Expert Opinion

Chemical permeation enhancers for transbuccal drug delivery

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Importance of the field: The buccal drug delivery system has been accepted as a potential non-invasive route of drug administration, with the advantages of avoidance of the first-pass metabolism, sustained therapeutic action and better patient compliance. However, transmucosal delivery of drugs by means of the buccal route is still very challenging. The main obstacles derive from the limited absorption area and from the barrier properties of the mucosa that have to be overcome for successful delivery drug molecules to the systemic circulation by this route.

Areas covered in this review: One long-standing approach for improving buccal drug delivery uses buccal absorption promoters, also called permeation enhancers. This requisite has fostered the study of permeation enhancers that will safely alter the permeability restrictions of the buccal mucosa. This review includes various classes of transmucosal chemical permeation enhancers and their mechanism of action. As enhancers influence drug delivery, further exploration of these compounds is required to understand their modifying action on the properties of buccal mucosa.

What the reader will gain: This review will help the readers in the selection of a suitable enhancer(s) for improving the buccal drug delivery for future endeavor.

Take home message: The authors imagine new buccal formulations bearing permeation enhancer(s) being commercialized in the coming years.

Keywords: buccal drug delivery, chemical permeation enhancer, permeation mechanism, sorption promoter

Expert Opin. Drug Deliv. (2010) 7(1):97-112

1. Introduction

The oral cavity is an attractive site for the delivery of drugs. The oral cavity includes the floor of the sublingual (mouth), palatal mucosa, buccal (the inside of the cheeks) and the gingival (gums) [1]. 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 [2].

Buccal and sublingual sectors are the most appropriate for drug delivery as it is possible to realize local effect (mucosal) and systemic effect (transmucosal) of drug administration [3]. The sublingual route is generally used for the delivery of drugs characterized by a high permeability across the mucosa and used in the treatment of acute disorders; because of the considerable surface area and high blood flow, it is a viable site when a rapid onset is desired [4], whereas the buccal route is generally used in the treatment of chronic disorders when a prolonged release of the active substance is necessary [3]. The buccal drug delivery system also provides many advantages, such as it can be used for local as well as for systemic effect [4], avoid hepatic first-pass effect, no presystemic metabolism, ease of administration and fast onset of action [1], and has a rapid cell recovery, unlike the skin [5]. It is estimated that

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10.1517/17425240903338758 © 2010 Informa UK Ltd ISSN 1742-5247

the permeability of the buccal mucosa is 4 – 4000 times greater than that of the skin [6].

The major challenges of buccal administration of drugs with systemic effect are limited absorption area and the barrier properties of the buccal mucosa, which implies low drug bioavailability [7,8]. The barrier properties of oral mucosa are related primarily to their natural structure as well as the physicochemical properties of the drug [9]. For example, rapid uptake and sustained delivery of lipophilic drugs (nicotine and fentanyl) can be achieved, however buccal delivery of high-molecular-mass drugs (peptides, proteins and polysaccharides) often results in a low bioavailability [1]. Conventionally, the oral route cannot be used for the delivery of macromolecular drugs such as proteins and peptides owing to limited transport across the epithelial membrane. This challenge can potentially be overcome through the use of chemical permeation enhancers, which affect transcellular and/or paracellular transport routes [10], for example, sodium glycodeoxycholate, 1-dodecylazacycloheptan-2-one (Azone®; Shanghai Worlder Corporation, China) and sodium 5-methoxy salicylate have been used as penetration enhancers for the delivery of macromolecules such as buserelin, octreotide acetate and protrelin, respectively [11-13]. Low permeability of the oral mucosa is a reason for exploring various permeation enhancers in order to obtain therapeutic levels, especially for protein and peptides.

2. Major route for mucosal drug penetration

The oral mucosa can be considered to consist of a laminate of several layers: a mucus layer that covers the epithelium; a keratinized layer on the surface of the epithelium; a basement membrane (basal lamina); a connective tissue (lamina propria); and a loose submucosa. There are ~ 40 – 50 cell layers, resulting in a buccal mucosa that is 500 – 600 μm thick [2,5]. Drug penetration through mucosa implies partitioning into and diffusion across each of the aforesaid layers, any one of which could possibly be the main barrier to drug penetration [9]. The permeability barrier in the oral mucosa is supposed to be the result of intercellular material resulting from the so-called 'membrane coating granules' (MCGs) [5]. Apart from the MCGs, the cellular membrane may present some resistance to permeation as well. The outer epithelium is also believed to be the rate-limiting step to mucosal penetration [14]. The drug transport mechanism through the buccal mucosa involves two principal routes: transcellular (intracellular) and paracellular (intercellular) pathways. The transcellular route involves the crossing of the cellular membranes with a polar and a lipid domain, whereas the paracellular route essentially implicates the passive diffusion through the extracellular lipid domain. The ionic drugs usually diffuse through the intercellular space, whereas the hydrophobic ones are able to pass through cellular membranes [4]. In the authors' opinion the lipophilic drugs, such as denbufylline [15], pass through the lipid structure of the membrane and show permeation via the transcellular pathway, whereas hydrophilic drugs, such as diltiazem hydrochloride [16], permeate through the buccal mucosa via the paracellular route. The transcellular pathway is found to be the main route, particularly for hydrophilic compounds [17]. The intracellular route offers greater surface area for absorption. Siegel and co-workers [18-20] investigated the permeability of canine and rabbit lingual frenula and the ventral surface of the tongue of rats of several structurally unrelated compounds. These workers projected that compounds having a partition coefficient less than water crossed the oral mucosa through pores in the membrane [21-29]. In the authors' opinion, the rat has a buccal mucosa with a very thick, keratinized surface layer, whereas the rabbit is the only laboratory rodent that has non-keratinized mucosal lining similar to human tissue; so the rabbits are closer to *in vivo* human studies as compared with rat studies [30], thus suggesting that such compounds cross the oral mucosa by means of an intracellular route. In contrast to the intracellular route, the intercellular route offers a small area for transfer of drug. However, it appears to be the main route for most compounds of pharmacological importance [31-37].

3. Permeation enhancers

Membrane permeability is the limiting feature for many drugs in the progress of the buccal adhesive delivery approach. The epithelium that lines the buccal mucosa is a very effective obstacle to the permeation and hence absorption of drugs. To mitigate this barrier and to facilitate the permeation through buccal mucosa, permeation enhancers are used [38]. The search for safe and effective penetration enhancers in drug delivery is possible by understanding the structure and mechanism of action of enhancers [39]. Besides these there are several factors that also affect the activity of penetration enhancers, such as intrinsic ability of peptides to cross biological membranes [40], differences in permeability resulting from variation in mucosal sites [41], potency of an enhancer [42], and rate of release of active from the delivery system [40].

According to Aungst [39] and Barry [43], an ideal penetration enhancer should be non-toxic and non-irritating, the absorption-enhancing action should be immediate and unidirectional, the effect of permeation enhancer should be reversible, that is, after removal of the material from the applied membrane the tissue should immediately fully recover its normal barrier property, and the enhancer should be physically compatible with a wide range of drugs and pharmaceutical excipients [44]. It has been reported in the literature that when the delivery system is removed from the buccal cavity or is exhausted, there is still drug being absorbed into the systemic circulation owing to the reversible binding of drug/penetration enhancer.

To enhanc buccal absorption different overtures have been investigated and developed, including the use of drug derivatives, drug-saturated systems, physical approaches and chemical penetration enhancers that facilitate the diffusion of drugs through the buccal mucosa. The most widely used

approach is use chemical penetration enhancers [45-47]. This review gives an overview of the use of various chemical penetration enhancers, such as: chelators [48-53], for example EDTA, citric acid, salicylates, *N*-acyl derivatives of collagen, and enamines (*N*-amino acyl-derivatives of 3-diketones); surfactants [54], such as sodium lauryl sulfate, polyoxyethylene-9-1aurylether, and polyoxyethylene-20-cetylether; and natural surfactant such as bile salts (sodium deoxycholate, sodium glycocholate, and sodium taurocholate), which act by extracting membrane protein or lipids, by membrane fluidization or by producing reverse micellization in the membrane and creating aqueous channels and/or by interference with calcium ions to maintain the dimension of the intercellular space, thereby permitting the paracellular transport of peptides and proteins [55,56]. Fatty acids and their derivatives, such as sodium caprylate, sodium caprate, sodium laurate, oleic acid, monoolein and acylcarnitines, have been shown to reduce the thickness of the unstirred water layer adjacent to the mucosal membrane, and by disrupting intercellular lipid packing [40], Azone acts by creating a region of fluidity in intercellular lipids, and alcohols work by reorganizing the lipid domains and by changing protein conformation [57,58]. Recently, chitosan and its derivates have been used extensively to enhance the permeation of medicaments by means of the buccal route and have been found to be a potential penetration enhancer for transmucosal (intestinal, nasal, buccal and vaginal) absorption of drugs [59-64]. The penetration enhancement properties of chitosan through mucosae (intestinal and nasal) mainly result from a transient widening of the tight junctions between the cells [62]. Other investigators such as Senel *et al.*, Portero *et al.* and Sandri *et al.* [65-67] also reported that chitosan was an effective absorption enhancer owing to its ability to effect transient widening of the tight junctions within the mucosa.

The classification of chemical buccal permeation enhancers and their mechanism of action are given in **Tables 1** and **2**. An overview of the information has been provided along with the literature so that readers requiring more details on a specific buccal enhancer can find the source easily. This would also be helpful for researchers working on buccal delivery in the selection of a suitable buccal chemical permeation enhancer.

4. Mechanism of penetration enhancers

Penetration enhancers work by one of the many mechanisms [68]. They may act by changing mucus rheology, that is, by reducing the viscosity of the mucus [55]. Mucus forms a viscoelastic layer of varying thickness that affects drug absorption. Most penetration enhancers act by disturbing the intracellular lipid packing by interaction with either lipid packing or protein components, thus increasing the fluidity of the lipid bilayer membrane [44,69,70]. Fluidization of the plasma membrane, loosening of the tight junctions between cells, and inhibition of proteases are a few of the mechanisms [45]. The penetration enhancers also act by increasing the thermodynamic activity of peptide drugs [71]. This may be affected by the vehicle composition, which influences solubility and micellization, and also by ion pair formation between the enhancer and the drug [72]. A brief introduction to buccal chemical permeation enhancer followed by various reports on the utility of buccal enhancers has been presented, and a summary is presented in **Table 3**.

5. Buccal chemical absorption promoters

5.1 Bile salts

Bile salts (steroidal detergents) are the natural or synthetic salts of cholanic acid, for example the salts of cholic and deoxycholic acid or combinations of such salts. All of the bile salts excreted from the liver cells are conjugated with either glycine or taurine. Bile salts have also been used extensively to enhance the absorption of drugs through oral mucosa [70,73,74]. It is generally considered that oral mucosal damage caused by bile salts is reversible [75]. These compounds are believed to act by extraction of membrane protein or lipids, membrane fluidization, and reverse micellization in membrane, creating aqueous channels [45,72]. In 1997, Hoogstraate *et al.* reported the concentration dependence effect of sodium glycodeoxycholate on the structural integrity of porcine buccal epithelium. The lipid analysis of the buccal epithelium indicated that only the epithelial lipid content was changed. Finally, the mechanism of action of glycodeoxycholate on the buccal epithelium was investigated by fluorescence spectroscopy. The results revealed an interaction with the epithelial lipids in the intercellular domain, possibly by forming mixed micelles or aggregates [76]. In the authors' opinion mixed micelles alter the hydrophobicity of the actives, resulting in enhanced drug permeability by means of the paracellular route. In another study, enhancement of transbuccal permeation of morphine sulfate was studied at two different concentrations (10 and 100 mM concentrations) of sodium glycodeoxycholate; the permeation of morphine sulfate across the bovine buccal epithelium was enhanced in the presence of 100 mM glycodeoxycholate by a factor of 5, whereas at lower concentrations no significant enhancement was obtained [77]. In the authors' opinion, below the critical micellar concentration the glycodeoxycholate does not form mixed micelles, thus leading to no significant enhancement of drug permeation in the above case. It has been reported that the sodium glycodeoxycholate can enhance the buccal permeation of macromolecules as well as peptide drugs. In this context, buccal delivery of fluorescein isothiocyanate-labeled dextran 4400 (FD4) and the peptide drug buserelin was investigated *in vivo*, in pigs. The co-administration of 10 mM glycodeoxycholate increased the absolute bioavailability 12.7% for FD4 and 5.3% for buserelin [78]. In another study the enhancing effects of dihydroxy and trihydroxy bile salts on buccal penetration were investigated using fluorescein isothiocyanate (FITC) as a model permeant. The presence of bile salts enhanced the permeability of FITC through the porcine buccal mucosa up to 100 – 200-fold

Table 1. Most commonly used buccal permeation enhancers [14,102,121].

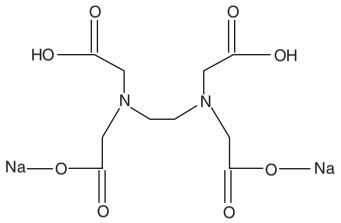
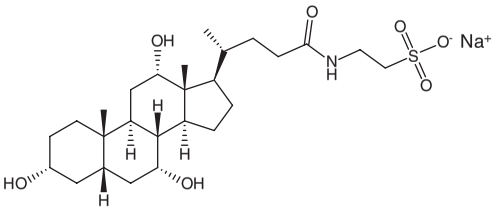
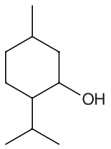
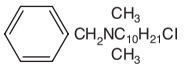
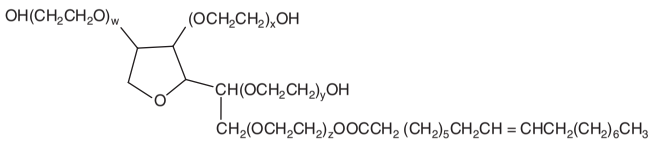
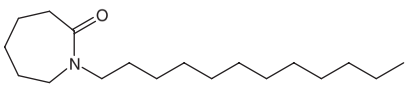
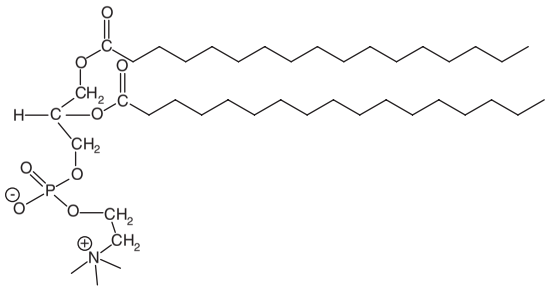
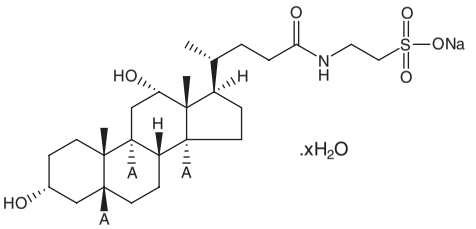
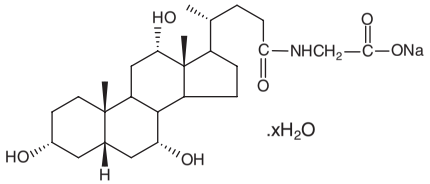
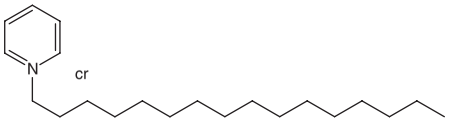
Sr. no	Buccal permeation enhancers	Structure	Sr. no	Buccal permeation enhancers	Structure
1	Sodium EDTA		11	Sodium taurocholate	
2	Menthol		12	Benzalkonium chloride	
3	Polysorbate 80		13	Azone®	
4	Phosphatidylcholine		14	Sodium taurodeoxycholate	
5	Sodium glycocholate		15	Cetylpyridinium chloride	

Table 1. Most commonly used buccal permeation enhancers [14,102,121] (continued).

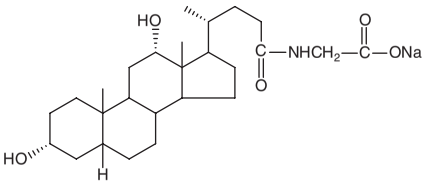
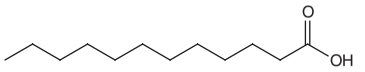
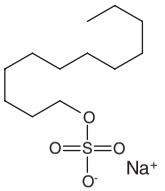
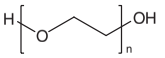
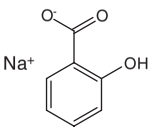
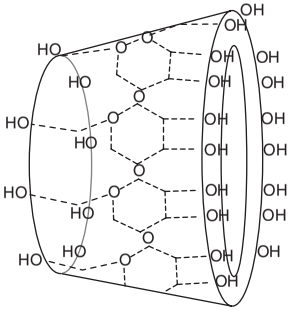
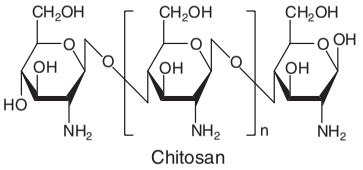
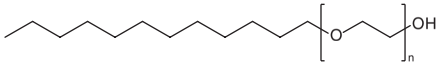
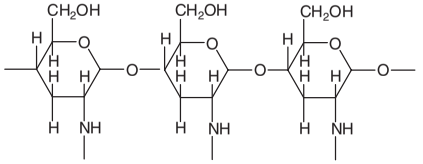
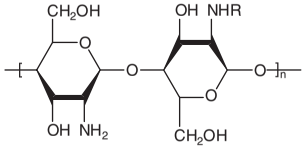
Sr. no	Buccal permeation enhancers	Structure	Sr. no	Buccal permeation enhancers	Structure
6	Sodium glycodeoxycholate		16	Lauric acid	
7	Sodium lauryl sulfate		17	Polyethylene glycol	
8	Sodium salicylate		18	Cyclodextrin	
9	Chitosan		19	Laureth-9	
10	Methylpyrrolidinone chitosan		20	Lysalbinic acid	

Table 2. Classes of absorption enhancers and their mechanisms of action [44,122].

Type	Examples	Mechanism of action
Synthetic surfactants	Sodium lauryl sulfate, Polyoxyethylene-9-laurylether	Phospholipids acyl chain disruption
	Laureth-9	Membrane interaction
	Polyethylene glycol-8 laurate, sorbitan laurate, glyceryl monolaurate, polysorbate 20 and 80	Extraction of membrane proteins and lipids Solubilization of peptides
Bile salts	Sodium-deoxycholate, Sodium-glycocholate, Sodium-taurocholate, Sodium fusidate, Sodium taurodihyrofusidate	Reduction of mucus viscosity Peptidase inhibition Denaturation of proteins
Fatty acids	Oleic acid, caprylic acid, lauric acid, palmitoylearnitine and other short fatty acids	Phospholipid acyl chain perturbation
Inclusion complexes	α-, β- and γ-cyclodextrins, methylated β-cyclodextrins	Inclusion of membrane compounds Increase solubility Enzyme inhibition
Chelators	Ethylene diamine tetra acetic acid (EDTA), citric acid, salicylates	Complexations of Ca^{2+}
	Polyacrylates	Opening of tight junctions
Polymers	Chitosan salts, trimethyl chitosan	Ionic interactions with negatively charged groups of glycocalix
Others	Azone®	Lipid structure perturbation

by modifying the cell membrane integrity in such a way that the intracellular domain was opened up and hence the transepithelial pathway significantly shortened. No significant difference was observed between the enhancing effects of dihydroxy and trihydroxy bile salts [79]. Hoogstraate *et al.* [78] investigated the combinational effect of four bile salts. The co-administration of 100 mM of the trihydroxy bile salts sodium glycocholate (GC) and sodium taurocholate (TC) and the dihydroxy bile salts sodium glycodeoxycholate and sodium taurodeoxycholate (TDC) increased the *in vitro* transport of FITC by a factor of 100 or more [80]. The effects of sodium glycodeoxycholate, pH and osmolarity on the permeability of three beta-blockers with different lipophilicities were investigated. The permeability studies were carried out using the cell culture model and compared with the results obtained from fresh porcine sublingual mucosa. The study revealed that enhancement effects caused by pH, osmolarity and glycodeoxycholate were highly lipophilicity-dependent and were in the order atenolol > metoprolol > propranolol. The apparent permeability coefficients of all three beta-blockers were significantly increased by increasing the pH. However, fewer enhancing effects were observed by osmolarity or the presence of sodium glycodeoxycholate [81]. In another investigation sodium glycodeoxycholate was used as the permeation enhancer for the buccal enhancement of 2,3-dideoxycytidine and was found to be effective for the permeation enhancement of the 2,3-dideoxycytidine by a factor of 32 [82]. Again sodium deoxycholate was found to be the best enhancer for the buccal delivery of triamcinolone acetonide in comparison with the non-ionic surfactants and glycols [83]. In another investigation the effect of permeation enhancers, namely sodium deoxycholate, sodium dodecyl sulphate, sodium tauroglycocholate and oleic acid, on the transbuccal delivery of 5-fluorouracil was studied. Sodium tauroglycocholate was found to be most effective for enhancing the buccal permeation of 5-fluorouracil compared with the other enhancers. The order of permeation enhancement was sodium tauroglycocholate > sodium dodecyl sulfate > sodium deoxycholate > oleic acid. Histological investigations were performed on buccal mucosa and indicated no major morphological changes on treatment of the aforesaid enhancers [84].

It has been reported that the 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 [85]. 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 [86]. In another investigation, Artusi *et al.* studied the delivery of thiocolchicoside through oral mucosa to improve the bioavailability. Thiocolchicoside *in vitro* permeation through porcine oral mucosa and *in vivo* buccal transport in humans were investigated. Two dosage forms, a bioadhesive disc and a fast dissolving disc for buccal and sublingual administration of thiocolchicoside, respectively, were designed. The *in vitro* permeation of thiocolchicoside through porcine buccal mucosa from these dosage forms was

Table 3. Applications of various buccal permeation enhancers in transbuccal drug delivery.

Permeant drug	Description	Ref.
Bile salts		
Morphine sulfate	The permeation of morphine sulfate across the bovine buccal epithelium was enhanced in the presence of bile salt five times	[77]
Fluorescein isothiocyanate-labeled dextran 4400 and buserelin	Bile salt increased the absolute bioavailability 12.7% for FD4 and 5.3% for buserelin	[78]
Fluorescein isothiocyanate	*In vitro* transport of fluorescein isothiocyanate was increased 100 times in the presence of bile salts	[78,79]
β-Blockers (propranolol, atenolol and metoprolol)	Permeation enhancement of bile salt was found to be highly lipophilicity-dependent. Atenolol presents the highest permeation, then metoprolol, followed by propranolol	[81]
2,3-Dideoxycytidine	Sodium glycodeoxycholate effectively enhanced the 2,3-dideoxycytidine up to 32 times	[82]
Triamcinolone acetonide	Sodium deoxycholate was found to be the best enhancer for the buccal delivery of triamcinolone acetonide	[83]
5-Fluorouracil	Sodium tauroglycocholate was found to be more effective for enhancing the buccal permeation of 5-fluorouracil than sodium dodecyl sulfate, sodium deoxycholate and oleic acid	[84]
Insulin	Sodium glycocholate inhibits insulin metabolism in homogenates of rabbit nasal, buccal rectal and intestinal mucosal membranes	[85]
Calcitonin	The bile salts effect on human calcitonin absorption is related to the inhibition of degradation of calcitonin in mucosal homogenates	[86]
Thiocolchicoside	Sodium taurocholate and sodium taurodeoxycholate retard the thiocolchicoside permeation across buccal tissue	[87]
New chitosan derivates		
Acyclovir	Methylpyrrolidinone chitosan was found to be the best penetration enhancer for buccal delivery of acyclovir	[88]
Transforming growth factor-β	Chitosan was found to exert a marked permeabilizing effect on buccal mucosa for peptide drug such as growth factor-β	[65]
Isothiocyanate dextran	*N*-trimethyl chitosans improve the bioavailability of isothiocyanate dextran via the buccal route	[59]
Fluorescein isothiocyanate dextran	Trimethyl chitosan and chitosan nanoparticulate systems were able to increase fluorescein isothiocyanate dextran permeation across buccal epithelium to a greater extent than the chitosan solution	[66]
Fluorescein isothiocyanate dextran	Reported that trimethylchitosan nanosystems are suitable carriers for the intestinal absorption of peptides such as fluorescein isothiocyanate dextran	[89]
Insulin	Nanoparticles consisting of chitosan and its quaternary ammonium derivatives are less effective in facilitating paracellular transport of insulin across Caco-2 cell monolayers than the corresponding free polymers	[91]
Terpenes		
Dideoxycytidine	Permeation of dideoxycytidine increased significantly in the presence of L-menthol	[95]
Propranolol	Menthol and lauric acid were effective at promoting the buccal absorption of propranolol only when the drug was ionized	[97]

Table 3. Applications of various buccal permeation enhancers in transbuccal drug delivery (continued).

Permeant drug	Description	Ref.
17β-Estradiol	Menthol increased the permeability of 17β-estradiol in a 40% (w/w) ethanol gel	[98]
Surfactants		
Piroxicam	1% SLS presents the highest rate of permeation of piroxicam across the excised buccal mucosa	[99]
α-Interferon	SLS 1% is superior to other types of absorption promoter, including sodium taurocholate at 1% concentration in enhancing the buccal absorption of α-interferon	[101]
Insulin	SLS 5% was equally effective as bile salts in enhancing buccal delivery of insulin	[102]
Salicylic acid	Sodium deoxycholate and sodium lauryl sulfate decrease the electrical resistance and increase the permeability of salicylic acid across rabbit buccal mucosa	[104]
Insulin	Non-ionic surfactant, laureth-9, effective at even lower concentrations for increasing the permeability of insulin	[102]
Cyclodextrins		
Omeprazole	β-Cyclodextrin enhanced the permeation 1.1-fold and methyl-β-cyclodextrin increased permeation 1.7-fold for omeprazole through buccal mucosa	[105]
Azone®		
Salicylic acid	Azone pretreatment enhanced the absorption rate of salicylic acid and also shortened the mean absorption time by one-fifth	[111]
Triamcinolone acetonide	Pretreatment of the buccal mucosa with azone increased tissue concentrations of triamcinolone acetonide	[112]
Cod-liver oil extracts		
Ergotamine	CLOE enhanced the permeation of the non-ionized form of ERG via a lipophilic route based on a passive-diffusion mechanism	[115,116]
Lysalbinic acid		
α-Interferon and insulin	lysalbinic acid increased significantly the oral mucosa permeability for α-interferon and insulin based on intercellular lipid solubilization	[119,120]

evaluated and compared with *in vivo* absorption. It was observed that thiocolchicoside is quite permeable across porcine buccal mucosa and permeation enhancers such as sodium taurocholate and sodium taurodeoxycholate do not cause any enhancement of thiocolchicoside, instead they suppress drug permeation across buccal tissue, thus behaving as permeation retardants [87]. This might be due to inhibition of membrane peptidase.

5.2 New chitosan derivates

Methyl-pyrrolidinone chitosan (MPC) is a chitosan derivative in which the amino groups of glucosamine units are partially replaced with 5-methyl-pyrrolidinone. MPC is a highly hydrophilic substance. It is soluble in water, saline and water–alcohol mixtures and it is able to yield viscous solutions and/or gels at physiological pH values [88]. Besides the aforementioned properties, its penetration enhancement, permeabilizing effect, biocompatibility, biodegradability and nontoxic nature make chitosan a promising candidate for a safe mucosal penetration enhancer [7].

Junginger and Verhoef reported that both weakly crosslinked poly(acrylic acid) derivatives and chitosan derivatives are safe penetration enhancers for hydrophilic compounds because they can exclusively trigger mechanisms that reversibly open the tight junctions of mucosal tissues and do not interfere with mucosal membrane components (i.e., do not induce transcellular transport) [44]. However, the exact mechanism of opening of the tight junctions is not reported. The mechanism still needs to be investigated by the scientists working in this area.

Different grades of chitosan derivates are available on the market to check the feasibility of chitosan as a buccal permeation enhancer. Four different types of new chitosan derivate, namely methylpyrrolidinone chitosan, partially reacetylated chitosan and two grades of partially depolymerized chitosan, were compared across porcine cheek mucosa for the buccal delivery of acyclovir, and among them methylpyrrolidinone chitosan was found to be the best for penetration enhancer effect as well as mucoadhesive properties across porcine cheek mucosa [88]. The investigators evaluated the mucoadhesive and penetration enhancement properties via the buccal and vaginal mucosae of four different chitosan derivatives, namely 5-methyl-pyrrolidinone chitosan (MPC), two low-molecular-mass chitosans (DC1 and DC2) and a partially reacetylated chitosan (RC). Chitosan HCl was used as a reference. Permeation studies were carried out using porcine cheek and vaginal mucosae as model membranes. Among the chitosan derivatives methyl-pyrrolidinone chitosan shows the best mucoadhesive and penetration enhancement properties in both buccal and vaginal environments. The penetration enhancement capacity of chitosan was decreased on partial depolymerization of chitosan and disappeared after partial reacetylation [60]. The derivative that revealed the best penetration enhancement possessed the greatest mucoadhesivity. The best penetration enhancement was thus due to increased residence time.

The enhancement effect of chitosan in gel form for oral mucosa was investigated with a large bioactive peptide, transforming growth factor-β (TGF-β). The effect of chitosan as a permeability enhancer was determined by measuring the flux of TGF-β across porcine oral mucosa in an *in vitro* system. Chitosan was found to exert a marked permeabilizing effect on buccal mucosa for peptide drug [65]. Sandri *et al.* [59] evaluated the influence of the degree of quaternization of *N*-trimethyl chitosans (TMCs) on penetration enhancement properties towards buccal mucosa. Fluorescein isothiocyanate dextran (molecular mass 4400 Da) was used as the model molecule. TMC derived from the lower molecular mass chitosan and characterized by the highest degree of quaternization shows the best mucoadhesive and penetration enhancement properties and is the most promising TMC to improve the bioavailability of hydrophilic and large molecular mass molecules (such as peptides and proteins) when administered by means of the buccal route. Sandri *et al.* compared the penetration enhancement properties of chitosan hydrochloride both as a polymeric solution and as a nanoparticulate system with those of trimethyl chitosan hydrochloride through buccal mucosa using fluorescein isothiocyanate dextran as a macromolecule model. The mechanism of penetration enhancement for both chitosan hydrochloride and trimethyl chitosan hydrochloride solutions and for chitosan hydrochloride nanoparticles involves a repackaging of the epithelial cells up to the basal membrane and a partial disarrangement of desmosomes. It was concluded that trimethyl chitosan and chitosan nanoparticulate systems were able to increase fluorescein isothiocyanate dextran permeation across buccal epithelium to a greater extent than the chitosan solution [66]. This might again be due to greater residence time of the nanoparticulate system in comparison with chitosan solutions. Recently, they reported that improvement of mucoadhesion and of nanoparticle internalization with respect to chitosan nanosystems makes the trimethylchitosan nanosystems suitable carriers for the intestinal absorption of peptides such as fluorescein isothiocyanate dextran [89]. An identical mechanism of enhancement of trimethyl chitosan was reported by Sahni *et al.* [90]. A similar study was undertaken with four quaternized derivatives of chitosan: trimethyl chitosan, dimethylethyl chitosan, diethylmethyl chitosan and triethyl chitosan. Their effect on the permeability of insulin across intestinal Caco-2 monolayers was studied and compared with chitosan both in free-soluble form and in nanoparticulate systems. The results revealed that the nanoparticles consisting of chitosan and its quaternary ammonium derivatives loaded with insulin are less effective in facilitating paracellular transport of insulin across Caco-2 cell monolayers than the corresponding free polymers [91].

5.3 Terpenes

Terpenes are a very safe and effective class of penetration enhancers obtained from natural sources, and the FDA classified them as generally regarded as safe (GRAS). The most terpenic structures result from the 'head-to-tail' condensation

of isoprene units, and this has become known as the 'isoprene rule'. Based on this generic rule, terpenes can be classified according to the number of isoprene units present as: monoterpenes have two isoprene units (C10); sesquiterpenes have three (C15); and diterpenes have four (C20). Terpenes may also be classified as acyclic/linear, monocyclic and bicyclic [92,93]. Terpenes have excellent permeation-enhancing effects to facilitate transdermal drug delivery. Terpenes can enhance the permeation of both lipophilic and hydrophilic drugs [94]. The enhancing effects of menthol on buccal permeation of a model hydrophilic nucleoside analogue dideoxycytidine have been studied. The permeation enhancement studies were performed with varying concentrations of l-menthol dissolved in Krebs buffer solutions containing dideoxycytidine. Permeation of dideoxycytidine increased significantly in the presence of l-menthol independent of the concentration of the terpene. The apparent 1-octanol: buffer partition coefficient (log K_p) of dideoxycytidine was also increased significantly in the presence of l-menthol and was also independent of the enhancer concentration. The *in vitro* transbuccal permeation of dideoxycytidine was enhanced in the presence of very low concentrations of l-menthol. The mechanism of this enhancement was due to the partition coefficient enhancing effects of the terpene [95]. In another investigation the mucosal permeation of the *Salvia desoleana* essential oil by means of an enhancer using Franz cells was also studied with porcine buccal mucosa as a septum between the formulations and the receptor phase chambers. All the formulations allowed a high permeability coefficient in comparison with the pure essential oil. In particular, the components with a terpenic structure (β-pinene, cineole, α-terpineol and linalool) have the highest capacity to pass through the porcine buccal mucosa when compared withthe other components (linalyl acetate and α-terpinil acetate) owing to their higher permeability coefficient [96]. In another study, menthol has been investigated as a permeation promoter for the transbuccal delivery of propranolol using hamster cheek pouch. The L-menthol, lauric acid, sodium salicylate and phosphatidylcholine were evaluated as penetration enhancers. Menthol and lauric acid were effective at promoting the buccal absorption of propranolol only when the drug was ionized. It was assumed that the mechanism of permeation enhancement was an interaction with the membrane components for L-menthol, increasing the diffusibility of propranolol, whereas lauric acid may form a more partitionable complex with the drug without any action on membrane permeability [97]. The combinatorial effects of terpene as a buccal penetration enhancer were also reported with other classes of absorption promoters. The combined effects of hydrogels and absorption enhancers on the permeability of 17β-estradiol through buccal membrane were investigated by measuring the rate of permeation of 17β-estradiol through hamster cheek pouch buccal mucosa *in vitro* and *in vivo*. Glycerylmonolaurate, L-menthol and sodium caprate were selected as absorption enhancers in hydrogels containing ethanol and propylene glycol. Menthol increased the permeability of 17β-estradiol in a 40% (w/w) ethanol gel. Regarding the mechanisms of these absorption enhancers in the ethanol gel, sodium caprate and menthol contributed mainly to the diffusion of 17β-estradiol in the mucosa, but glycerylmonolaurate, owing to its surfactant property, increased the solubility of 17β-estradiol in the hydrogel [98].

5.4 Surfactant

Sodium lauryl sulfate (SLS) or sodium dodecyl sulfate (SDS or NaDS) is an anionic surfactant used in many cleaning and hygiene products. The molecule has a tail of 12 carbon atoms, attached to a sulfate group, giving the molecule the amphiphilic properties required of a detergent. The effect of 1% SLS, 3% sodium deoxycholate (NaDC) and 3% sodium tauroglycocholate (NaTGC) on the rate of permeation across the excised buccal mucosa of gel formulations containing piroxicam was investigated. The addition of 1% SLS provided the highest permeation rate in comparison with the bile salts, which had nearly similar enhancement characteristics [99]. Siegel and Gordon reported that SLS has a high deep tissue penetrant potential and can enter into blood following application to the surface of the oral epithelium, thereby facilitating the intercellular as well as transcellular transport of the permeant, thus indicating the higher enhancing effect of SLS [68,100]. It was also suggested that SLS, an ionic surfactant, disorganizes the entire membrane architecture, affecting both protein and lipid structures. Expansion of intercellular spaces and insertion of SLS molecules into the lipid structure have also been observed [57]. In another investigation, Steward *et al.* revealed SLS (1%) to be superior to other types of absorption promoter, including sodium taurocholate at 1% concentration, in enhancing the buccal absorption of α-interferon [101]. However, Aungst and Rogers [102] reported that SLS (5%) was equally effective as bile salts such as NaDC and sodium glycocholate used at 5% concentration in enhancing buccal insulin delivery [101-103]. To clarify the enhancement mechanism of sodium deoxycholate and sodium lauryl sulfate, an *in vitro* permeation study across rabbit buccal mucosa was performed using salicylic acid as a model compound. The promoting action of penetration enhancers on salicylic acid flux was studied using differential scanning calorimetry, electrophysiology and microscopy techniques. The enhancers sodium deoxycholate and sodium lauryl sulfate decreased the electrical resistance and increased the permeability of salicylic acid across rabbit buccal mucosa. The results indicated the major effect of penetration enhancers on the protein domain. The possible mechanism of action of the above enhancers may involve the uncoiling and extending of the protein helices, thereby opening up the polar pathway [104]. In another observation, the effects of various classes of transmucosal and transdermal absorption promoters, including sodium lauryl sulfate, sodium laurate, palmitoyl camitine, and a lauric acid/propylene glycol vehicle on buccal insulin absorption in rats, were evaluated. All steroidal detergents

examined as absorption promoters markedly improved buccal insulin absorption. The non-ionic surfactant and laureth-9 were also effective absorption promoters and were found to be effective at lower concentrations. The sodium lauryl sulfate showed similar effects in another study on buccal insulin absorption, whereas the ester non-ionic surfactants had no effects. As detergents, these agents solubilize lipids, and they are used to solubilize membrane proteins; so solubilization of membrane components is probably involved in their actions on buccal insulin absorption [102]. This solubilization of membrane components leads to changes in cellular membrane permeability.

5.5 Cyclodextrins

Cyclodextrins make up a family of cyclic oligosaccharides, composed of 5 or more α-D-glucopyranoside units linked $1 \rightarrow 4$, as in amylose (a fragment of starch). Cyclodextrins are produced from starch by means of enzymatic conversion. The production of cyclodextrins is relatively simple and involves treatment of ordinary starch with a set of easily available enzymes. Cyclodextrins are able to form host–guest complexes with hydrophobic molecules given the unique nature imparted by their structure. As a result, these molecules have found several applications in a wide range of fields. Cyclodextrins can be used in environmental protection: these molecules can effectively immobilize inside their rings toxic compounds, such as trichloroethane or heavy metals, or can form complexes with stable substances, such as trichlorfon (an organophosphorus insecticide) or sewage sludge, enhancing their decomposition.

The enhancing effect of cyclodextrins on the buccal permeation of a hydrophobic model drug, omeprazole, was studied [105]. The *in vitro* transbuccal permeation of omeprazole non-complexed and complexed with β- and methyl-β-cyclodextrin and in the presence of L-arginine was examined using freshly obtained porcine buccal mucosa. The permeation studies indicated an increase on drug permeation of 1.1- and 1.7-fold for β-cyclodextrin and methyl-β-cyclodextrin complexed forms, respectively. The presence of L-arginine increased drug permeation 1.4-fold in omeprazole complexed with β-cyclodextrin and 2.4-fold in the inclusion complex formed with methyl-β-cyclodextrin. The mechanism of action of methylated β-cyclodextrins as absorption enhancers for hydrophilic drugs is probably by transiently changing the mucosal permeability (by extraction of membrane cholesterol) and opening of the tight junctions [106-108].

5.6 Azone

Azone (1-dodecylazacycloheptan-2-one) is an agent that enhances the dermal penetration with a wide variety of compounds [109,110]; but there are several reports that claim the use of Azone as a buccal absorption promoter. The enhancing effect of the pretreatment with Azone on the absorption of salicylic acid from keratinized oral mucosa was investigated *in vivo* using a hamster cheek pouch. The absorption was increased significantly after the 4 h pretreatment with Azone emulsion when the pretreatment medium contained > 0.2% Azone. The pharmacokinetic analysis of the plasma concentration of salicylic acid after the intra-cheek-pouch administration revealed that Azone pretreatment enhanced the absorption, that is, increased the absorption rate constant and shortened the mean absorption time by one-fifth and increased the peak plasma concentration by a factor of approximately two [111]. In another investigation, the buccal mucosal uptake and retention of triamcinolone acetonide (TAC) were assessed in the presence of Azone. Incorporation of Azone into proprietary product Kenalog® in Orabase® (Bristol-Myers Squibb, Park Avenue, New York), which is the trade name for an off-white sticky paste (Bristol-Myers Squibb Australia Pty Ltd) that contains the drug triamcinolone acetonide used for relieving tenderness, pain, inflammation and ulceration of the inside of the mouth or the gums, did not result in an enhanced tissue concentration of TAC. However, when the tissue was pretreated with Azone, significantly higher amounts of TAC accumulated in the tissue. Pretreatment of the buccal mucosa with Azone results in increased tissue concentrations of TAC, which may be of clinical benefit in the treatment of oral mucosal inflammatory conditions [112]. Azone is a hydrophobic substance specially developed as a skin penetration enhancer showing no protein interaction. It has been demonstrated that Azone enhances only intercellular drug diffusion [113]. The mechanism of Azone is probably the same in skin and in buccal mucosa. Hadgraft *et al.* proposed that Azone is able to form ion pairs with anionic drugs, thereby promoting their permeation [114].

5.7 Cod liver oil extracts

Cod liver oil is a nutritional supplement derived from the liver of cod fish. It has high levels of omega-3 fatty acids and very high levels of vitamins A, D and E. It is widely taken to ease the symptoms of arthritis, as well as having other health benefits. It was once commonly given to children. High-quality cod liver oil is a pale-yellow, thin, oily liquid having a slightly fishy and bland taste. The effect of cod liver oil extracts (CLOE) on the buccal permeation of ionized and non-ionized forms of ergotamine (ERG) has been investigated and it was found to be the best enhancer for the permeation of the non-ionized form of ERG. The enhancing activity of CLOE was found to be even greater than that of oleic acid. CLOE may distribute in the lipid-rich region of the buccal membrane and may change the barrier structure of the lipoidal pathway in the keratinized epithelial-free membrane separated from hamster cheek pouch [115]. It is likely that non-ionized ERG permeates the membrane by means of a lipophilic route based on a passive-diffusion mechanism [116]. The penetration enhancing effect of cod liver oil is associated with the unsaturated fatty acid portion [117].

5.8 Lysalbinic acid

Lysalbinic acid was found to be a new absorption enhancer for the buccal delivery of peptide drugs. The delivery of peptide drugs by means of the buccal mucosa is a more convenient and safe approach than most other delivery methods. New generations of absorption promoters that would sufficiently enhance penetration and at the same time not cause irritation or an unpleasant taste should be developed. Lysalbinic acid, a product of the alkaline hydrolysis of egg albumin, meets these requirements [118]. Lysalbinic acid was shown to increase significantly oral mucosa permeability for α-interferon and insulin [119]. The mechanism by which lysalbinic acid increases transport is not completely clear so far, but it may be similar to that of other detergent enhancers based on intercellular lipid solubilization, thus resulting in altered permeability leading to enhanced permeation [120].

6. Expert opinion

Owing to the simplicity of the administration, the oral cavity is an attractive site for the delivery of drugs. The buccal route is the most appropriate for drug delivery because it avoids first-pass hepatic or intestinal metabolism and yields sustained plasma concentration with minimal fluctuations. Further benefits presented by the buccal route are accessibility, administration and withdrawal, retentivity, low enzymatic activity, it is economical, and high patient compliance. Through this route it is possible to realize local (mucosal) and systemic effects (transmucosal) of drug administration. The drug transport mechanism through the buccal mucosa involves two major routes, namely transcellular (intracellular), which involves the crossing of the cellular membranes with a polar and a lipid domain, and paracellular, (intercellular), which implies passive diffusion through the extracellular lipid domain. The triumph of this approach is shown by the fact that at present the market shares for buccal delivery are $3 billion and are expected to increase 11% annually through 2007. There remains a large number of drugs for which buccal delivery is desirable but unfeasible at present because of shortcomings of delivery by means of this route. Several potential barriers to oral mucosal drug absorption have been identified. The main obstacles that drugs meet when administered by means of the buccal route derive from the limited absorption area and the barrier properties of the mucosa. In the current global scenario, various methodologies have been applied to promote the bioavailability of drugs, including supplemental administration of enzyme inhibitors, new formulation strategies, reversible chemical modifications and the use of absorption enhancers. The substances that facilitate the permeation through buccal mucosa are referred to as permeation enhancers. The use of permeation enhancers to compromise the barrier properties of buccal mucosa has been continuing for decades, and will permit in future the delivery of broader classes of drugs through the buccal mucosa. The selection of enhancer and its efficacy depend on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. So far, many chemical penetration enhancers such as surfactants (anionic and non-ionic), bile salts, chelators, fatty acids and alcohols have been tested and found to be effective in facilitating buccal drug administration experimentally. Nevertheless, no formulation for buccal administration containing a penetration enhancer has been introduced to the market so far. Among the reported permeation enhancers, bile salts were found to be the most widely used buccal penetration enhancer; it is generally considered that oral mucosal damage caused by bile salts would be less and reversible. The next category among the enhancers that was found to be safe and effective even at low concentration is terpenes; at present terpenes are receiving a great deal of attention in pharmaceutical applications as potential permeation enhancers, owing to their low systemic toxicity and high enhancement activity. Chitosan and its derivatives, besides their permeabilizing effect, non-toxicity, biocompatibility and biodegradability properties, recently showed good permeation enhancement capacity for transmucosal absorption of drugs, which makes it a promising and safe mucosal penetration enhancer. There are few reports available on the effect of fatty acids on the buccal delivery of peptides. The next most promising agents for buccal delivery are surfactants. However, the action depends on the kind of surfactant used, the concentration and exposure time. Mostly surfactants induce side effects such as protein denaturation or extraction, enzyme inactivation, swelling of tissue and extraction of lipid components. Different permeation enhancers have been utilized alone above and have shown a particular mechanism of permeation. It is also anticipated that with the use of permeation enhancers in combinations, a combined mechanism of permeation may lead to higher permeation. Further research is in progress across the globe to harness the enhancement potential of some new buccal permeation enhancers. A judicious selection of buccal enhancer would be very helpful in the successful development of transmucosal buccal products.

Acknowledgments

A Ahad expresses his thanks to the Council for Scientific and Industrial Research (CSIR), India, for providing financial assistance in the form of a senior research fellowship.

Declaration of interest

The authors state no conflicts of interest and have received no payment in the preparation of this manuscript.

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