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A REVIEW NOVEL MUCOADHESIVE BUCCAL PERMEATION ENCHANCERS

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ABSTRACT

To boost the bioavailability of various controlled drug delivery systems (CDDS), there has been a recent focus on administering medications through the buccal mucosa. In this context, mucoadhesion—the ability of an object to stick to mucous membranes—holds a special place. API delivery via the buccal cavity offers a practical method of administration for both systemic and local activities. Direct entrance into the systemic circulation prevents hepatic first-pass action and gastrointestinal tract degradation. However, the oral mucosa's permeability is a limiting factor because it is less than that of the skin and intestinal mucosa. The buccal membrane is shown to be more permeable when differences in permeability between various oral area organs are taken into account. It is necessary to lessen the mucosa's barrier potential to transport a wider range of medication classes over the buccal mucosa. This requirement forced researchers to investigate buccal penetration enhancers that could get through the buccal mucosa's permeability barrier. Many substances, such as bile salts, surfactants, fatty acids, and their derivatives, ethanol, cyclodextrins, and chitosan, have been tested for their ability to increase penetration. This review's objectives are to define the structural and chemical makeup of the buccal mucosa's permeability barrier and to explain how buccal penetration enhancers work.

KEYWORDS: Penetration enhancers, endocytosis, membrane fluidity, Hydrophilic molecules.

INTRODUCTION

Permeation enhancers are substances that aid in the permeation through the mucosa. The development of mucoadhesive delivery systems for many medications is constrained by membrane permeability. Particularly in the buccal mucosa, the epithelium that lines the mucosa serves as a highly effective barrier to the absorption of medicines[1] . Because of variations in cellular shape, membrane thickness, enzymatic activity, lipid composition, and possible protein interactions, which are structural and functional features, the efficacy of an enhancer in one location is not the same in the other site.[2]

PROPERTIES OF PERMEABILITY ENHANCERS

Safe, non-toxic, non-irritant, non-allergenic, and pharmacologically and chemically inert permeation enhancers are ideal.[3]

By disrupting intercellular lipids, surfactants like anionic, cationic, nonionic, and bile salts improve drug permeability. Chelators work by obstructing calcium ions. The way fatty acids work is by making phospholipids more fluid. Positively charged polymers work by ionizing with the mucosal surface's negative charge.[4]

PERMEABILITILY

Oral mucosa has a lower degree of permeability than skin and intestinal mucosa. The buccal membrane is more permeable when permeability differences between various oral area organs are taken into account.[6] Drug penetration is prevented by the buccal mucosa. Drug administration is influenced by buccal absorption and the efficacy of this barrier.[7] Since buccal mucosa is less permeable than intestinal epithelium, the application of permeation enhancers in buccal drug administration dosage forms has received considerable research.[8] The buccal mucosa is similar to the intestinal mucosa and epidermis in that it has some leaky epithelia. The buccal mucosa's permeability is thought to be 4–4000 times greater than that of the skin.[9]The order of mouth cavity permeability is sublingual > buccal > palatal. The relative thickness and level of keratinization are used to determine the rank order.

MODE OF PERMEATION

Hydrophilic molecules may enter the buccal mucosa via the paracellular route since the cell membranes are somewhat lipophilic and may act as a barrier to polar hydrophilic permeants.[10] Drug passage through the buccal epithelium's intercellular domain is more advantageous than the intestine, even though tight junctions are uncommon in oral mucosa and their presence between intestinal epithelial cells is the major

barrier to paracellular drug transport through the intestine.[11]

There are various permeation methods, including
1) Passive diffusion, transcellular routes, and intracellular routes (crossing the cell membrane and entering the cell).
2) Pathway that is intracellular or paracellular (passing between the cells).
3) Transport mediated by a carrier.
4) The endocytosis.

THE ENDOCYTOSIS

The process by which the medication molecules were taken up by the cells is known as endocytosis. There are two types.
1) Phagocytosis: Solid Drug molecules are absorbed.
2) Pinocytosis: Intake of liquid medication compounds.

PENETRATION ENHANCERS

To fully exploit the oral mucosa as a site for medication administration, it is likely necessary to break through the permeability barrier. Permeability enhancers have been studied as a means of lowering this barrier.[12,13] When an API must travel through the buccal mucosal pathway to the systemic circulation to exert its effect, permeation enhancers are also necessary. Azone, bile salts (which function by removing membrane protein or lipids, fluidizing the membrane, inducing reverse micellization in the membrane, and establishing aqueous channels), and fatty acids (which act by breaking intercellular lipid packing) are some examples of enhancers. alcohols and lipids (by causing a zone of fluidity in intercellular lipids) (by reorganizing the lipid domains and by changing protein conformation).

The selection and effectiveness of permeation enhancers are influenced by several factors.
1) Physicochemical properties of the drug
2) Site of administration
3) Nature of the vehicle
4) Other excipients

Individual penetration enhancer use often has less of an impact than combination penetration enhancer use. The effectiveness of a penetration enhancer in one place may not be the same in another due to changes in structural and functional characteristics such as membrane thickness, lipid content, cellular shape, enzymatic activity, and possible protein interactions. Drug-specific increase of buccal membrane penetration.[14]

Specialized forms include
Safety, non-toxicity, irritability, and allergenicity; pharmacological and chemical inertness; lack of pharmacological activity in the body; compatibility with both excipients and pharmaceuticals; and compatibility with penetration enhancers.

However, the assessment of the buccal drug delivery penetration route is crucial since it is fundamental to choose the right penetration enhancer to increase drug permeability.

MECHANISMS OF ACTION

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

(i) Modifying the rheology of mucus
The viscoelastic layer thickness of mucus has a major impact on drug absorption. Furthermore, saliva that covers the mucus layers also prevents absorption. Saliva breaks down this barrier by thinning the mucus viscosity, which is how some permeation enhancers work.

(ii) Enhancing the lipid bilayer membrane's fluidity
The intracellular route is the most preferred method of medication absorption through the buccal mucosa. By interacting with lipid or protein components, some permeation enhancers disturb the intracellular lipid packing.

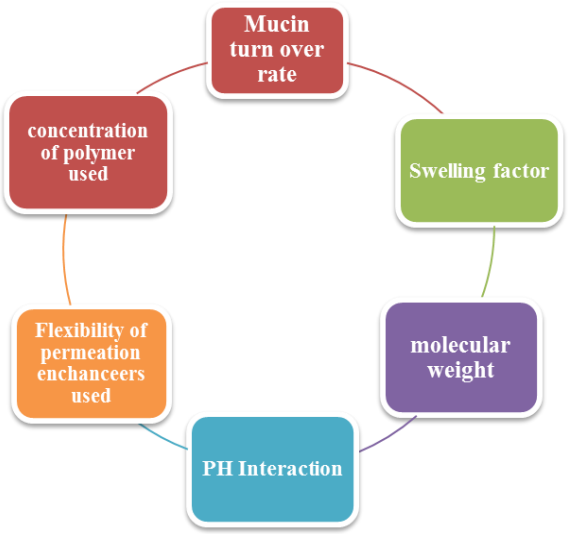

Fig. 1: Factors Affecting Mucoadhesion.

(iii) Manipulating the elements at tight junctions
Some permeation enhancers work on desmosomes, a key element at tight junctions, improving medication absorption in this way.

(iv) Obtaining it through an enzymatic barrier
These permeation enhancers function by preventing the various peptidases and proteases from working within the buccal mucosa, thus overcoming the enzymatic barrier. Additionally, changes in membrane fluidity indirectly impact enzymatic activity.

(v) The drug thermodynamic activity rising
Some permeation enhancers change the API's partition coefficient, increasing solubility as a result. As a result, there is a rise in thermodynamic activity, which improves medication absorption.

Table 1: List of permeation enhancers.[5]

Chelators	EDTA, Citric acid, Sodium salicylates, Methoxy salicylates
Surfactants	Sodium lauryl sulphate, Polyoxyethylene, Polyoxyethylene-9-laurylether , Polyoxythylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, Cetylpyridinium chloride, Cetyltrimethyl ammonium bromide
Bile Salts	Sodium glycocholate, Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxycholate, Sodium taurodeoxycholate
Fatty Acids	Oleic acid, Capric acid, Lauric acid, Lauric acid/ propylene glycol, Methyloleate, Lysophosphatidylcholine, Phosphatidylcholine
Non Surfactants	Unsaturated cyclic ureas.
Inclusion Complexes	Cyclodextrins
Thiolated Polymers	Chitosan-4-thiobutylamide, Chitosan-cysteine, Poly (acrylic acid)-homocysteine, Polycarbophil-cysteine, Polycarbophil-cysteine/gsh, Chitosan-4-thioethylamide/gsh, Chitosan- 4-thioglycholic acid

ENHANCERS FOR CHEMICAL PENETRATION

A chemical penetration enhancer, also known as an absorption promoter, is an ingredient added to a formulation to speed up a drug's permeation through the buccal membrane or rate of absorption without harming the buccal membrane. The impact of chemical penetration enhancers on the distribution of medications across the buccal mucosa has been the subject of numerous investigations.

Surfactants and bile salts

Only medications that travel through the buccal mucosa via the polar (paracellular) pathway will be made more permeable by the surfactants. However, it seems that both the polar and nonpolar pathways are impacted at extremely high surfactant or bile salt concentrations. Cellular membrane lipids may be removed at increased surfactant and bile salt concentrations, improving transcellular transport. Additionally, bile salts have been thoroughly researched for their capacity to improve buccal penetration. The volume and rate of buserelin absorption through the buccal mucosa were both accelerated by glucodeoxycholate (GDC).[15] Sodium glycocholate, a conjugated bile salt, improved peptide absorption.[16]

Vehicles and adjuvants (co-solvent)

To facilitate transport, API can be dissolved or dispersed in a solvent. The mechanism falls under the following categories: By raising the level of vehicle saturation, (a) the thermodynamic activity will alter; (b) the API will be easier to partition from the vehicle in the mucosa. The best solution for oral insulin absorption was propylene glycol (10%) laureate.[17] The absorption of peptides was similarly improved by ethanol at different concentrations (5 and 30 percent).[18] It has been demonstrated that pretreatment with ethanol increases the permeability of caffeine through the porcine buccal mucosa.[19] Because ethanol can disrupt lipid molecules from their regular, orderly structure, it has an enhanced influence on the permeability of tritiated water over the oral mucosa.[20]

Chitosan

Hydrocortisone and transforming growth factor-h have been demonstrated to have improved in vitro permeability through porcine buccal mucosa when combined with chitosan, a biocompatible and biodegradable polymer.[21,22]

Chitosan's bioadhesive properties are credited with improving the drug's retention at the buccal mucosal surface.[23] Additionally, it has been proposed that chitosan's boosting action is brought about by an interference with the buccal epithelium's intercellular lipid arrangement.[24]

Solubility Modifiers

Drug absorption and bioavailability can be improved by complexing poorly water-soluble medications with cyclodextrins and administering them through the buccal mucosa. According to reports, felodipine is released completely and continuously from buccal tablets containing hydroxypropyl—cyclodextrin-felodipine complex and hydroxyl propyl methyl cellulose, which has been linked to improved buccal permeability.[25] It was discovered that adding a miconazole and clotrimazole hydroxypropyl cyclodextrin inclusion complex to chewing gums increased the medication release from the gums.[26]

MERITS OF PERMEATION ENHANCERS

1) Comparing buccal medication delivery to other non-oral drug delivery methods, buccal drug delivery has a high patient acceptance.
2) Compared to the oral route, rapid action can be accomplished, and the formulation can be removed if therapy needs to be stopped.
3) Greater patient compliance as a result of the absence of injection-related pain.
4) It is more accessible for the administration and removal of a dose form and abundantly vascularized.
5) In addition, there was a limited location on the buccal mucosa's smooth surface where cells recovered quickly.
6) Continued medication delivery.

7) Greater perfusion results in more rapid and efficient absorption.
8) It is very important to avoid nausea and vomiting.
9) Used when a patient is unconscious and uncooperative.
10) Hepatic portal bypass, which increases the bioavailability of medicines taken orally that are subject to hepatic first-pass metabolism.
11) It is easy to deliver medicines that exhibit low oral bioavailability.[27]

DEMERITS OF PERMEATION ENHANCERS

It is impossible to design medications that irritate the oral mucosa, have a bitter taste, or trigger allergic reactions or tooth discoloration.

1) The natural bacteria in the buccal cavity are impacted if the formulation contains antimicrobial drugs.
2) This approach can only be used to give medications that are absorbed through passive diffusion.
3) This route cannot be used to give medications that are unstable at buccal pH.
4) The loss of a medication that has been dissolved or suspended could also result in saliva swishing.
5) The buccal membrane has a low permeability as compared to the sublingual membrane.
6) The medicine is diluted as a result of the continuous salivation (0.5-2 l/day).[27]

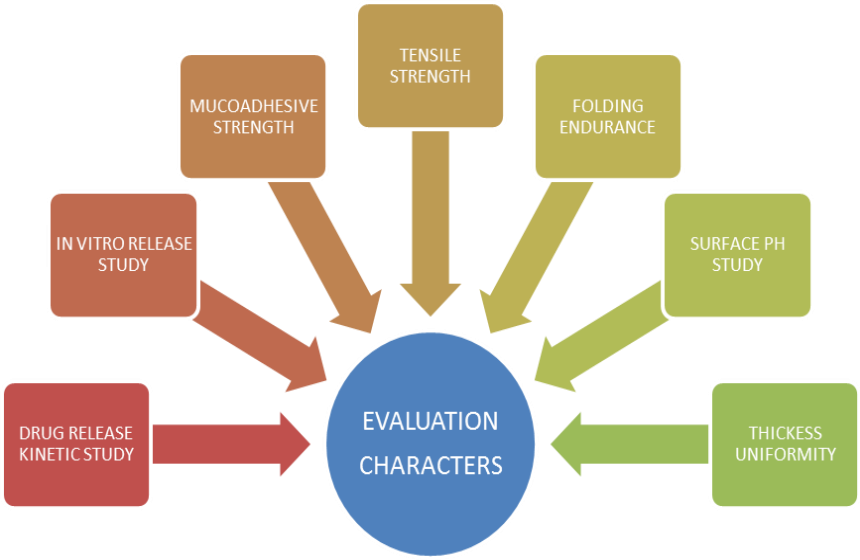

Figure 2: Evaluation characters.

CONCLUSION

Future advancements will have significant difficulty in maximizing the concentration of the enhancer to reduce its toxicity while enabling a reproducible boosting impact. Many medications that would previously require injection or water ingestion can now be delivered effectively and practically through buccal administration thanks to advancements in permeability regulation and formulation with the right enhancers. Instead, agents that can increase drug partitioning into the buccal epithelium, extract (and not disrupt) intercellular lipids, interact with epithelial protein domains, and/or increase drug retention at the buccal mucosal surface appear to be the cause of buccal penetration enhancement.

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