

BUCCAL PENETRATION ENHANCERS-AN OVERVIEW**SUMANJALI DODLA, SELLAPPAN VELMURUGAN***

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*Received: 17 April 2013, Revised and Accepted: 18 May 2013***ABSTRACT**

Over the last decade, there has been a particular interest in delivering drugs in buccal mucosa and aiming to increase bioavailability of varied controlled drug delivery systems (CDDS), mucoadhesion (the capability of a object to adhere to mucous membranes) occupies a unique position. Buccal administration of API provides a convenient route of administration for both systemic and local actions. It provides direct entry into the systemic circulation thus avoiding the hepatic first-pass effect and degradation in the gastrointestinal tract. However permeability of oral mucosa is limiting factor which relatively low compared to intestinal mucosa and the skin. When permeability differences between various organs of the oral region are taken into consideration, buccal membrane found to be more permeable. In order to deliver wider classes of drugs across the buccal mucosa, the barrier potential of mucosa must be reduced. This requisite has forced the study of buccal penetration enhancers that will overcome the permeability barrier of the buccal mucosa. Numerous compounds have been evaluated for penetration enhancing activity, including bile salts, surfactants, fatty acids and derivatives, ethanol, cyclodextrins and chitosan etc. The purpose of this review is to identify the structural and chemical nature of the permeability barrier the buccal mucosa, to clarify the mechanisms of action of buccal penetration enhancers.

Keywords: Penetration enhancers, buccal mucosa, Drug delivery system; Intercellular lipids**INTRODUCTION**

Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological are held together by means of interfacial forces, when the associated biological system is mucous, it is called mucoadhesion [1]. In General, Bioadhesion is a term which broadly includes adhesive interactions with any biological or biologically derived substance. The observable fact of mucoadhesion has been put in plain words by pertaining the five theories of adhesion into the contact of the dosage form and the biological substrate [2].

Amongst the diverse routes of drug delivery, oral route is possibly the most favored to the patient and the clinician alike. Among all oral mucosal cavity, the buccal region is one of the convenient route of administration for systemic drug delivery [3]. Buccal drug delivery can be defined as delivery of drugs through buccal mucosa in order to treat local/systemic pharmacological actions [4]. Buccal drug delivery is a attractive method of sustained drug delivery due to following reasons.

Firstly due to difference in the permeability characteristics of the oral cavity, where the buccal mucosa is less permeable and so unable to give a rapid absorption window. Second being that, the buccal mucosa has a vastness of smooth muscle and relatively unmovable mucosa which is the purpose to make it a more enviable expanse for retentive systems. Thus the buccal mucosa is more fitted for sustained drug delivery applications, delivery of lipophilic molecules, and perhaps peptide drugs [5]. Human buccal mucosa is a remarkably efficient barrier; this barrier property causes difficulties for buccal delivery of therapeutic agents. Aiming to increase bioavailability of varied controlled drug delivery systems (CDDS), mucoadhesion (the capability of an object to adhere to mucous membranes) occupies a unique position.

However buccal membrane permeation can be a limiting factor for many drugs administered via the buccal route. Buccal penetration enhancers are capable of decreasing penetration barrier of the buccal mucosa. 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. The penetration enhancers will safely alter the permeability barrier of the buccal mucosa. Buccal penetration can be improved by using various types

of penetration enhancers such as bile salts, surfactants, fatty acids and derivatives, chelators, ethanol, cyclodextrins, enzyme inhibitors and chitosan etc. These compounds are act by increasing cell membrane fluidity, extracting intercellular lipids, interacting with epithelial protein domains, altering mucus structure and rheology. Current research is focused on developing penetration enhancers specifically for buccal drug delivery but without membrane toxicity. Now a day's researcher's concentrates on the design of formulations to enhance their retention time [6]. Hence, buccal adhesivedrug delivery systems choose as envisaging option for continued research [7].

Advantages [8]

- Buccal drug delivery has a high patient acceptability compared to other non oral routes of drug administration.
- Rapid action can be achieved relative to the oral route and the formulation can be removed if therapy is required to be discontinued.
- Improved patient compliance due to the elimination of associated pain with injections.
- It is richly vascularized and more accessible for the administration and removal of a dosage form.
- Moreover, rapid cellular recovery and achievement of a localized site on the smooth surface of the buccal mucosa.
- Sustained drug delivery.
- Extent of perfusion is more therefore quick and effective absorption.
- Nausea and vomiting are greatly avoided.
- Used in case of unconscious and less Co-operative patients.
- Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally undergoing hepatic first-pass metabolism drugs.
- Drugs, which show poor bioavailability via the oral route, can be administered conveniently.

Ex: - Drugs, which are unstable in the acidic environment of the stomach are destroyed by the enzymatic or alkaline environment of the intestine.

Limitations [9]

Drugs which irritate oral mucosa or have bitter taste, or cause allergic reactions, discoloration of teeth cannot be formulated.

- If formulation contains antimicrobial agents, affects the natural microbes in the buccal cavity.
- Only those drugs which are absorbed by passive diffusion can be administered by this route.
- Drugs which are unstable at buccal pH cannot be administered by this route.
- Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug.
- Low permeability of the buccal membrane specifically when compared to the sublingual membrane.
- The continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.

OVERVIEW OF THE BUCCAL MUCOSA [6]

Structure

Light microscopy reveals several distinct patterns of maturation in the epithelium of the human oral mucosa based on various regions of the oral cavity. The oral mucosa is comprised of an outermost layer of stratified squamous epithelium (Figure 1), below this lies a basement membrane, intermediate layer lamina propria followed by the submucosa as the innermost layer.

EPITHELIUM

The epithelium, as a protective layer for the tissues beneath 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 [8,9].

It is divided into

- Non-keratinized surface in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth, alveolar mucosa, vestibule, lips, and cheeks and do not contain acylceramides and only have small amounts of ceramide [10]. 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 [11, 12].
- Keratinized epithelium which is found in the hard palate and non-flexible regions of the oral cavity. The epithelial cells, originating from the basal cells, mature, change their shape, and increase in size while moving towards the surface. Keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water

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 3-8 days [13, 17] and this is probably representative of the oral mucosa as a whole. While the mucosal thickness (40-50 cell layers) of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae varies from 100-200 μm . The thickness of mucosa in humans, dogs, and rabbits has been determined to be approximately 500-800 μm .

THE BASEMENT MEMBRANE

The basement membrane forms a distinctive layer between the connective tissues and the epithelium. It provides the required adherence between the underlying connective tissues and the epithelium, and functions as a mechanical support for the epithelium. The underlying connective tissues provide many of the mechanical properties of oral mucosa.

LAMINA PROPRIA

The buccal epithelium is classified as a non-keratinized tissue. It is penetrated by tall and conical-shaped connective tissues. These tissues, which are also referred to as the lamina propria, consist of collagen fibers, a supporting layer of connective tissues, smooth muscles and blood vessels. The rich arterial blood supply to the mucosa membrane is derived from the external carotid artery. The buccal artery, some terminal branches of the facial artery, the posterior alveolar artery, and the infra-orbital artery are the main source of blood supply to cheek lining of the buccal cavity.

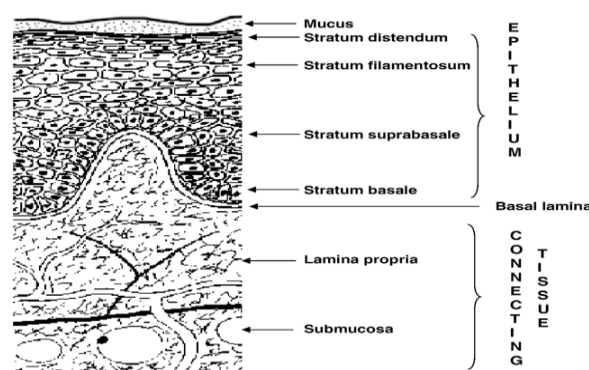


Fig. 1: Cross-section of buccal mucosa [7]

SUBMUCOSA

A gel-like secretion known as mucus, which commonly contains water-insoluble glycoproteins, covers the entire oral cavity. Mucus acts as a protective layer to the cells below and it is a visco-elastic hydrogel. It mostly consists of 1-5% of the above-mentioned water insoluble glycoproteins, 95-99% water, and other components in small quantities, such as proteins, enzymes, electrolytes, and nucleic acids. This composition of mucus can vary based on the origin of the secretion in the body.

PERMEABILITY

Permeability of oral mucosa is relatively low compared to intestinal mucosa and the skin. When permeability differences between various organs of the oral region are taken into consideration, buccal membrane found to be more permeable [14]. The buccal mucosa forms a barrier to drug permeation. The effectiveness of this barrier and buccal absorption are the factors affecting drug administration [15]. Buccal mucosa is less permeable compared to the intestinal epithelium, the make use of permeation enhancers has been extensively investigated in buccal drug delivery dosage forms [16]. The buccal mucosa is leaky epithelia to some extent and found midway to that of the intestinal mucosa and epidermis. It is estimated that the buccal mucosa permeability is 4-4000 times greater than that of the skin [17]. The permeability order of the oral cavity sublingual >buccal>palatal. The rank order is based on the relative thickness and degree of keratinisation.

The permeability coefficient of a drug is used to measure of the ease with which the drug can permeate a membrane. The permeability coefficient is a function of the degree of keratinization of these tissues, physicochemical properties of the drug (e.g., molecular weight, size, and lipophilicity) and the membrane thickness (i.e., inverse to its thickness) [18]. It is presently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called membrane coating granules (MCG) these are of two types. They are Keratinized tissues and non-keratinized tissues. Keratinized tissues composed of lamellar lipid stacks, which consist of sphingomyelin, glucosylceramides, ceramides exhibit a less permeability than non-keratinized tissues, non-lamellar lipid components are cholesterol esters, cholesterol, and glycosphingolipids [19].

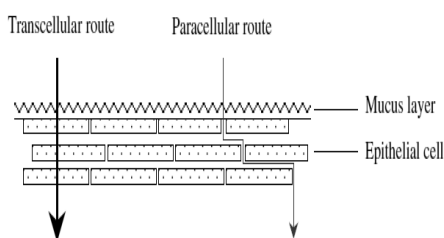
MODE OF PERMEATION

The cell membranes are relatively lipophilic and may create a barrier to polar hydrophilic permeants, and therefore, hydrophilic molecules perhaps permeate the buccal mucosa via the paracellular route [20]. Though tight junctions are rare in oral mucosa and their existence between intestinal epithelial cells is the key barrier to paracellular drug transport through the intestine consequentially, passage of drugs through the intercellular domain of the buccal epithelium is more favorable than intestine [21].

There are different modes of permeations

- Passive diffusion
 - ✓ Transcellular or intracellular route (crossing the cell membrane and entering the cell)
 - ✓ Paracellular or intercellular route (passing between the cells)
- Carrier mediated transport
- Endocytosis

Permeants can use these two routes simultaneously, but one route is usually chosen over the other based upon the physicochemical properties of the diffusant. Since the cytoplasm and intercellular spaces are hydrophilic in character, lipophilic compounds would



have low solubilities in this environment.

Fig. 2: Schematic representation of penetration routes in buccal drug delivery [24]

The paracellular membrane drug flux under sink condition can be written as Eq. (1)

$$J_p = D_p \epsilon / h_p \cdot C_d$$

Where, D_p diffusion coefficient of the permeate in the intercellular space, h_p path length of the paracellular route, ϵ area fraction of the paracellular route, C_d donor drug concentration.

Similarly, transcellular membrane drug flux under sink condition can be written as Eq. (2)

$$J_c = (1 - \epsilon) D_c K_c / h_c \cdot C_d$$

Where, K_c = partition coefficient between lipophilic cell membrane and the aqueous phase, D_c diffusion coefficient of the drug in the transcellular spaces and h_c path length of the transcellular route.

The diffusion of drugs across buccal mucosa was not related to their degree of ionization as calculated from the Henderson-Hasselbalch equation and thus it is not helpful in the prediction of membrane diffusion of weak acidic and basic drugs.

ENDOCYTOSIS

Endocytosis is the process where the drug molecules were engulfed by the cells. It is of two types

- Phagocytosis- solid drug molecules are engulfed.
- Pinocytosis- liquid drug molecules are engulfed.

PENETRATION ENHANCERS

The permeability barrier is probably the greatest challenge to overcome in order to be able to fully utilize the oral mucosa as a site

for drug delivery. Attempts to reduce this barrier have been researched in the form of permeability enhancers [22, 23]. Permeation enhancers are also required when an API has to reach the systemic circulation through the buccal mucosal route to exert its action. Enhancers include surfactants and, among these, bile salts (by extracting membrane protein or lipids, by membrane fluidization, by producing reverse micellization in the membrane and creating aqueous channels), fatty acids (that act by disrupting intercellular lipid packing), azone (by creating a region of fluidity in intercellular lipids) and alcohols (by reorganizing the lipid domains and by changing protein conformation). Factors that affect the permeation enhancer selection and its efficacy are

- Physicochemical properties of the drug
- Site of administration
- Nature of the vehicle
- Other excipients

Generally usage of individual penetration enhancers shows less effect than the combination penetration enhancers. Due to differences in structural and functional properties like membrane thickness, lipid composition, cellular morphology, enzymatic activity and potential protein interactions the efficacy of penetration enhancer in one site is not similar in the other site. Penetration enhancement to the buccal membrane is drug specific [24].

IDEAL CHARACTERISTICS

- Safe and non toxic, non irritating and non allergenic
- Pharmacologically and chemically inert
- They should have no pharmacological activity within the body
- The penetration enhancers should be compatible with both excipients and drugs.

However, buccal drug delivery penetration route assessment is significant because it is deep-seated to opt for the appropriate penetration enhancer to get better the drug permeability.

Mechanisms of action

Mucosal absorption are picked up by usage of penetration enhancers. The mechanism of action of penetration enhancers are as follows

Changing mucus rheology

Drug absorption mainly affect by the thickness of mucus viscoelastic layer. Additional, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers' perform by diminishing the viscosity of the mucus and saliva overcomes this barrier.

Increasing the fluidity of lipid bilayer membrane

The most preferential mechanism of buccal mucosa drug absorption is intracellular route. Some permeation enhancer perturb the intracellular lipid packing by interaction with lipid or protein components.

Acting on the components at tight junctions

Some permeation enhancers act on desmosomes, a foremost component at the tight junctions by this means enhances drug absorption.

By overcoming the enzymatic barrier

These permeation enhancers work by hinder the action of various peptidases and proteases present inside buccal mucosa, in this manner prevail over the enzymatic barrier. In addition, modification in membrane fluidity also alters the enzymatic activity indirectly.

Increase in the thermodynamic activity of drugs

Some permeation enhancers alter the partition coefficient of the API there by increase the solubility. This increase the thermodynamic activity resulting better drug absorption.

Table 1: List of penetration enhancers and its mechanism of action [25]

Classification	Examples	Mode of transport	Mechanism of action
Surfactants	Anionic Sodium lauryl sulfate Sodium laurate Laureth-9 Sodium dodecyl sulfate(SDS) Diocetyl Sodium sulfosuccinate	Paracellular	Perturbation of intercellular lipids, Protein domain integrity
	Nonionic Polyoxyethylene-9-lauryl ethe(PLE) Tween80 Nonylphenoxypolyoxyethylene(NPPOE) Polysorbates Sodium glycocholate	Paracellular	Perturbation of intercellular lipids, Protein domain integrity
	Cationic cetylpyridinium chloride Chitosan, trimethyl chitosan, Poly-L-arginine, L-lysine	Paracellular	Ionic interaction with negative charge on the mucosal surface
Fatty acids and derivatives	Oleic acid Caprylic acid Mono(di)glycerides,Lauric acid Linoleic acid, Acylcholines,Acylcarnitine ,Sodium caprate, Oleic acid	Paracellular	Increase fluidity of phospholipids domains
Bile salts and derivatives	Sodium deoxycholate Sodium taurocholate Sodium taurodihydrofusidate(STDHF) Sodium glycodihydrofusidate Sodium glycocholate Sodium deoxycholate	Paracellular	Perturbation of intercellular lipids, Protein domain integrity
Sulfoxides	Dimethyl sulfoxide(DMSO) Decylmethyl sulfoxide		Perturbation of intercellular lipids, Protein domain integrity
Chelating agents	EDTA Citric acid Salicylates	Paracellular	Interfere with Ca ²⁺
Monohydric alcohols	Ethanol Isopropanol	Paracellular	Disrupt arrangement of intercellular lipids
Polyols	Propylene glycol Polyethylene glycol Glycerol Propanediol	Paracellular	
Others (non-surfactants)	Urea and derivative Unsaturated cyclic urea Azone(1-dodecylazacycloheptan-2-one) (laurocapram) Cyclodextrin	Paracellular	Perturbation of intercellular lipids, Protein domain integrity

Table 2: List of drugs delivered via buccal route with penetration enhancers

Drug	Polymer	Penetration enhancers	Type	Reference
Carvedilol	Hydroxy Propyl Methyl Cellulose (HPMC E 15) & Hydroxy Propyl cellulose (HPC JF).	Propylene Glycol	Mucoadhesive buccal Patches	26
Cetylpyridinium chloride	Polyvinylalcohol (PVA), Hydroxyethyl cellulose (HEC) and chitosan.	Polyvinyl pyrrolidone	Mucoadhesive patches	27
Clotrimazole	Sodium Carboxy Methyl cellulose Carbopol 974p	Glycerol	Buccal Bioadhesive Films	28
Diltiazem	HPMC, Eudragit, Ethyl cellulose	PVP	Mucoadhesive	29

hydrochloride			buccal films	
Enalapril maleate	Sodium carboxy methylcellulose, Hydroxyl propyl methylcellulose, Hydroxyl ethyl cellulose	PVP	Mucoadhesive buccal films	30
Glibenclamide	Different grades of Hydroxyl propyl methyl cellulose	Propylene glycol	Mucoadhesive buccal films	31
Glipizide	Hydroxy propyl methylcellulose, Sodium carboxymethylcellulose, Carbopol-934P and Eudragit RL-100	Propylene glycol	Mucoadhesive buccal films	32
Insulin	Eudragit RL 100, sodium CMC (medium viscosity) Chitosan, HPMC(50cps)	Glycerin	Buccal films	33
Losartan potassium	Hydroxy Propyl methyl cellulose (HPMC) and retardant polymers ethyl cellulose (EC) or Eudragit RS 100.	Propylene glycol	Mucoadhesive buccal films	34
Ranitidine	Hydroxy propyl methyl cellulose-15 cps	Poly vinyl pyrrolidone.	Mucoadhesive buccal film	35
Rasagiline mesylate	Carbopol P 940 and sodium alginate	Glycerin	Intraoral buccal films	36
Triamcinolone	Carbopol 934 and Hydroxyl Propyl Methylcellulose (HPMC)	Glycerin	Buccal films	37
Valsartan	Chitosan, Hydroxy propyl methylcellulose (15 cps), Ethyl cellulose.	Propylene glycol	Buccal patches	38
Pimozide	HPMC (15 & 47 cPs), Carbopol 934, Poly vinyl alcohol	Poly vinyl pyrrolidone.	Buccal Mucoadhesive Patches	39
Isoxsuprine hydrochloride	Hydroxyl propylmethylcellulose(HPMC), Polyvinyl pyrrolidone K-30 (PVP K-30) and Hydroxyl ethyl cellulose (HEC).	Glycerin	Buccal films	40
Miconazole	Propylene glycol 10% w/w, polyethylene glycol 3% w/w, tween20 6% w/w, and oleic acid 5% w/w) chitosan	Propylene glycol (PG), polyethylene glycol	Mucoadhesive buccal films	41
Famotidine	Hydroxy Propyl Methyl Cellulose, sodium carboxymethylcellulose (SCMC) poly vinyl alcohol	Glycerin	Mucoadhesive buccal films	42
Salbutamol sulphate	Eudragit S-100 & Eudragit RSPO HPMC k4 M and HPMC k15M	Triethanolamin	Mucoadhesive Buccal patches	43
Ondestron hydrochloride	HPMC E15	Propylene glycol (PG),	Mucoadhesive Buccal patches	44
diltiazem hydrochloride	Sodium carboxymethyl cellulose(SCMC), Hydroxy Propyl cellulose (HPC).	Propylene glycol (PG),	Mucoadhesive Buccal patches	45
Aceclofenac	Gelatin, Poly Sodium CMC	Poly Vinyl Alcohol.	Mucoadhesive Buccal patches	46
Flurbiprofen	Carbopol, Sodium Carboxyl methyl cellulose Sodium, Hydroxy propyl methyl cellulose	Polyethylene glycol,	Mucoadhesive Buccal patches	47
Methotrexate	sodium alginate with carbopol-934	Glycerol	Mucoadhesive Buccal patches	48
Montelukast sodium	Hydroxyethyl Cellulose (HEC), Sodium carboxymethylcellulose (Nacmc), Eudragit RL-100 Polyvinylpyrrolidone K-30	Polyethylene glycol	Mucoadhesive Buccal patches	49
Resperidone	Hydroxy Propyl Methyl Cellulose (HPMC 47cps & 15 Cps), Chitosan, Poly Vinyl Alcohol, Poly Vinyl Pyrrolidone Polymer	Glycerine	Mucoadhesive Buccal patches	50

Table 3: List of brand name and company name [51]

BRAND NAME	COMPANY	DOSAGE FORMS
Buccastem®	Reckitt Benckiser	Buccal tablet
Corlan pellets®	Celltech	Oromucosal pellets
Suscard®	Forest	Buccal tablet
Gaviscon liquid®	Reckitt Benckiser	Oral liquid
Orabase®	Convatech	Oral paste
Corsodyl gel®	GalaxoSmithKline	Oromucosal gel (st)
Oralgen (us)	GenerexBiotechnology	Insulin Buccal Spray
Oralin (canada)	Corporation	Heparin Buccal Delivery System Fentanyl Buccal Delivery Systems
Straint	Columbia Laboratories Inc.	Testosterone Buccal Tablet Desmopressin Buccal Tablet
Cyclo-diolsr	Ergo Pharm	Androdiol Buccal Tablets
Cyclo-nordiolsr		Norandrodiol Buccal Tablets
Piobuc	Cytokine Pharma Sciences Inc.	Pilocarpine Buccal Tablet
Buccastem	Britannia Pharmaceuticals Ltd	Prochlorperazine Buccal Tablet
Glyceryl trinitrate	Pharmax Limited	(Suscard Buccal Tablet)
Actiq	Cephalon, Inc.	Oral Transmucosal Fentanyl Citrate Solid

Temestaexpidet	Wyeth Pharmaceuticals	Dosage Form Lorazepam Buccal Tablets
Seresta expidet		Oxazepam Buccal Tablets
Ivax	IVAX Corporation	Estrogen Buccal Tablet
Vitamins trans	Regency Medical research	Buccal Spray
Nicorette	Leo Pharmaceuticals	Nicotine Mucoadhesive Tablet
Nicotinell		Nicotine Chewing Gum
Aftach	Teijin Ltd.	Triamcinolone acetonide tablet
Tementil	Rhone-Poulenc Rorer	Prochlorperazine Bioadhesive Buccal Tablet
Buccastem	Reckitt Benckiser	
Subutex	Reckitt Benckiser	
Suboxane	Reckitt Benckiser	
Fentanyl Oralet	Lexicomp	Lozenge
Emezine TM	BDSI's	BDSI's
Bema fentanyl	BDSI's	
Straint tm SR	Ardana	
Zilactin	Zila	Buccal film
Luborant	Wyvem	Artificial Saliva
Saliveze	Tibotec	Artificial Saliva
Tibozole	Tejin Ltd	Tablet
Aphtach	Reckitt	Tablet
Povidone	Benkner Plc	
Oralin - gencrex	Generex Biotechnology (Phase II trials)	Solution
Lauriad (Phase III trials)	BioAlliance Pharma	Tablet
Striant SR buccal	Ardana Bioscience Ltd	Tablet

Chemical penetration enhancers

A chemical penetration enhancer, or absorption promoter, is a substance added to a formulation in order to increase the buccal membrane permeation or absorption rate of a drug, without damaging the buccal membrane. There have been many studies investigating the effect of chemical penetration enhancers on the delivery of drugs across the buccal mucosa.

Surfactants and bile salts

Surfactants and bile salts have enhanced the permeability of various drugs across the buccal mucosa, both in vitro and in vivo [52-54]. The enhancement in buccal permeability is due to an effect on the mucosal intercellular lipids. For example, the in vitro permeability of 2V,3Vdideoxycytidine through porcine buccal mucosa was enhanced with sodium glycodeoxycholate [55]. Sodium lauryl sulfate (SLS) is an ionic surfactant, which perturbs the entire membrane composition affecting both protein and lipid structures. Expansion of intercellular spaces and insertion of SLS molecules into the lipid structure has also been observed [56]. Sodium lauryl sulphate promoting an extensive enhancement of the buccal absorption of human calcitonin [57] and insulin [58]. Polyoxyethylene-9-lauryl ether (laureth 9), a non-ionic surfactant, was shown to significantly promote insulin absorption through buccal mucosa when used at 5 percentage [59].

However, the surfactants only enhance the permeability of drugs which traverse the buccal mucosa via the polar (paracellular) route. However, at very high concentrations of surfactant or bile salt, it appears that both the polar and nonpolar routes are affected. At higher concentrations of surfactant and bile salt, cellular membrane lipids may be extracted, resulting in enhanced transcellular transport. Bile salts have also been extensively investigated for their ability to enhance buccal penetration. The glucodeoxycholate (GDC) increased both the amount and the rate of buserelin absorption across the buccal mucosa [60]. The conjugated bile salt, sodium glycocholate, enhanced absorption of peptides [61].

Fatty acids

Fatty acids have been shown to enhance the permeation of a number of compounds through the buccal mucosa. However, no mechanism of action was investigated. The permeability of insulin from Pluronic F-127 gels was assessed through rat buccal mucosa [62]. The

improvement in ergotamine tartrate permeation through keratinized epithelial-free hamster cheek pouch by cod-liver oil extract [63].

Azone

The buccal penetration enhancing effects of Azone® have been extensively studied on several compounds, using a range of permeants. Azone® has been shown to increase the in vitro and in vivo permeability of salicylic acid through hamster cheek pouch buccal mucosa [64]. In addition, the enhancing effect of Azone® on buccal mucosa has been attributed to increase the fluidity of lipids extracted from the hamster cheek pouch [65]. The in vitro permeability of triamcinolone acetonide was improved 3.8 fold by pretreating porcine buccal mucosa with an ethanolic solution of Azone® [66]. Azone, also shown to increase the uptake and retention of estradiol [67] and triamcinolone bacetonide by increasing the reservoir capacity of the buccal epithelium [68].

Vehicles and adjuvants (co-solvent)

API can be dissolved or dispersed in a solvent to improve transport. Basically, the mechanism can be categorized as follows: (a) change in the thermodynamic activity (by increasing the degree of saturation in the vehicle); (b) facilitate partitioning of API from the vehicle in the mucosa). Lauric acid (10%) in propylene glycol was the most effective for buccal insulin absorption [69]. Ethanol at various concentrations (5 and 30%) was also effective in enhancing peptide absorption [70]. Pretreatment with ethanol has been shown to enhance the permeability of caffeine across porcine buccal mucosa [71]. The enhancing effect of ethanol on the permeability of tritiated water across the oral mucosa was due to the ability of ethanol to perturb the lipid molecules from their normal orderly arrangement [72].

Chitosan

Chitosan, a biocompatible and biodegradable polymer, has been shown to improve the in vitro permeability of hydrocortisone and transforming growth factor-h through porcine buccal mucosa [73, 74]. The enhancing effect of bioadhesive nature of chitosan, attributed to increased retention of the drug at the buccal mucosal surface [75]. It has also been suggested that the enhancing effect of chitosan is due to an interference with the intercellular lipid organization in the buccal epithelium [76].

Solubility Modifiers

Solubilization of poorly water-soluble drugs by complexation with cyclodextrins and delivering via the buccal mucosa is advantageous in increasing drug absorption and bioavailability. It has been reported that the release of felodipine from buccal tablet comprising hydroxypropyl- β -cyclodextrin-felodipine complex and hydroxypropyl methyl cellulose and is a complete and sustained release of the drug associated with an enhanced buccal permeation [77]. Formulating hydroxypropyl β cyclodextrin inclusion complex of miconazole, clotrimazole into chewing gums was found to increase the drug release from the chewing gums [78].

Enzyme inhibitors

The environment of the oral cavity and oral epithelium is highly enzymatic. This causes degradation of API before they are absorbed, therefore reducing bioavailability. In order to overcome this drawback research has begun into the use of enzyme inhibitors. Co-administration of a drug with enzyme inhibitors improves the buccal absorption of drugs, particularly peptides [79]. Some protease inhibitors, such as aprotinin, bestatin, puromycin and bile salts have been shown to stabilize peptides against buccal mucosal enzymes [80,81]. The enzyme inhibitor glutathione improved the delivery of pituitary adenylate cyclase-activating polypeptide via a buccal delivery system for type II diabetes [82].

CONCLUSION

Over the last few decades, research in buccal drug delivery becoming more popular because it does have significant advantages like avoidance of first pass metabolism, pre-systemic elimination in the gastrointestinal tract, low enzymatic activity, economy and high patient compliance. Buccal drug delivery is potential delivery system for orally inefficient drugs as well as a feasible and attractive alternative for peptide and protein drug molecules. Since the introduction of Orabase in 1947, the market share of bioadhesive drug delivery systems is increasing. Despite many advantages this route is still very challenging; permeability of oral mucosa is potential limiting factor. The strategies studied to overcome such barriers include use of materials that combine mucoadhesive and penetration enhancer properties and the design of novel formulations. Penetration enhancers improve buccal drug delivery by one or more of the following mechanisms: (i) increasing the partitioning of drugs into the tissue, (ii) extracting intercellular lipids, (iii) interacting with epithelial protein domains (iv) increasing the retention of drugs at the buccal mucosal surface. However, the need for safe and effective buccal permeation enhancers is a crucial component for a prospective future of buccal drug delivery systems.

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