Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 703-711 | ISSN:2251-6727

Mucoadhesive Drug Delivery System: A Comprehensive Overview of Penetration Enhancers

Sunmon Raj Dutta[1], Srikanth Parepalli[2], Satya Obbalareddy[3], Raghunandan Nerella[4], Kumara Swamy Samanthula[1]*

[1]Department of Pharmaceutics, Faculty of Pharmaceutical Science, Assam down town University, Sankar Madhab Path, Gandhi Nagar, Panikhaiti, Guwahati, Assam, India, PIN – 781026.

[2]Vaagdevi Pharmacy College, Bollikunta, Warangal, Telangana, India, PIN-506005.

[3]Department of Pharmacognosy & Phytochemistry, Pratiksha Institute of Pharmaceutical Sciences, Guwahati, Assam, India, PIN – 781026.

[4]KVK College of Pharmacy, Surmaiguda, Lashkar Guda, Hayathnagar, Abdullapurmet, Ranga Reddy, Telangana, India, PIN-501512

***Corresponding Author:**

Dr. Kumara Swamy Samanthula

Associate Professor,

Faculty of Pharmaceutical Science, Assam Down Town University, Sankar Madhab Path, Gandhi Nagar, Panikhaiti, Guwahati, Assam, 781026, India.

(Received: 04 February 2024 Revised: 11 March 2024 Accepted: 08 April 2024)

KEYWORDS

Buccal drug delivery, penetration enhancers, first-pass metabolism, bioavailability.

ABSTRACT:

Buccal medication administration is a relatively new technique that has gained favor in recent years as a result of its many benefits over more conventional dose forms. It is ideal for the buccal distribution of drugs that have a short biological half-life, a low molecular weight, poor water solubility, an unstable stomach pH, a low dose, and a high first-pass metabolism. Drug absorption is hindered by the buccal mucosa's complicated structure. Therefore, penetration enhancers are used in conjunction with the medications to increase the bioavailability of the delivered drug by improving drug absorption across the buccal membrane. Improved drug partitioning across the buccal mucosa, interactions with intracellular lipids and proteins, and an extended retention time surrounding the mucosa are all mechanisms by which penetration enhancers exert their effects. In order to better understand the function of penetration enhancers and how they considerably boost medication absorption via the buccal mucosa, this review will attempt to do just that.

1. Introduction

The term "bioadhesion" describes the phenomenon wherein interactions keep two materials, one biological in origin, bound together for long durations. The process is called mucoadhesion when it sticks to mucus or a mucous membrane. Patients and doctors alike may find that the oral route is the most convenient way to take their medications.

The traditional oral method of medicine administration is not always effective, according to our present knowledge of the biochemical and physiological variables impacting absorption and metabolism. It is often seen that there is a strong lack of correlation between membrane permeability, absorption, and bioavailability. This is mostly due to the medications' substantial pre-systemic clearance after delivery [1]. The ability of alternative drug delivery techniques to enhance the bioavailability of pharmaceuticals has generated increasing interest in them in recent years. Even though rectal, vaginal, and ocular mucosae all have their advantages, the unwillingness of patients to utilize them restricts their usage to local applications rather than systemic medication delivery [2-5].

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 703-711 | ISSN:2251-6727

The ability of mucoadhesion to enhance localized medication delivery has led to its increasing recognition. This involves securing a dose form at the exact site of action, like the GI tract, or encouraging systemic administration by maintaining the formulation near the absorption site, like the buccal cavity, to name a few examples. Both buccal and sublingual absorption of medications from the oral cavity are possible through the oral mucosa. Orabase's introduction in 1947 marked the beginning of buccal drug delivery. Recently, there has been a tremendous amount of interest in delivering medicinal agents via various transmucosal routes. Buccal drug delivery offers an attractive alternative to normal oral medication administration, which helps to overcome the limitations of the standard dosing approach [6]. Drug deterioration in the hostile gastrointestinal environment and extensive first-pass metabolism can be avoided by using the buccal route and other lipid carrier systems [7]. Tablets, films, disks, ointments, gels, and strips are some of the many mucoadhesive devices invented recently. Besides buccal patches, they are more convenient and flexible than other devices.

Furthermore, patches address the issue of the short residence period of oral gels on the mucosa, which is rapidly eliminated by saliva. The buccal method of medication administration greatly improves bioavailability since it directly enters the systemic circulation via the jugular vein, so avoiding first-pass hepatic metabolism. Plus, it's easy to administer, has a smooth withdrawal process, and can be formulated to include pH modifications, enzyme inhibitors, permeation enhancers for local or systemic action, and it has low enzymatic activity, so it's suitable for medications or excipients that gently irritate or damage the mucosa [8].

In a modified-release thin matrix dosage form, the buccal device does not dissolve. The device comprises one or more layers of polymer containing the medicine and additional excipients. The device can be designed with a mucoadhesive polymer layer that sticks to the teeth, gums, or oral mucosa. This layer allows for controlled release of the medication into the oral mucosa, the oral cavity, or both. After the recommended time has passed, the device is taken out of the mouth and discarded [9-10].

2. The buccal mucosa

2.1 The structure

When we look at the human mouth under a light microscope, we can see that different parts of the mouth develop differently. The oral mucosa is composed of the externalmost layer of stratified squamous epithelium. Underneath this layer are the basement membrane, the intermediate lamina propria layer, and the innermost submucosa layer (Fig 1) [11].

2.2 Components of buccal mucosa

2.2.1 Epithelium

As with other stratified squamous epithelia throughout the body, the epithelium acts as a barrier that keeps potentially hazardous chemicals from penetrating the deeper tissues below. The process begins with a layer of rapidly increasing basal cells, and then it ascends through numerous layers of intermediate cells that are developing until it reaches the surface epithelial cells that are discharged in the superficial layers. It is subdivided into

2.2.2 Not keratinized Epithelium: There is no keratinization on the alveolar mucosa, floor of the mouth, lips, cheeks, soft palate, ventral surface of the tongue, or vestibule mucosa. Neither ceramide nor acylceramides are present in these regions. Some polar but neutral lipids, such as cholesterol sulfate and glucosyl ceramides, are also slightly lacking in their ding to the research, the water permeability of these epithelia is much higher than that of keratinized epithelia [12-13].

2.2.3 Keratinized Epithelium: In the cavity inside the mouth, keratinized epithelium is found in the hard palate and other non-flexible areas. On their journey to the surface, the epithelial cells undergo a metamorphosis from their basal cell origins. Keratinized epithelia contain neutral lipids such as ceramides and acylceramides, which are associated with barrier function. When it comes to water, these epithelia are relatively impermeable.

2.2.4 The basement membrane

Separating the epithelium among the connective tissues is the basement membrane, a distinct layer. The epithelium relies on this membrane for mechanical

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 703-711 | ISSN:2251-6727

support because it ensures the epithelium's critical adherence to the underlying connective tissues. Importantly, its mechanical characteristics are dictated by the connective tissues under the oral mucosa.

2.2.5. Submucosa

Typically, glycoproteins that are insoluble in water are found in mucus, a material that has the consistency of a gel and covers the mouth cavity. By forming a barrier in the form of a viscoelastic hydrogel, mucus serves the purpose of protecting the cells that lie behind it. The primary constituents consist of water (with a concentration ranging from 95 to 99%), the water-insoluble glycoproteins stated earlier (with a concentration ranging from 1 to 5 percent), enzymes, nucleic acids, electrolytes, and trace amounts of other chemicals. Different mucus compositions may be found in different body parts, depending on where it is located [14].

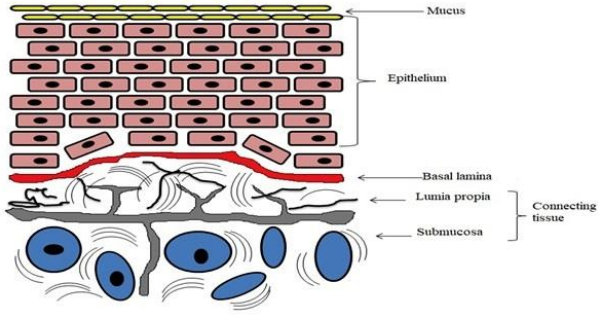

Figure 1: Schematic diagram of Structure of buccal mucosa

3. Permeability of oral mucosa

The oral mucosa is less permeable than the skin and intestinal mucosa. After accounting for variations in permeability among the oral organs, however, it becomes clear that the buccal membrane is the most absorbent. The buccal mucosa acts as a barrier to the penetration of drugs. Important factors influencing medication administration include the efficacy of this barrier and the buccal absorption process. The buccal mucosa is less permeable than the intestinal epithelium. The use of permeation enhancers in buccal drug delivery formulations has thus been extensively studied. Compared to the intestinal mucosa and the epidermis, the buccal mucosa has a moderate permeability. According to estimates, porous skin has a permeability that is four to four thousand times lower than buccal mucosa. The oral cavity's permeability is ranked sublingually, followed by buccally and palatally. This ranking is based on the relative thickness and degree of keratinization. For this ranking, relative thickness and keratinization level are important factors [15].

Permeability coefficients are crucial in measuring the ease with which drugs can cross biological membranes. The process, however, is more complex. It involves considering factors such as the drug's size, weight, lipophilicity, and the extent to which these tissues are keratinized. An intriguing inverse relationship exists between membrane thickness and the permeability coefficient. The oral mucosa's permeability barrier, caused by intercellular material, is believed to originate from one of two kinds of membrane-coating granules (MCG). These MCGs are found in keratinized and nonkeratinized tissues, with the former appearing less permeable due to their ceramides, glucosylceramides, and sphingomyelin composition in lamellar lipid stacks. Lipids that aren't part of keratinized tissues include glycosphingolipids, cholesterol, and cholesterol esters, among others [16].

3.1 Mode of permeation

The high lipophilicity of cell membranes, which can act as a barrier to the passage of polar hydrophilic permeants, underscores the significance of the paracellular route as the primary means by which hydrophilic compounds penetrate the buccal mucosa. While tight junctions between intestinal epithelial cells, though uncommon in the oral mucosa, pose a significant obstacle to paracellular drug transport across the intestines, medications may find it easier to penetrate the buccal epithelium due to its larger intercellular domain [17-18]. Various permeations happen in various ways.

3.1.1 Passive diffusion

- A transcellular or intracellular pathway entails entering the cell by piercing the membrane.
- Pathways that span between cells are referred to as paracellular or intercellular pathways. (Fig 2)

3.1.2 Carrier mediated transport: This process combines chemical reactions and diffusion processes. In this transport mechanism, known as carrier mediated

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 703-711 | ISSN:2251-6727

transport, the solute must first react with the carrier to form a solute-carrier complex before it can be released at the permeate side of the membrane.

3.1.3 Endocytosis

Both pathways can be utilized simultaneously by permeants, but in most cases, the physicochemical properties of the diffusant determine which route is chosen. Lipophilic compounds usually have poor solubility in hydrophilic environments like the intercellular spaces and cytoplasm (Fig 3) [19].

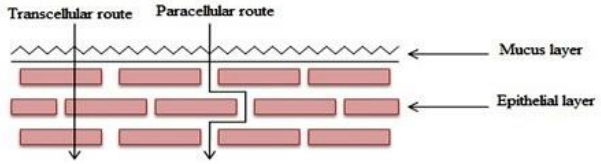

Figure 2: Tanscellular and paracellular

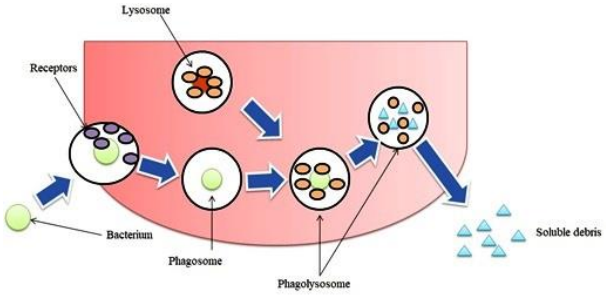

Figure 3: Phagocytosis

4. Penetration enhancers

The permeability barrier is one major obstacle to utilizing the oral mucosa for drug delivery. Researchers have looked at permeability enhancers as a possible remedy for this issue. Permeability enhancers are also necessary when an Active Pharmaceutical Ingredient (API) demands to reach the systemic circulation across the buccal mucosa to begin functioning. Enhancers contain various surfactants, one of which is bile salts. For bile salts to function, the membrane must be free of lipids or proteins, fluidized, reverse micellization initiated, and aqueous channels created. Azone produces a fluid area in intercellular lipids, fatty acids disrupt the intercellular lipid packing, and alcohols rearrange lipid domains and alter the conformation of proteins. The following are some elements that influence permeation enhancer selection and effectiveness:

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

Combining penetration enhancers usually yields a more noticeable result than using each enhancer separately. The efficiency of a penetration enhancer varies at different sites due to variations in structural and functional features, such as membrane thickness, lipid composition, cellular morphology, enzymatic activity, and potential protein interactions. Increasing buccal membrane penetration can take different forms depending on the medication [20].

4.1 Prime features of penetration enhancers:

For penetration enhancers to be considered fully functional, they must be compatible with drugs and excipients, completely risk-free, and free of known irritants, toxins, or allergies. Specifically, they must not have any pharmacological effects on the human body without any discernible chemical or pharmacological effects.

4.2 Mechanisms of action of penetration enhancers

The mechanisms by which penetration enhancers work are as follows (Table 1):-

4.2.1 Alterations in mucus rheology

The thickness of the mucus viscoelastic layer is the primary factor affecting medication absorption. Saliva can also obstruct absorption by coating the mucous membranes. Certain permeation enhancers can reduce mucus viscosity, enabling it to pass through the salivary barrier.

4.2.2 Enhancing the lipid bilayer membrane's fluidity

When drugs are absorbed through the buccal mucosa, they are most commonly absorbed through the intracellular route. Certain permeation enhancers can disturb intracellular lipid packing through interactions with lipid or protein components.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 703-711 | ISSN:2251-6727

4.2.3 Influencing the components at their tight junctions

Some permeation enhancers increase drug absorption via this pathway by focusing on desmosomes—vital components of tight junctions.

4.2.4 By bypassing the enzymatic barrier

This permeation enhancer gets through the enzymatic barrier by inhibiting the action of various peptidases and proteases found in the buccal mucosa. A change in membrane fluidity can indirectly affect enzyme activity.

4.2.5 By increasing the thermodynamic activity of pharmaceuticals

Some permeation APIs alter their partition coefficient to improve the API's solubility. This rise in thermodynamic activity improves drug absorption. The following are examples of the many kinds of penetration enhancers and how they work in the creation of buccal drug delivery systems [21].

4.3 Properties of penetration enhancers

4.3.1 Surfactants and bile salts

Surfactants and bile salts enhance the buccal mucosa's permeability to several medicines, according to in vitro and in vivo investigations. Researchers believe the increase in buccal permeability is due to a change in mucosal intercellular lipids. For example, adding sodium glycodeoxycholate increased the in vitro permeability of 2V and 3V-dideoxycytidine through the porcine buccal mucosa. An ionic surfactant such as sodium lauryl sulfate (SLS) modifies the composition of membranes by interfering with lipid and protein structures. It has also been observed that SLS molecules have been inserted into the lipid structure and that intercellular gaps have expanded. The buccal absorption of human calcitonin is significantly increased when sodium lauryl sulfate and insulin are used. Evidence suggests that the non-ionic surfactant polyoxyethylene-9-lauryl ether (laureth 9) at a concentration of 5% greatly enhances insulin absorption via the buccal mucosa [23-26].

However, surfactants can only enhance the buccal mucosa permeability of polar (paracellular) drug pathways. Surprisingly, it seems that very high concentrations of surfactant or bile salt impact both the polar and nonpolar pathways. Extracting lipids from cell membranes at high surfactant and bile salt concentrations might enhance transcellular transport. Much research has also been done into the possibility that bile salts could improve buccal penetration. It was shown that glutamate deoxycholate enhanced the quantity and rate of buserelin absorption via the buccal mucosa. Sodium glycocholate, a conjugated bile salt, improved peptide absorption [27].

4.3.2 Fatty acids

Research has shown that fatty acids may improve the buccal mucosa penetration of several substances. However, the mechanism of action was not investigated. The permeability of Pluronic F-127 gels to insulin was assessed using rat buccal mucosa. Researchers observed that an extract from cod liver oil improved the uptake of ergotamine tartrate into a keratinized epithelial-free hamster cheek pouch [28].

4.3.3 Azone

Many chemicals and permeants have been thoroughly investigated for their potential to enhance buccal penetration with azo. The buccal mucosa of hamster cheek pouches is more permeable to salicylic acid when treated with azone, according to both in vitro and in vivo studies. Additionally, azone's impact on the buccal mucosa has been linked to improving lipid fluidity, as retrieved from the hamster cheek pouch. Triamcinolone acetonide's in vitro permeability was enhanced by a factor of 3.8 when ethanolic Azone solution was applied to porcine buccal mucosa before treatment. Azone also increases the reservoir capacity of the buccal epithelium, which improves the absorption and retention of triamcinolone acetonide and estradiol [29-31].

4.3.4 Chitosan

It has been proven that chitosan, a biocompatible and biodegradable polymer, may increase the permeability of hydrocortisone and transform growth factor-H via the buccal mucosa of porcine animals in vitro. Because of the medication's greater retention at the buccal mucosal

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 703-711 | ISSN:2251-6727

Table 1: List of penetration enhancers, there mechanism of action and mode of transport [22]

Classification	Examples	Mechanism of action	Mode of transport
Surfactants	**Anionic** Sulfate(SDS) Dioctyl Sodium lauryl sulfate Sodium dodecyl Sodium Sodium laurate Laureth-9 Sulfosuccinate	Intercellular lipids are disrupted while preserving the integrity of the protein domains	Paracellular
	Nonionic Tween80 Polyoxyethylene-9-lauryl ethe(PLE) Polysorbates Sodium glycocholate Nonylphenoxypolyoxyethylene(NPPOE)	Intercellular lipids are disrupted while preserving the integrity of the protein domains	Paracellular
	Cationic cetylpyridinium chloride Chitosan, trimethyl chitosan Poly-L-arginine L-lysine	Interaction of ions with the mucosal surface, which is negatively charged	Paracellular
Bile salts and derivatives	Taurodihydrofusidate(STDHF) Sodium Taurocholate Sodium Glycodihydrofusidate Sodium Glycocholate Sodium deoxycholat Sodium deoxycholate Sodium	Intercellular lipids are disrupted while preserving the integrity of the protein domains	Paracellular
Fatty acids and derivatives	Oleic acid Caprylic acid Mono(di)glycerides,Lauric acid Linoleic acid Acylcholines,Acylcarnitine Sodium caprate Oleic acid	Improve the fluidity of phospholipid domains.	Paracellular
Chelating agents	EDTA Citric acid Salicylates	Disrupt the Ca2+ ion exchange	Paracellular
Sulfoxides	Dimethyl sulfoxide(DMSO) Decylmethyl sulfoxide	Intercellular lipids are disrupted while preserving the integrity of the protein domains	Paracellular
Monohydric alcohol	Ethanol Isopropanol	Interference with the intercellular lipid assembly.	Paracellular
Polyols	Propylene glycol Polyethylene glycol Glycerol Propanediol		Paracellular
Others (nonsurfactants)	Urea and derivative Unsaturated cyclic urea Azone(1-dodecylazacycloheptan-2-one) (laurocapram) Cyclodextrin	Intercellular lipids are disrupted while preserving the integrity of the protein domains	Paracellular

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 703-711 | ISSN:2251-6727

surface, chitosan has better bioadhesive properties. This is the reason for the improvement. Chitosan's ability to improve the condition of the buccal epithelium has been hypothesized to be because it disrupts the intercellular lipid arrangement of the intercellular matrix [32].**4.3.5 Vehicles and adjuvants (co-solvent)**

It is possible to dissolve the active pharmaceutical ingredient (API) in a solvent or to disperse it throughout the solvent in order to make transportation more convenient. In general, the mechanism may be broken down into the following groups depending on its characteristics:

a. Altering the thermodynamic activity, which may be accomplished by increasing the saturation level of the vehicle;
b. Promoting the separation of the active pharmaceutical ingredient (API) from the vehicle at the mucosal level.

It was discovered that a combination consisting of 10% lauric acid in propylene glycol was the most effective for buccal insulin absorption. Furthermore, ethanol at concentrations of 5% and 30% showed potential for improving the absorption of peptides throughout the experiment. It has been proven that the permeability of caffeine through the buccal mucosa of pigs is increased when ethanol pretreatment is performed. Ethanol can disrupt the regular and ordered arrangement of lipid molecules that is responsible for the enhanced permeability of tritiated water over the oral mucosa [33-34].

4.3.6 Enzyme inhibitors

It is characteristic of the oral cavity and the oral epithelium to have a highly enzymatic environment. As a consequence of this, active pharmaceutical ingredients (APIs) degrade before absorption, which results in a decrease in bioavailability. To overcome this constraint, research into the use of enzyme inhibitors has started. Therefore, when enzyme inhibitors are supplied at the same time as medications, particularly peptides, the buccal mucosa can absorb the pharmaceuticals more effectively. Certain protease inhibitors, such as bile salts, bestatin, puromycin, and aprotinin, have been shown to stabilize peptides against enzymes in the buccal mucosa. This has been proved via research. When glutathione, an enzyme inhibitor, was employed in conjunction with a buccal administration method, the pituitary adenylate cyclase-activating polypeptide could be administered with more efficiency for treating type II diabetes [35].

4.3.7 Solubility Modifiers

Cyclodextrin complexation enhances the solubility of pharmaceuticals that are not very water-soluble and distributes them through the buccal mucosa, making it possible to boost the bioavailability and absorption of drugs. When felodipine is released from a buccal tablet that comprises a combination of hydroxypropyl-β-cyclodextrin-felodipine and hydroxypropyl methylcellulose, research has shown that the medication is released in a manner that is both full and sustained and that it also improves buccal penetration. It has been discovered that the incorporation of hydroxypropyl β-cyclodextrin inclusion complexes containing miconazole and clotrimazole into chewed gums results in an enhancement in the release of the medication from the gums [36].

5. Conclusion

New methods of medication delivery are getting a lot of interest lately because of the possibility that they might improve drug bioavailability. With buccal administration, the medicine enters straight into the systemic circulation via the mucosal membranes lining the cheeks rather than the digestive tract, which improves bioavailability and avoids first-pass metabolism. This is a major improvement over oral drug delivery techniques. In buccal medication distribution, the buccal patch plays a crucial role. One of the numerous components needed to make it is buccal patch penetrating enhancers. This review seeks to provide a brief understanding of the various penetration enhancers used in the formulation of buccal drug delivery systems and understand their mechanisms of action. And also the effect that the different types of penetration enhancers will have on a buccal drug delivery system.

Interest Declaration:

The authors declare that there is no conflict of interest.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 703-711 | ISSN:2251-6727

Reference

1. Harris, D. and Robinson, J.R., 1992. Drug delivery via the mucous membranes of the oral cavity. Journal of pharmaceutical sciences, 81(1), pp.1-10.
2. Janga, K.Y., Tatke, A., Dudhipala, N., Balguri, S.P., Ibrahim, M.M., Maria, D.N., Jablonski, M.M. and Majumdar, S., 2019. Gellan gum based sol-to-gel transforming system of natamycin transfersomes improves topical ocular delivery. Journal of Pharmacology and Experimental Therapeutics, 370(3), pp.814-822.
3. Donthi, M.R., Dudhipala, N.R., Komalla, D.R., Suram, D. and Banala, N., 2015. Preparation and evaluation of fixed combination of ketoprofen enteric coated and famotidine floating mini tablets by single unit encapsulation system. Journal of Bioequivalence & Bioavailability, 7(6), p.279.
4. Mamatha, Y., Selvi, A., Prasanth, V.V., Sipai, M.A.B. and Yadav, V., 2012. Buccal drug delivery: a technical approach. Journal of Drug Delivery and Therapeutics, 2(2).
5. Reddy, P.C., Chaitanya, K.S.C. and Rao, Y.M., 2011. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. DARU Journal of Pharmaceutical Sciences, 19(6), p.385.
6. Samanthula, K.S., Satla, S.R. and Bairi, A.G., 2021. Bioadhesive polymers, permeation enhancers and types of dosage forms for buccal drug delivery. Journal of Drug Delivery and Therapeutics, 11(1), pp.138-145.
7. Dudhipala, N., 2019. A comprehensive review on solid lipid nanoparticles as delivery vehicle for enhanced pharmacokinetic and pharmacodynamic activity of poorly soluble drugs. International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN), 12(2), pp.4421-4440.
8. Teotia, D., 2020. A comprehensive review on buccal patches. GSC Biological and Pharmaceutical Sciences, 13(1), pp.130-135.
9. Zhang, J., Niu, S., Ebert, C. and Stanley, T.H., 1994. An in vivo dog model for studying recovery kinetics of the buccal mucosa permeation barrier after exposure to permeation enhancers: apparent evidence of effective enhancement without tissue damage. International journal of pharmaceutics, 101(1-2), pp.15-22.
10. Shojaei, A.H. and Li, X., 1996. In vitro permeation of acyclovir through porcine buccal mucosa. In Proceedings of International Symposium on Controlled Release of Bioactive Materials (Vol. 23, pp. 507-508).
11. Shakya, P., Madhav, N.S., Shakya, A.K. and Singh, K., 2011. Palatal mucosa as a route for systemic drug delivery: A review. Journal of controlled release, 151(1), pp.2-9.
12. Diaz-del Consuelo, I., Jacques, Y., Pizzolato, G.P., Guy, R.H. and Falson, F., 2005. Comparison of the lipid composition of porcine buccal and esophageal permeability barriers. Archives of oral biology, 50(12), pp.981-987.
13. Humphrey, S.P. and Williamson, R.T., 2001. A review of saliva: normal composition, flow, and function. The Journal of prosthetic dentistry, 85(2), pp.162-169.
14. Galey, W.R., Lonsdale, H.K. and Nacht, S., 1976. The in vitro permeability of skin and buccal mucosa to selected drugs and tritiated water. Journal of investigative dermatology, 67(6), pp.713-717.
15. Prasanth, V.V., Mudiyala, S., Mathew, S.T. and Mathapan, R., 2011. Buccal tablet-as mucoadhesive drug delivery: An over view. Journal of Pharmacy Research, 4(3), pp.706-709.
16. Magnusson, B.M., Walters, K.A. and Roberts, M.S., 2001. Veterinary drug delivery: potential for skin penetration enhancement. Advanced drug delivery reviews, 50(3), pp.205-227.
17. Hearnden V, Sankar V, Hull K, Juras DV, Greenberg M, Kerr AR, Lockhart PB, Patton LL, Porter S, Thornhill MH. New developments and opportunities in oral mucosal drug delivery for local and systemic disease. Advanced drug delivery reviews. 2012 Jan 1;64(1):16-28.
18. Nicolazzo, J.A., Reed, B.L. and Finnin, B.C., 2005. Buccal penetration enhancers—how do they really work?. Journal of controlled release, 105(1-2), pp.1-15.
19. Reddy, P.C., Chaitanya, K.S.C. and Rao, Y.M., 2011. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. DARU Journal of Pharmaceutical Sciences, 19(6), p.385.
20. Steward, A., Bayley, D.L. and Howes, C., 1994. The effect of enhancers on the buccal absorption of

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 703-711 | ISSN:2251-6727

hybrid (BDBB) α-interferon. International journal of pharmaceutics, 104(2), pp.145-149.

21. Şenel, S. and Hıncal, A.A., 2001. Drug permeation enhancement via buccal route: possibilities and limitations. Journal of Controlled Release, 72(1-3), pp.133-144.
22. Moser, K., Kriwet, K., Naik, A., Kalia, Y.N. and Guy, R.H., 2001. Passive skin penetration enhancement and its quantification in vitro. European journal of pharmaceutics and Biopharmaceutics, 52(2), pp.103-112.
23. Xiang, J., Fang, X. and Li, X., 2002. Transbuccal delivery of 2′, 3′-dideoxycytidine: in vitro permeation study and histological investigation. International journal of pharmaceutics, 231(1), pp.57-66.
24. Ganem-Quintanar, A., Kalia, Y.N., Falson-Rieg, F. and Buri, P., 1997. Mechanisms of oral permeation enhancement. International journal of pharmaceutics, 156(2), pp.127-142.
25. Oh, C.K. and Ritschel, W.A., 1990. Absorption characteristics of insulin through the buccal mucosa. Methods and findings in experimental and clinical pharmacology, 12(4), pp.275-279.
26. Aungst, B.J. and Rogers, N.J., 1989. Comparison of the effects of various transmucosal absorption promoters on buccal insulin delivery. International journal of pharmaceutics, 53(3), pp.227-235.
27. Hoogstraate, A.J., Verhoef, J.C., Pijpers, A., van Leengoed, L.A., Verheijden, J.H., Junginger, H.E. and Boddé, H.E., 1996. In vivo buccal delivery of the peptide drug buserelin with glycodeoxycholate as an absorption enhancer in pigs. Pharmaceutical research, 13, pp.1233-1237.
28. Tsutsumi, K., Obata, Y., Takayama, K., Loftsson, T. and Nagai, T., 1998. Effect of cod-liver oil extract on the buccal permeation of ergotamine tartrate. Drug development and industrial pharmacy, 24(8), pp.757-762.
29. Sudhakar, Y., Kuotsu, K. and Bandyopadhyay, A.K., 2006. Buccal bioadhesive drug delivery—a promising option for orally less efficient drugs. Journal of controlled release, 114(1), pp.15-40.
30. Nicolazzo, J.A., Reed, B.L. and Finnin, B.C., 2005. Enhanced buccal mucosal retention and reduced buccal permeability of estradiol in the presence of padimate O and Azone®: a mechanistic study. Journal of pharmaceutical sciences, 94(4), pp.873-882.
31. Caon, T., Jin, L., Simões, C.M., Norton, R.S. and Nicolazzo, J.A., 2015. Enhancing the buccal mucosal delivery of peptide and protein therapeutics. Pharmaceutical research, 32, pp.1-21.
32. Portero, A., Remuñán-López, C. and Nielsen, H.M., 2002. The potential of chitosan in enhancing peptide and protein absorption across the TR146 cell culture model—an in vitro model of the buccal epithelium. Pharmaceutical research, 19, pp.169-174.
33. Yang, T.Z., Zhang, Q., Chen, D.B. and Nagai, T., 2001. Comparison of the effects of various transmucosal absorption enhancers on buccal insulin delivery: in vitro and in vivo studies. STP pharma sciences, 11(6), pp.415-419.
34. Dodla, S. and Velmurugan, S., 2013. Buccal penetration enhancers—An overview. Asian J. Pharm. Clin. Res, 6(3), pp.39-47.
35. Samanthula, K.S., Kumar CB, M., Bairi, A.G. and Satla, S.R., 2022. Development, in-vitro and ex-vivo evaluation of muco-adhesive buccal tablets of hydralazine hydrochloride. Brazilian Journal of Pharmaceutical Sciences, 58, p.e18635.
36. Satheesh Madhav, N.V., Semwal, R., Semwal, D.K. and Semwal, R.B., 2012. Recent trends in oral transmucosal drug delivery systems: an emphasis on the soft palatal route. Expert opinion on drug delivery, 9(6), pp.629-647.