechanisms of action.

In fact there has been little work done that is targeted specifically to the oral mucosa and in contrast to skin a clearly defined structure/effect relationship has not yet been established for buccal mucosal enhancers. Enzyme inhibitors, the description of which are precluded due to the brevity of the current article, have also been shown to enhance buccal permeation.

The permeability of buccal epithelium and the efficacy of penetration enhancers have been investigated in numerous in vivo and in vitro models. Various kinds of diffusion cells including continuous flow perfusion chambers, Ussing chambers, Franz cells, Grass–Sweetana cells have been used in which buccal mucosa is mounted [4–6]. Cultured epithelial cell lines have been developed as an in vitro model for studying drug transport and metabolism at biological barriers as well as to elucidate the possible mechanisms of action of penetration enhancers [7]. In vivo study of the effects of penetration enhancers is usually performed by administering the drugs noninvasively with or without a penetration enhancer. A full literature review of in vivo studies on buccal mucosal absorption of drugs reported within the last decade was just recently given by Squier et al. [8]. In Table 2, studies on peptide/protein drugs where penetration enhancers were used are given.

Table 1
Mucosal penetration enhancers and mechanisms of action

Classification	Examples	Mechanism
Surfactants	Anionic: sodium lauryl sulfate, sodium laurate Cationic: cetylpyridinium chloride Nonionic: poloxamer, Brij, Span, Myrj, Tween Bile salts: sodium glycodeoxycholate, sodium glycocholate, sodium taurodeoxycholate, sodium taurocholate Azone®	Perturbation of intercellular lipids, protein domain integrity
Fatty acids	Oleic acid, caprylic acid	Increase fluidity of phospholipid domains
Cyclodextrins	α-, β-, γ-cyclodextrin, methylated β-cyclodextrins	Inclusion of membrane compounds
Chelators	EDTA, sodium citrate Polyacrylates	Interfere with Ca ²⁺
Positively charged polymers	Chitosan, trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface
Cationic compounds	Poly-L-arginine, L-lysine	

Table 2

In vivo studies on buccal absorption of peptide/protein drugs

Drug	Model	Penetration enhancer	Results	Ref.
Insulin	Dog	GC (10% in the core)	0.5% (RB)	[9]
	Rabbit	No enhancer	12% (AB)	[10]
	Rat	No enhancer;	No significant	[11]
		Associated with erythrocyte-ghosts and liposome vesicles	therapeutic effect	
	Dog	No enhancer	No effect	[12]
Octreotide Acetate		TC (3%)	Decrease in glucose levels	
		LPC (2%)		
	Rat	EDTA (3%)+3% SC	Increase in bioavailability	[13]
		TC (3%)	Azone>EDTA+SC>	
		GC (3%)	Bacitracin	
		TDC (3%)	No enhancing effect	
		STDHF (3%)	with TC, GC, TDC, STDHF	
		EDTA (3%)		
		Bacitracin (3%)		
		Azone (3%)		
Recombinant human interferon-alpha B/D hybrid			Azone>SC> EDTA+TC>SC	
	Rat	No enhancer	0.05% (RB)	[14]
	Rabbit	No enhancer	0.05% (RB)	
	Dog	SC (5%)	Higher bioavailability	[15]
		SDC (5%)	SDC>SC>TC>TDC	
Buserelin		TC (5%)		
		TDC (5%)		
	Pig	No enhancer	1.8% (AB)	[16]
Luteinizing hormone-releasing hormone		GDC (10 mM)	12.7%	
	Dog	No enhancer	100% (RB)	[17]
		SC (5%)	151%	
		SDC (5%)	237%	
		STDHC (5%)	84%	
Glucagon-like-peptide I	Human	TC ^a	41% (RB) ^b	[18]
			(fasting)	
			23% (post prandial)	

AB, relative bioavailability; RB, relative bioavailability; TC, sodium taurocholate; STDHF, sodium taurodihydrofusidate; LPC, lysophosphatidylcholine; SC, sodium cholate; SDC, sodium deoxycholate; TDC, sodium taurodeoxycholate.

^a Concentration was not stated in the reference.

^b Relative bioavailability compared with subcutaneous data.

1.1. Permeability of buccal mucosa and drug permeation

Buccal mucosa has a surface lining consisting of a non-keratinized, squamous epithelium supported by a connective tissue lamina propria. The superficial layers (approximately the outermost quarter) of the buccal epithelium represent the primary barrier to the entry of substances from the exterior. The principle barrier to the movement of compounds across the

buccal epithelium is provided by an accumulation of neutral lipids and glycolipids in the intercellular spaces of these superficial cell layers. This material originates from the extrusion of the contents of the membrane-coating granules as the epithelial cells move superficially. For more detail on structure and permeability properties of buccal mucosa, the reader is referred to excellent reviews by Squier and coworkers [19,20].

The epithelial barrier must be crossed by the drug

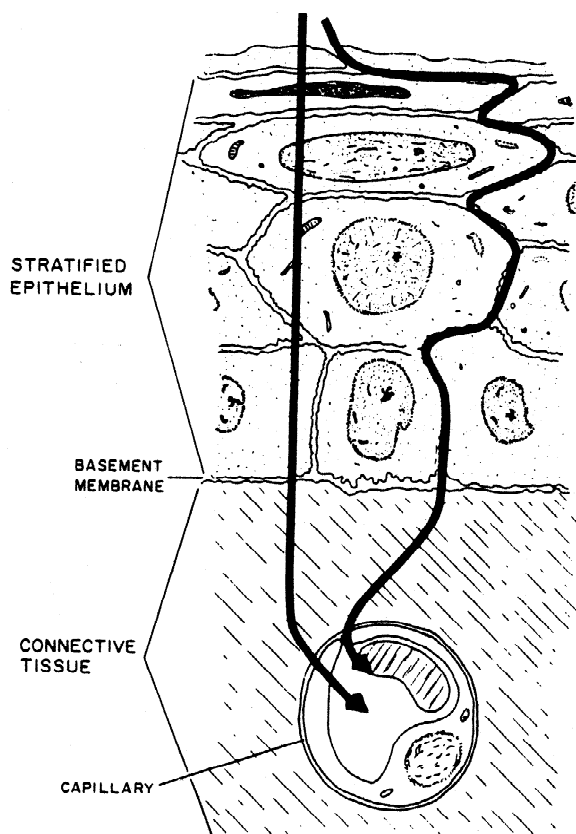


Fig. 1. Routes of epithelial penetration: transcellular route and paracellular route (reproduced with permission from Wertz and Squier [13]).

molecules in order to reach their intended sites of action. The basic drug transport mechanism for buccal epithelium is the same as for other epithelia in the body. There are two major routes involved: transcellular (intracellular) route and paracellular (intercellular) [21] (Fig. 1). In general, for many of the drugs, permeation across the buccal epithelium is thought to be through paracellular route by passive diffusion. Nevertheless, Kurosaki et al. [22] suggested the presence of a specialized transport system for cephadroxy in the human buccal membrane.

2. Bile salts for buccal permeation enhancement

It is well known that bile salts play an important role as physiological surfactants in the intestinal

absorption of lipids and lipid soluble vitamins. Bile salts have also been employed extensively to enhance the absorption of drugs through various epithelia such as nasal, rectal, pulmonary, ocular and vaginal [23–25]. These compounds are believed to act by extraction of membrane protein or lipids, membrane fluidization, and reverse micellization in membrane, creating aqueous channels [26]. Although this has been shown in different studies for different mucosae, the evidence is complicated by the fact that many bile salts also have inhibitory effects on mucosal membrane peptidases. Sodium glycocholate was found to inhibit insulin metabolism in homogenates of rabbit nasal, buccal rectal and intestinal mucosal membranes [27]. The promoting effects of bile salts on human calcitonin absorption through the rat oral mucosa were related to the inhibition of degradation of calcitonin in mucosal homogenates [28].

As most of the penetration enhancers promote drug absorption by perturbing membrane integrity, it is inevitable that varying extents of insult would occur to the mucosal tissues, which are in intimate contact with the enhancer. The most pressing safety concerns associated with the use of bile salts as penetration enhancers to promote the buccal absorption of drugs are: (a) irritation of mucosal tissue; (b) extent of damage in the mucosal cells; and (c) rate at which such damage recovers. Despite its importance as a potentially negative factor limiting the routine use of penetration enhancers in mucosal drug delivery, the relationships between irritation and structure of the enhancer and between irritation and penetration efficacy of the enhancer have not been addressed.

In the following section, recent studies on the enhancing effect of bile salts on buccal permeation carried out in sequence will be reviewed in correlation with mucosal irritation data.

2.1. *In vitro* studies on enhancing effect of bile salts on buccal permeation of compounds

2.1.1. Fluorescein isothiocyanate (FITC)

The effects on the buccal epithelial permeability of dihydroxy bile salts, sodium glycodeoxycholate (GDC) and sodium taurodeoxycholate (TDC) and tri-hydroxy bile salts, sodium glycocholate (GC) and

sodium taurocholate (TC) at 100 mM concentration were investigated, and permeability changes were correlated with the histological effects [29]. Fluorescein isothiocyanate (FITC) was used as the model compound.

Freshly obtained buccal mucosa was dermatomed at a thickness of 500 μm and mounted in Ussing diffusion chambers with a diffusion area of 0.75 cm^2 and a compartment volume of 7 ml. The receptor side was filled with Krebs and the donor side with 500 μM FITC in Krebs buffer either alone or with the bile salt. The diffusion studies were carried out at 34°C and carbogen was circulated through the cells in order to maintain the viability of the tissue and to provide stirring. Samples were assayed using a fluorescence spectrophotometer.

The results showed that bile salts were quite capable of enhancing the permeation of FITC across porcine buccal mucosa with an enhancement factor of 200 (Table 3). In regard to light microscopy and freeze-fracture electron microscopy results, it was concluded that, they most likely do so by modifying the cell membrane integrity in such a way that the intracellular domain is opened up, and hence the transepithelial pathway significantly shortened. Both the flux data and histological observations showed that of di- and tri-hydroxy bile salts behaved identically in both aspects.

2.1.2. Morphine sulfate

As no difference was found between the bile salts in their enhancing effect, studies were continued with GDC. Morphine sulfate was chosen as the

model compound. In order to explain the transbuccal permeation of drug and its modification by the penetration enhancer, a combination of infrared spectroscopy, histological studies and in vitro flux studies was performed where bovine buccal mucosa with a non-keratinized epithelium was used as a model for non-keratinized human buccal mucosa [30].

The underlying tissue was removed from the mucosa with surgical scissors, then the epithelium was separated carefully from most of the connective tissue using a scalpel. Slice thickness was around 700 μm . Mucosa was mounted in Ussing diffusion chambers with a diffusion area of 1.08 cm^2 and a compartment volume of 5 ml. Isotonic phosphate buffer solution (PBS) was used on the receptor side. The donor side was filled with 10 mg/ml morphine sulfate in PBS alone or with GDC (at 10 or 100 mM concentration). The samples were assayed spectrophotometrically.

It was shown that the permeability of bovine buccal mucosa to morphine sulfate was significantly enhanced in the presence of GDC used at 100 mM concentration with an enhancement factor of 5 whereas no enhancement was observed at 10 mM concentration (Table 3). In a previous study where the effect of bile salts on the transbuccal permeation of FITC-labelled dextrans covering a wide molecular weight range was also investigated, an optimal in vitro enhancement was obtained at 10 mM [31]. The difference in enhancing effect of GDC for different molecules shows that its effect is dependent on the permeant as well.

Table 3
Enhancing effect of bile salts on permeation across buccal mucosa

Drug	Model	Bile salt	Permeability coefficient (P) ($\times 10^{-6}$ cm/s)
FITC	Porcine buccal mucosa	No enhancer	0.03 $\pm$ 0.03 ($n=9$)
		100 mM GDC	1.39 $\pm$ 1.07 ($n=10$)
		100 mM GC	1.46 $\pm$ 0.83 ($n=6$)
		100 mM TDC	1.20 $\pm$ 0.34 ($n=6$)
		100 mM TC	4.37 $\pm$ 2.03 ($n=5$)
Morphine hydrochloride	Bovine buccal mucosa	No enhancer	0.25 $\pm$ 0.09 ($n=6$)
		10 mM GDC	0.12 $\pm$ 0.05 ($n=6$)
		100 mM GDC	2.34 $\pm$ 0.21 ($n=5$)
Morphine sulfate	Porcine buccal mucosa	No enhancer	1.31 $\pm$ 0.39 ($n=7$)
		10 mM GC	0.94 $\pm$ 0.18 ($n=5$)
		100 mM GC	3.92 $\pm$ 1.20 ($n=5$)

For infrared spectroscopy studies, tissues were incubated with 100 mM GDC solution as described above, and at the end of each incubation period, pieces of tissue were soaked in PBS for about 10 s to rinse GDC from the mucosal surface and then placed in a dessicator for drying. For comparison lipid extracted tissue was also examined. Lipids were extracted from the fresh tissue by chloroform/methanol solutions, and then the solvents were evaporated. Dry samples were cut into small pieces (1×3 mm), mixed with dry potassium bromide. The mixture was pressed into a disc and infrared spectra were obtained using a Fourier transform infrared spectrometer. The data were normalized using the quantitative software of the system.

Of particular interest in the study were the peaks near 2850 and 2920 cm^{-1} due to symmetric and asymmetric carbon–hydrogen stretching, respectively, which are thought to belong to the lipids in buccal epithelium. The areas under the C–H symmetric stretching absorbance (over the frequency 2862.0–2854.6 cm^{-1} range) and asymmetric stretch-

ing absorbance (over the frequency 2945–2911 cm^{-1} range) were computed and it was shown that the areas were decreased after 4 h treatment with GDC when compared to intact tissue (Fig. 2) whilst *in vitro* flux of morphine sulfate was increased. Thus removal of the lipids corresponds to a highly permeable tissue. These results showed significant parallels with other biomembranes [32].

The results of permeation, histological and infrared studies indicated that GDC interacts with the epithelial lipids hence decreases the diffusional resistance to the permeants.

2.1.3. Morphine hydrochloride

Similar experiments as described above were carried out using porcine buccal mucosa. The enhancing effect of GC on transbuccal permeation of morphine hydrochloride (MPH) was investigated. Permeation of GC itself across the tissue and accumulation in the tissue was also studied and correlated with the enhanced permeation of MPH [33]. (*N*-methyl- ^3H) morphine was purchased and its

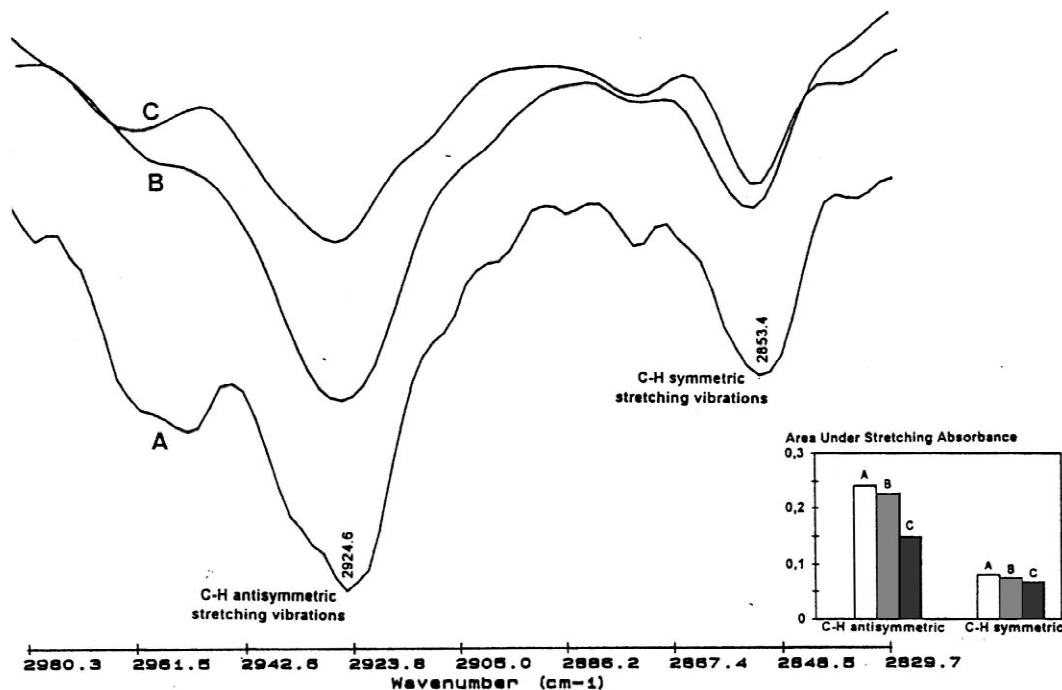


Fig. 2. Normalized IR spectra of bovine buccal mucosa: (A) intact (untreated); (B) after lipid extraction; (C) after 4 h treatment with 100 mM GDC; inset: calculated areas under stretching absorbances.

hydrochloride form was prepared under laboratory conditions. Sodium glycocholate ($1\text{-}^{14}\text{C}$) was used in the experiments.

Freshly obtained and dermatomed porcine buccal mucosa (500–600 μm thickness) was mounted in Franz diffusion cells with a diffusion area of 0.64 cm^2 . The donor side was filled with MPH in PBS alone or with GC (at 10 mM and 100 mM concentrations). Uniform mixing of the receptor side (12 ml PBS) was provided by magnetic stirring. The samples were counted in a liquid scintillation counter. For accumulation studies, the buccal tissue incubated with GC solutions was solubilized by Soluene-350, and then counted in a liquid scintillation counter.

GC was able to enhance permeation of MPH through the buccal mucosa at 100 mM concentration with an enhancement factor of 2 but not at 10 mM concentration (Table 3). On the other hand, there was a significant permeation of GC through the porcine buccal mucosa at 100 mM concentration whereas at 10 mM concentration permeation was not significant. At 100 mM concentration, accumulation of GC was found to be higher in the tissue. Furthermore, the permeability of the tissue increased following the accumulation of the bile salt in the tissue, which indicated an interaction between the bile salt and the tissue. A lag time of 1 h was observed in flux of GC whereas for accumulation in the tissue there

was no lag time. This result showed that GC begins to accumulate in the tissue directly after exposure to mucosa and starts changes in the buccal epithelium. The changes occurring in the epithelium during the early hours allows the permeation of both the permeant and GC itself. As GC diffuses into the buccal epithelium, it affects the barrier resulting in enhancement of the paracellular transport of the permeant. After reaching a certain level in the tissue, GC perturbs the epithelial cell membrane and diffuses into the cell thus facilitating the transcellular pathway. Our results showed that at 10 mM concentration, the accumulated amount of GC in the tissue (Fig. 3) was not sufficient to open the diffusion pathways for the permeant. The difference observed between the permeability coefficients in the presence of a bile salt for MPH and morphine sulfate can be related to structural properties of morphine salts. The differences in tissue properties in animal models used could be another reason for that.

2.2. Mucosal irritation

As a significant accumulation of the bile salt, sodium glycocholate in the buccal tissue was observed, studies on reversibility of the enhancing effects of bile salts on the tissue were carried out in vivo for assessment of the safety of bile salts as penetration enhancers [34].

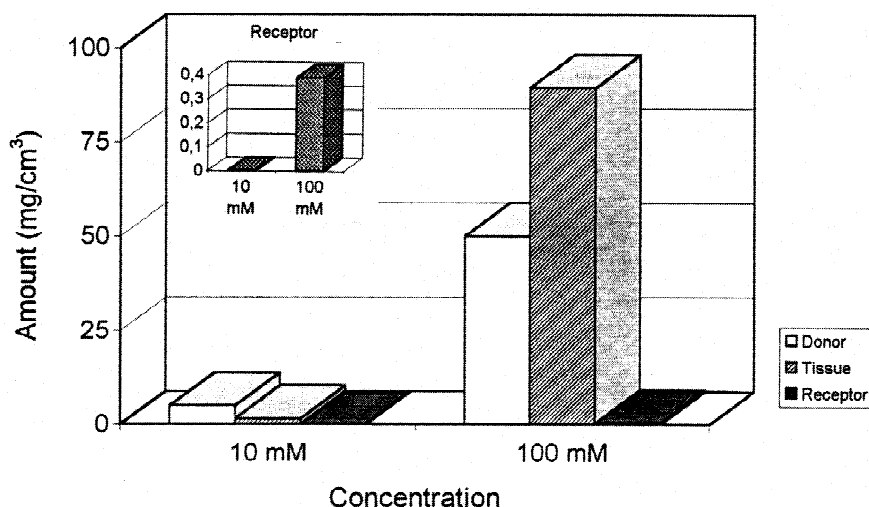


Fig. 3. Concentration of GC in donor phase, receptor phase and in the tissue after 8 h in vitro treatment.

Table 4
Effects of bile salts on different buccal mucosae after 4 h exposure

Bile salt	Concentration	Model	Application	Histological changes ^a
GDC	100 mM ^b	Porcine	In vitro, solution in	Loss of upper cell layers
GC	100 mM	buccal	Krebs buffer	Split of epithelium from the connective tissue
TDC	100 mM	mucosa		Decrease in number of desmosomes
TC	100 mM			
GDC	100 mM	Bovine	In vitro,	Formation of vacuoles within the prickle cell layer
		buccal	solution in PBS	Swelling inside the cells
		mucosa		Increase in intercellular space
				Decrease in number of desmosomes
GDC	5%	Human	In vivo,	Loss of upper cell layers
		buccal	tablet	Swelling inside the cells and vacuole formation
		mucosa		Decrease in the number of desmosomes
				Recovery observed in 24 h

^a Right after the exposure to the bile salts.

^b 100 mM concentration of GDC corresponds approximately to 5%.

Bioadhesive tablets were prepared by direct compression of a mixture of hydroxypropyl methylcellulose and carbomer at a ratio of 8:2. GDC was incorporated at 5% concentration. Control tablet contained no GDC but only the polymer mixture and the lubricant (1% magnesium stearate). Surface area of the tablet exposed to buccal mucosa was 1.15 cm². Non-smoker volunteers were used in studies for histological evaluations. Before placing, in order to obtain unidirectional contact and avoid an interaction with saliva, sides of the tablet, which are not in contact with the mucosa, were coated with polymethylmethacrylate. The tablet was placed on the buccal mucosa in the region of the upper molar and fixed with a slight manual press. At the end of a 4-h period, the tablet was removed and from that region biopsies were taken and examined in light and transmission electron microscopy.

The results of the in vivo histological studies are summarized in Table 4, together with the in vitro studies. Changes were observed in buccal epithelium right after 4 h application of the bioadhesive tablet incorporated with a bile salt whereas the control tablet did not cause any serious change or damage in the buccal mucosa. Further studies were carried out to investigate the reversibility of these changes [35]. Light and electron microscopy results showed that following removal of the tablet, epithelia cells recovered gradually within 24 h indicating that mucosal irritation is reversible. The changes in the appearance of the buccal mucosa were also followed for 24 h and pictures were taken at certain time intervals (Fig. 4). The mucosal irritation for erythema and edema formation which occurred at the site of application right after tablet removal was observed to be close to zero at 24 h which also indicated a

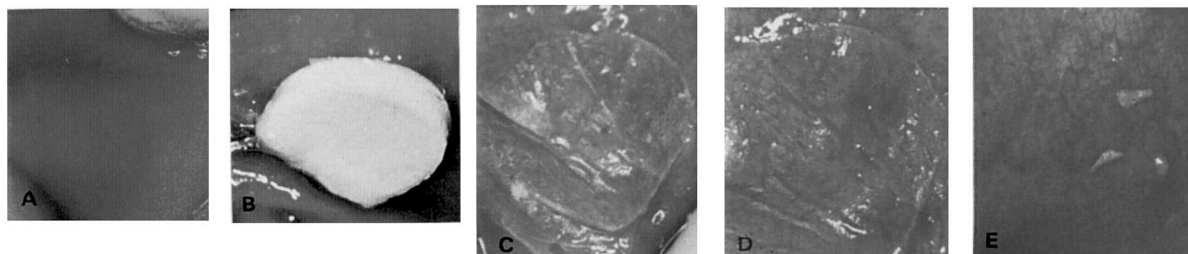


Fig. 4. Appearance of human buccal mucosa: (A) intact; (B) with GDC containing tablet attached for 4 h; (C) right after removal of the tablet; (D) 8 h after removal; (E) 24 h after removal.

reversible mucosal irritation. Changes occurring after exposure to bile salts exhibited wide interspecies and intersubject variation.

Nakane et al. [17] studied the mucosal irritation of a transmucosal therapeutic system (TmTs) developed for buccal delivery of luteinizing hormone-releasing hormone, containing various bile salts for permeation enhancement. The extent of irritation was observed with the naked eye and evaluated in regard to erythema, eschar formation and edema formation. Similar to ours, their results indicated that TmTs containing a bile salt was relatively safe and capable of achieving enhanced and controlled transbuccal delivery. Yet, further studies involving more frequent and prolonged applications are still needed for assessment of safety for a clinical application.

3. Chitosan for buccal permeation enhancement

Recently, chitosan has been shown to promote absorption of small polar molecules and peptide/protein drugs through nasal mucosa in animal models and human volunteers [36,37]. Other studies have shown an enhancing effect on penetration of compounds across the intestinal mucosa and cultured Caco-2 cells [38,39].

Results of our recent studies showed that chitosan also has a significant enhancing effect on permeation of drugs across the buccal mucosa [40,41]. Microscopic examination of histological sections of porcine buccal mucosa exposed to chitosan gel for up to 8 h did not show any deleterious effects. The enhancement potential of chitosan in gel form for oral mucosa was studied for two potential therapeutic compounds, hydrocortisone (HC), a commonly used topical oral anti-inflammatory agent, and transforming growth factor beta (TGF- β), which is a bioactive peptide. Chitosan-H (Lot 337) (M_w 1,400,000; DA: 80%) was used in the studies. Drugs were incorporated into 2% chitosan gels prepared in dilute lactic acid; control solution consisted of the drug in PBS. Chitosan gel or PBS was applied to the surface of porcine buccal mucosa dermatomed to a thickness of ~ 700 μm , mounted in continuous flow perfusion chambers. After 1 h the topical formulations were removed and replaced with artificial saliva and the tissue maintained for 12 h at 37°C. The flux (cpm

$\text{cm}^{-2} \text{min}^{-1}$) of drug was determined by collecting the perfusate on the connective tissue side and measuring activity (dpm). At the time of the formulation removal and at 1, 2 and 7 h, the relative proportion of the labelled drugs in four tissue strata (at ~ 100 μm thickness): outer epithelium, middle epithelium, inner epithelium and the remaining underlying connective tissue was also determined.

In vitro flux of both compounds across buccal mucosa was significantly ($P < 0.05$) increased with chitosan gel with a greater lag time for TGF- β , which is a large peptide [42]. In general, chitosan increased the quantity of compounds in the superficial layers of the epithelium as compared to PBS. However the hydrophilicity of the compound also had an effect; for HC, there was relatively less penetration into the deeper tissue layers whereas more of the hydrophilic TGF- β reached the deeper layer. Tissue sectioning revealed that there were higher concentrations of HC in the outer 200 μm of the epithelium with chitosan than with PBS for up to 4 h, after which it appears in the deeper epithelial and connective tissue layers (Fig. 5). The results showed a sixfold enhancement of permeability by chitosan for a compound to which the oral mucosa is relatively impermeable. One explanation for this effect may be the bioadhesive nature of chitosan, which increases the retention of the drug at its application site. However, it may also reflect a direct permeabilizing effect of chitosan on the organized intercellular lipid lamellae that are known to make up the permeability barrier in epidermis and oral epithelium. In this regard, it is interesting that chitosan is believed to interfere with lipid micelle organization in the intestine so as to reduce absorption and lead to weight loss. Further studies are being carried out with chitosans at different molecular weights and degree of deacetylation.

4. Conclusion

To date, many penetration enhancers of diverse chemical nature have been tested and found to be effective in facilitating buccal drug administration experimentally. Nevertheless, no formulation for buccal administration containing a penetration enhancer have been introduced to market so far. This

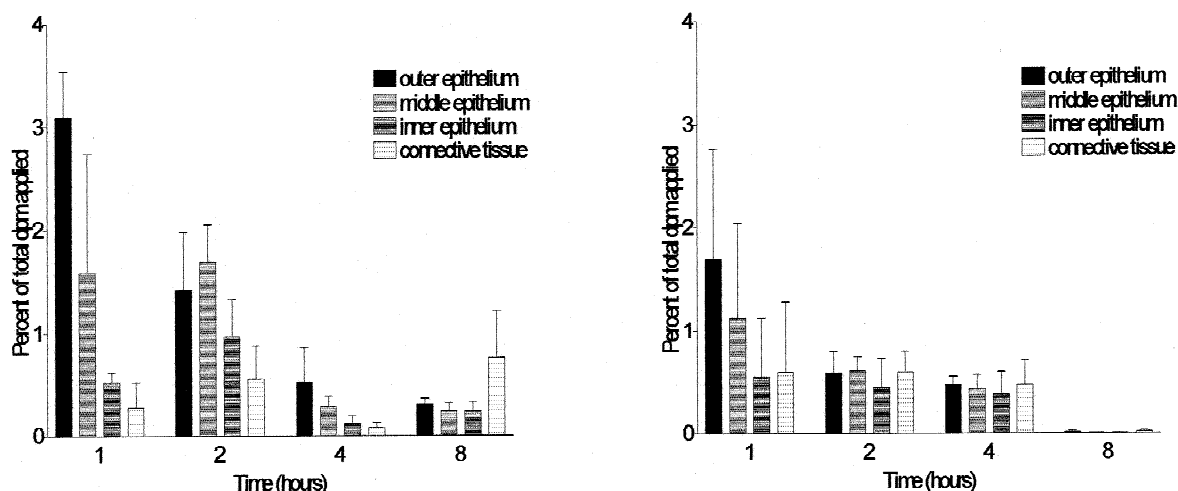


Fig. 5. Distribution of hydrocortisone in different tissue strata applied for 1 h: (a) in 2% chitosan gel, and (b) in PBS.

can be attributed to the lack of a satisfactory profile with respect to irritation. It is generally considered that oral mucosal damage caused by bile salts would be reversible and less serious than nasal mucosal damage due to the nature of oral mucosa. Yet further long-term safety studies are needed to evaluate practicality of bile salts before any clinical application can be attempted. Research is now directed towards a search for penetration enhancers that are reversible in action, selective only against the target cells and inert with respect to cells participating in irritation. Recent studies showed that, besides its permeabilizing effect, its favorable biological properties such as nontoxicity, biocompatibility and biodegradability makes chitosan a promising candidate for a safe mucosal penetration enhancer.

In regard to the recent studies carried out intensively in this field, it can be concluded that it is not very far away from us to design a drug delivery system in combination with a permeation enhancement technology to achieve better therapeutic efficacy along with the reduction of systemic toxicities.

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