Advancing Buccal Drug Delivery Systems: Challenges and Opportunities – A Review

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Abstract

There are many ways to deliver drugs into the body, oral (through swallowing), submucosal (through buccal and sublingual mucosa), parenteral (through injection) , transdermal (through skin) , pulmonary (through inhalation) etc.Oral cavity is a site where both local and systemic delivery of drugs can take place and therefore oral drug delivery is the most preferred and convenient option as it provides maximum active surface area compared to other drug delivery systems.Local delivery of drugprovides topical treatment of different oral mucosal infections. However, treatment can be influenced if the medications can be focused on specifically to the site of injury, accordingly lessening the systemic side effects. Buccal delivery of medication gives a convenient route of administration for both local and systemic effects. The objective of writing this review on buccal drug delivery system is to assemble the recent literature, provide knowledge about the advantages and limitations of buccal drug delivery system, pathways of absorption of drugs, theories of mucoadhesion and the newer drugs that can be administered along this route

Introduction

Oral route has been the most prevalent and effectively utilized route for controlled medication conveyance, in view of its comfort, greater flexibility in the design of dosage form and furthermore minimal effort and simplicity of production[1]. Medical practitioners and manufacturers preferably adopt for oral routes for its high patient compliance, ease of ingestion, high versatility, non-invasive and pain avoidance[2]. However administration of drug orally can be a hindrance in absorption, distribution and metabolism in the desired location, also the hepatic first pass effect brings to the drawback of this system. It is evaluated that 25% of the populace thinks that it's hard to swallow tablets and capsules and in this way don't take their drug as recommended by their specialist bringing about high frequency of rebelliousness and ineffectual treatment. Trouble is experienced specifically by paediatrics and geriatric patients, yet it likewise applies to individuals who are bedbound and to those dynamic working patients who are working or travelling, particularly the individuals who have no access to water[3]. In these cases medication conveyance through the mucosal route is generally favoured. Delivery of drugs within the oral mucosal cavity can be through 4 potential regions, buccal , sublingual, palatal, and gingival[4]. Among them sublingual and buccal sectors are most desired routes for delivery of drugs and hence used for therapeutic purpose of local and systemic diseases. The oral mucosa differs in its permeability and absorption capability, which is associated with the thickness and degree of keratinization. its permeability is highest in the sublingual region followed by the buccal and palatal mucosa[5]. Sublingual mucosa has larger surface area and higher rate of blood flow therefore is an attainable site for rapid onset of drugs. Drug administration through sublingual mucosa is widely used for acute diseases (angina pectoris and myocardial infarction). However it has some pitfalls, as the drug tends to lose its contact with mucosa due to activity of tongue and gets washed away constantly by saliva. Accordingly buccal mucosa presents with many advantages as it has immobile, relatively smooth surface and provides a relatively easy placement of controlled –release system. Hence administration through this route is generally agreed and acknowledged by patients. Oral controlled release system is designed as continuous release system, ie release of drug continuously over an extended period of time and pulsatile release system, which is characterized by a time period of no release followed by a rapid and complete or extended drug release[6]. In comparison to other oral mucosal tissues, buccal mucosa is relatively more permeable and has an increased potential for tolerating allergens which can cause irreversible damage or irritation to the tissue. Continuous formation of saliva and its constituent add to adjustment of medications chemically and diminish in ingestion from the site, because of voluntary gulping, loss of retention in the

assimilation site over a broadened period of time. This continuousscavenging of saliva draws an impediment to this conveyed route[7]. Over the years, it is yet been proved by the researchers that delivery of drug through buccal route as a dormant site for chronic systemic therapies. Administration of drugs via both buccal and sublingual routes has improved the bioavailability of drugs and rapid onset of action. Furthermore, there is a good potential for prolonged delivery of the drug through the mucus membrane within the oral cavity[8].Bio adhesive polymers have markedly improved the drug delivery through the buccal cavity, as they have prolonged retention with the tissues[9]. Therefore the goal of this review is to provide knowledge about the advantages and limitations of buccal drug delivery system and the newer drugs that can be administered along this route.

History

Back in 1925 attempts were made for insulin delivery through the buccal mucosa. But due to the limited permeability of insulin across the buccal mucosa, repeated attempts have been made to improve its absorption (either by adding chemical enhancers or by altering the physiochemical properties of the peptide). Later a drug formulation was made with insulin and adding chemical enhancers to it for better penetration of the drug through the membrane. This formulation was used for the treatment of type I and type II diabetes[10].In 1947, endeavours were made to define a penicillin drug conveyance system for delivering the bioactive operator to the oral mucosa utilizing gum tragacanth (a dental adhesive powder) was used for the mucoadhesive polymers. These dental adhesive polymers further improved the utilization of the pharmaceutical formulations. Enhanced outcomes were accounted for when carboxy methyl cellulose (CMC) and petrolatum were utilized for development of drug formulations. Consequent research brought about the improvement of a mucoadhesive delivery vehicle which comprised of finely ground sodium CMC (SCMC), pectin, and gelatin. The definition was later promoted as OrahesiveR. Another drug formulation which went into the clinical trials is OrabaseR which is a mixture of polymethylene/mineral oil base. This was trailed by the advancement of a system where polyethylene sheet was overlaid with a mix of SCMC and polyisobutylene which gave an additional preferred advantage of securing the mucoadhesive layer by the polyethylene backing. The polyethylene backing prevented any physical impedance from the outer environment[11],[12].Throughout the years, different polymers, for instance, sodium alginate, SCMC, guar gum, hydroxy ethyl cellulose, karya gum, methyl cellulose, polyethylene glycol, and tragacanth have been found to display mucoadhesive properties. Amid the 1980s, poly acrylic corrosive, hydroxypropyl cellulose, and SCMC were broadly investigated for the advancement of formulations having mucoadhesive properties. From that point forward, the utilization of acrylate polymers for the improvement of mucoadhesive formulations has expanded many folds. Different researchers have examined the mucoadhesive properties of various polymers with fluctuating molecular design. After thorough research, the scientists are of the view that a polymer showsadequate mucoadhesive property as it can frame solid intermolecular hydrogen bonding with the mucosal layer. Because of the high sub-atomic weight of the polymer chain, it allows infiltration of the polymer into the mucous network and simple wetting of mucosal layer. The perfect character of a mucoadhesive polymer lattice incorporates the quick adherence to the mucosal layer with no adjustment in the physical property of the delivery matrix, least impedance to the discharge of the active agent, biodegradable without creating any lethal by products, constrains the enzymes introduced at the conveyance site, and improves the entrance of the active agent[13],[14].

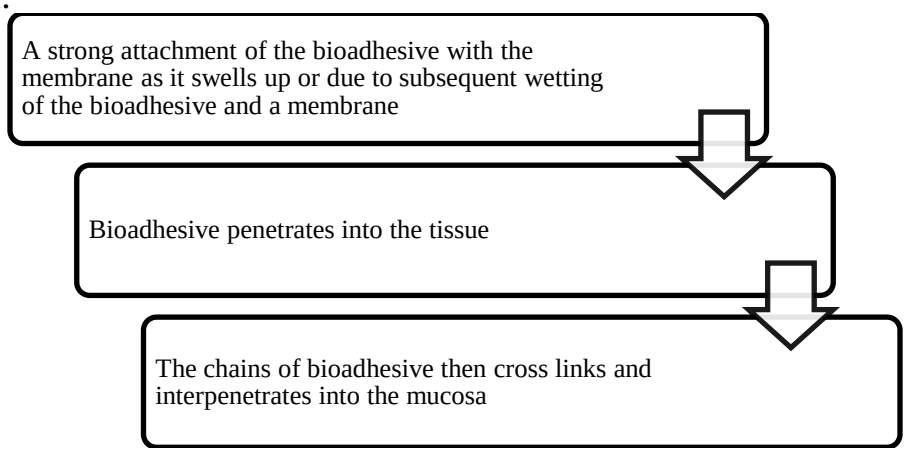
Mucoadhesion and its mechanism

The use of mucoadhesive polymers for the formulation of viscous gels and mouthwashes has always provided with better lubrication and retention. They are widely used for the symptomatic relief of ulcerated oral mucosa.An example of this is,Oraqix® gel which is a noninjectible periodontal gel. It contains a eutectic mixture of lidocaine and prilocaine, thus providing anaesthetic effect during scaling and root planning (SRP)[15].It has been reviewed that various enzymes present in both oral mucosal surface and in saliva creates a barrier for peptide and protein drugs [10],[16].The lack of enzymes responsible for hydrolysis like pepsin, trypsin and chymotrypsin, makes the enzymatic activity of buccal mucosa less effective than gastrointestinal tract[10]. Proteolytic enzymes namely endopeptidases, aminopeptidases, esterases, carboxypeptidases and phosphatases have been explored in the buccal mucosa of humans, rat, pig, rabbits[10], [17]. Therefore this gives rise to the addition of mucoadhesive polymers, as these enzymes are the prime cause for proteolytic degradation of the peptides or protein drugs in buccal mucosa. Mucoadhesive polymers acts as enzyme inhibitors and allows safe delivery of protein and peptide drugs[18]17]. According to the principles of mucoadhesion, hydrogels have been given considerable amount of attention in this regard.Hydrogels are 3D, hydrophilic, polymeric networks which has the capacity to absorb large amount of water. They can act as semisolid forms of oral mucosal drug delivery.Because of its swelling capacity in aqueous and bounding to the mucosal surface through hydrogen bonds, these hydrogels are used to provide adhesiveness in the

mucosa and increase the residence time of the drug in oral mucosa. Hydrogel-based systems are gaining a lot of interest in recent times, like nanogels and microgels.

Bioadhesion is defined as a mechanism by which a substance is capable of interacting with biological membrane like buccal mucosa. It can be retained on the mucosal surface for persistent period of time. Bioadhesion usually is a three step event:

Figure 1:



Events of bioadhesion

Binding of the mucus and the bioadhesive material takes place primarily through chemical and physical interactions. The chemical bond develops due to electrostatic interaction, hydrophobic interaction, hydrogen bonding and dispersion forces[19]·[20]·[21]. Few theories have been explored and considered for understanding the mechanism of bioadhesion or mucoadhesion which includes[22]·[21]·[23]:

1. Wetting theory
2. Diffusion theory
3. Electronic theory
4. Fracture theory
5. Adsorption theory

There are various factors that determine the period of contact of the bioadhesives namely[24]:

1) Polymer related factors
    i) Molecular weight
    ii) Concentration of active polymers
    iii) Flexibility of polymer chain
    iv) Spatial conformation
2) Environment related factors
    i) pH
    ii) Strength
    iii) Initial contact time
    iv) Selection of the model substrate substance
    v) Swelling

Though the delivery of the drugs through the buccal mucosa has been markedly increased in recent times it still presents with some limitations. The properties and its related advantages and disadvantages have been enlisted in the table below:

Advantages and disadvantages of buccal drug delivery

Property	Advantage
Accessibility	Easy accessibility to different sites in the oral cavity. Therefore it increases patient compliance and precise placement of the drug in a specific target area.
Administration	The ease of accessibility simplifies the mode of administration
Withdrawal	It can be easily removed from the site of administration in case of adverse reactions
Patient compliance	Widely accepted site for drug delivery by the patient
First-pass metabolism	The oral mucosa is highly vascularised and the blood vessels drain into the jugular vein through which it enters the systemic circulation directly, avoiding hepatic first-pass metabolism
Enzymatic barriers	The enzymes in the buccal mucosa causes hydrolysis of the peptides and proteins enabling better absorption and decreased metabolisms of drugs are seen in oral cavity avoiding toxicity
Cellular turnover rate	The cellular turnover rate of oral mucosa is 4-14 days. Therefore it can be worn for prolonged period of time without interfering in its adhesion. The oral mucosa rapidly divides as compared to skin and comparatively slower than the gastro intestinal tract mucosa
Surface area	Buccal mucosa measures 500-800µm as compared to gingiva and floor of the mouth, which measures 100-200 µm providing a larger surface area for absorption

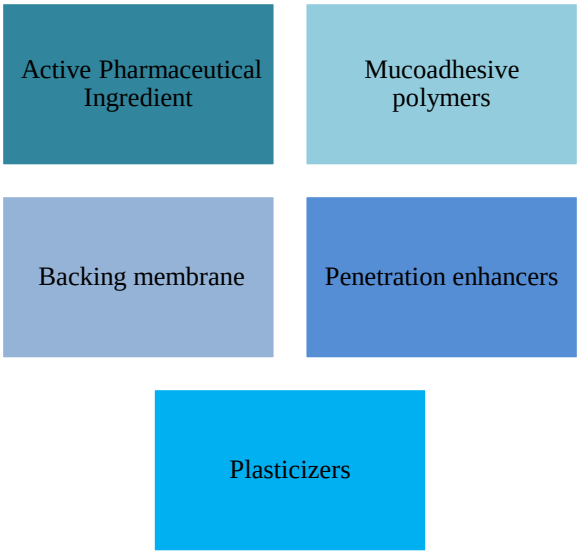
Property	Disadvantage
Membrane permeability	Lesser permeability of drug as compared to other mucosa of the gastrointestinal tract, vagina etc.
Surface area	The surface area of oral mucosa is small as compared to gastric mucosa
Saliva	The continuous secretion of saliva from the major and minor salivary glands leads to the fast dissolution of the drug. But in patients with less saliva secretion it can lead to insufficient dilution and absorption of the drug.
Swallowing	Continuous salivation can lead to the removal of the drug from its target site and therefore reduces its efficacy.
Taste receptors	The taste receptors that are present in the tongue may reduce patient compliance to drugs that taste bitter
Choking hazard	Swallowing of the drug involuntarily may lead to choking
Inconvenience	Buccal drug delivery may cause hindrance in drinking or eating.
Tissue irritation	Some drugs may cause tissue irritation at the site of application, leading to pain and discomfort

Drug availability	The list of drugs that can be administered via the buccal mucosa is relatively less because of it less permeability and absorbability through the site

Constituents of buccal patches

The basic composition of buccal bioadhesive drug delivery system are[25]:

Figure 2:



Constituents of buccal patches

Drugs delivered via buccal route[11],[26],[27],[28]

Table 1: Drugs delivered via the buccal route in various form

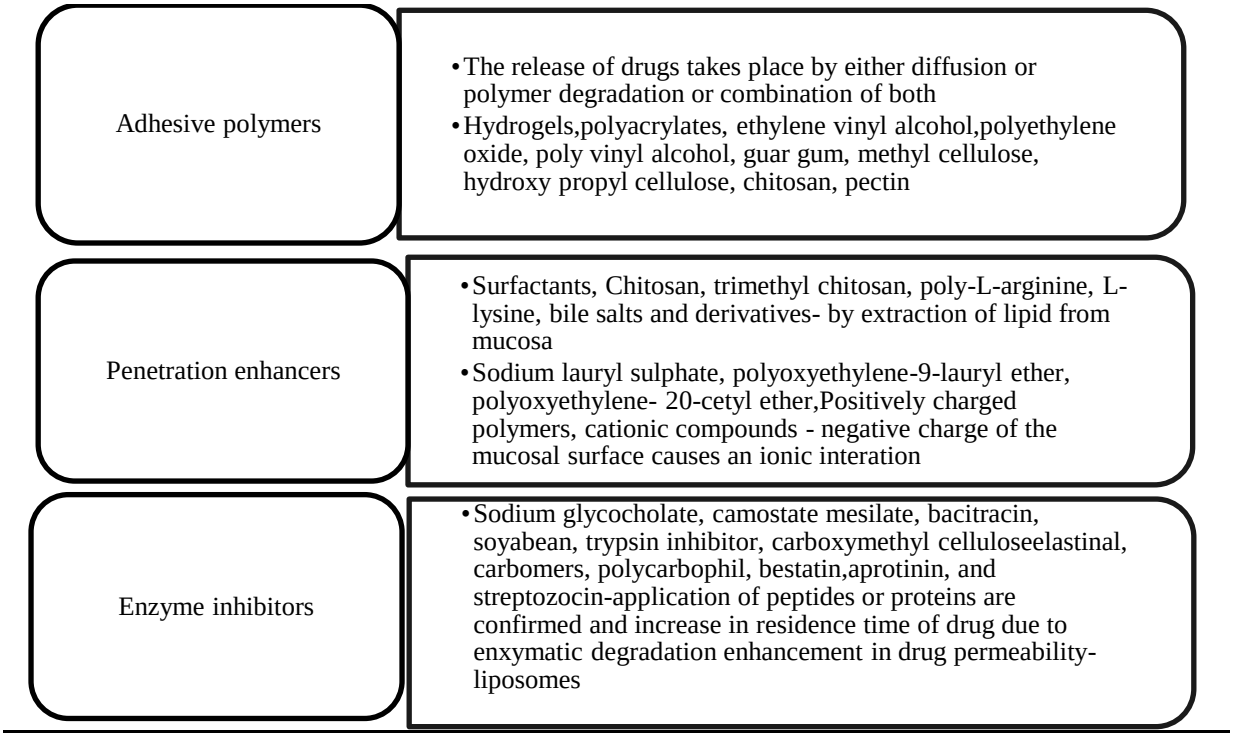
DRUGS	MODE OF DELIVERY	ACTIONS
Fentanyl[24],[29]	Lozenge, tablet,film	Narcotic pain relief
Nicotine[30],[31]	Tablet	Smoking cessation
Chlorhexidinegluconate[32]	Patches, films	Antiseptic and disinfectant action
Clobetasol propionate.[33]	Tablet	To treat oral lichen planus
Ondansetron[34]	Tablet	Antiemetic
Benzocaine[35]	Tablet, disks	Pain relief from oral mucositis, sore throat relief
Donepezil [36]	Patches	Alzheimer's treatment

Diphenhydramine, phenylephrine [37]	Lozenges	Cough and cold, to treat Allergic reactions
Buprenorphine. Martin et al 2017[38]	Tablets, films	To treat opioid addiction, moderate acute pain and moderate chronic pain
Piroxicam[39]	Tablet	Inflammatory conditions
Ergotamine tartrate[40]	Tablet	Acute migraine attacks
Ketoprofen[41]	Tablet	Analgesic and antipyretic effect
Propranolol[42]	Tablet	Inhibits isoprenaline-induced tachycardia, hypertension, angina pectoris, tachyarrhythmia, myocardial infarction, tachycardia, portal hypertension, and anxiety
Diltiazem[43]	Tablet	Hypertension
Metoclopramide[44]	Tablet	Nausea and vomiting
Omeprazole[45]	Tablet	Gastroesophageal reflux disease, peptic ulcer disease
Clotrimazole[46]	Tablet, film	Oral candidiasis
Calcitonin [11],[47]	Tablet	Pagets disease and osteoporosis
Triamcinolone acetonide[48]	Tablet, films, sprays	Anti-inflammatory effects and anti-proliferative properties.
Lidocaine.[49]	Tablet, films	Local anaesthetic effect
Bupivacaine.[50]	Lozenge	To treat oral mucositis
Miconazole[51]	Tablet	Antifungal treatment
Morphine sulphate.[52]	Tablet, films	To treat acute and chronic pain
Cholin salicylate.[53]	Film	To treat apthous lesions
Metronidazole. [54]	Tablet, patches	Antibiotic and antiprotozoal medication
Nifedipine[55]	Tablets, patches	Treatment of angina pectoris
Chlorpheniramine maleate [56]	Tablet	To treat allergic reactions
Acyclovir [57]	Patches, gels	For the treatment of viral infections

Amelexanox[58],[15]	Tablet, patches	For the treatment of recurrent apthous ulcer, oral lichen planus
Carbamazepine[59]	Patches	Epilepsy and neuropathic pain
Nystatin.[30]	Tablets	To treat oral candidiasis

Various approaches to enhance drug absorption[4]

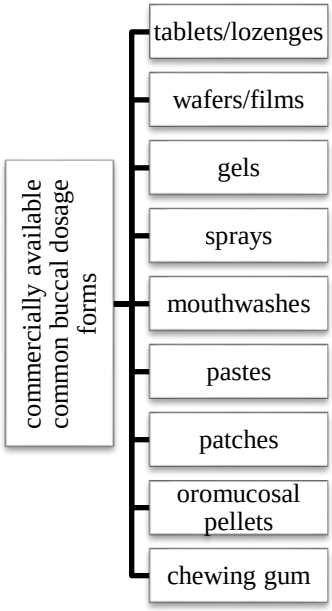
Figure 3:



Various approaches to enhance the absorption of drugs

Recent advances in drugs designed for buccal administration

For several years buccal mucosa has been considered as an effective route for delivery of drugs. Forms of various buccal mucosal drugs are enlisted below[28]:



Discussion

Extensive research and clinical trials have been performed over the years for drug delivery through the buccal mucosa for both local and systemic effects.**Hengzhong** et al conducted an invitro study for treatment of mouth ulcers by application of very thin oral fast disintegrating films composed of lignocaine (97.10% – 99.90%) with thickness ranging from 0.15mm – 0.35mm. The authors concluded that effectiveness of lignocaine was increased as compared to the control group.[49] Another study by **Zdeneck et al** was conducted for the treatment of apthous ulcers where an additional mucoadhesive film was applied over theoral gel containing choline salicylate. It was observed that utilization of a mucoadhesive film prolonged the stay of the medication in the lesion, reducing the time of healing and pain sensitivity.[53]. **Mogensen et al** conducted a study where, a populace pharmacokinetic model was produced for bupivacaine regulated by means of oral capsules in normal healthy controls and patients with neck and head cancer. The relative bioavailability was about 2 times higher in HNC patients with oral mucositis grade 1 and 2 relative to healthy individuals, and 3 times higher in HNC patients with oral mucositis grade 3 and 4 relative to healthy individuals. The outcomes showed that the lozenge may have a positive impact on pain intensity in HNC patients with oral mucositis. The consequences of this study showed that bupivacaine delivered as a lozenge can be utilized securely without systemic toxic plasma levels of bupivacaine or development of adverse effects in both patients with head and neck growth and sound controls[50]. **Hussein et al** stated in his study that fluticasone propionate, which is studied as an effective corticosteroid drug, often used as an anti-inflammatory drug helps in treatment of erosive lesions that affects the buccal mucosa. Their study aimed at designing a mucoadhesive film containing fluticasone and was found to be a potential approach for local treatment of erosive lesions.[60]**Ranjith et al** conducted a studyin which the formulation of a mucoadhesive buccal film composed of valdecoxib,a COX-2 inhibitor was used for the treatment of oral sub mucous fibrosis, a limiting buccal disease. The

amount of concentration of the drug was 98.5 ± 1.3%. 69.34% of the drug release was noted for up to 6 hours in vitro.From the outcomes it was presumed that the medication was discharged locally at the target site of action and a minimal amount may have been consumed systemically.The advantage of the adhesive buccal films was that, it contained a lower medicamentdose, adequate for therapeutic impact as it is found acting directly on the inflammatory site, when contrasted with conventional oral administration. In addition, this mucoadhesive buccal film is acceptable because of the fact that it is non-irritant and self-administration is possible[61]. Also an *in vitro* study had been performed by **Shah et al** where Irinotecan (CPT-11) was administered through the buccal route. Irinotecan is used for the treatment of colorectal cancer. The efficacy of this drug was improved across porcine buccal mucosal membrane and therefore was suggested as a potent route in contrast to systemic delivery of CPT-11[62]. However a study conducted by **Renee et al** stated that buccal administration of morphine to relieve pain in children with both life – threatening conditions and illness did not meet the required therapeutic concentration when experimented on ex vivo porcine[52].**Francesco et al**compared the efficacy of 24 µg clobetasol-17 propionate (CP) for the treatment of oral lichen planus with 125µg CP in a conventional ointment in Orabase. It was designed with a combination of a mucoadhesive polymer, i.e. poly(sodium methacrylate, methylmethacrylate), with hydroxypropylmethylcellulose and MgCl2. This formulation was chosen to modify the tablet erosion rate so that a release of CP over a 6-h period could be obtained. The administration of mucoadhesive tablet containing 24 µg CP 3 times per day seemed to be compelling, keeping away the side effects of systemic treatment.[33].**Giannola et al**conducted a study to expand the medication of 5- FU levels at tumour areas in oral squamous cell carcinomas (OSCCs). The tablets were designed by applying direct pressure of the matrix comprising of the medication and the biocompatible polymer Eudragit® RS-100. The researchers demonstrated reproducible 5-FU discharge from the matrix tablets in a buccal-like condition exhibiting diminished drug resistance and systemic adverse effects thus proving effective locoregional chemotherapy of OSCC.Buccal drug delivery is non-invasive and less unapproachable for patients when compared to other routes of administration (e.g. intravenous, intramuscular). Not all medications, however, can be efficiently absorbed through the buccal mucosa. For example, peptides and proteins have their systemic bioavailability less than 5% of administered dose with buccal mucosal delivery due to the physicochemical barrier of the buccal mucosa, which contains enzymes that break down peptides. In addition, the epithelium provides an efficient barrier to drug penetration, allowing only lesser quantities of a drug to penetrate. Therefore, buccal mucosal delivery is appropriate only for drugs with a high potency. Lastly, buccal mucosal delivery can be challenging in certain pathological conditions such as blisters or mucositis, which affects the integrity of the mucosa.[62]

Conclusion

Buccal drug deliverysystem provides an achievable and alluring alternative option to oral drug delivery systems and other non-oral routes of drug administration. The buccal mucosa adds on to a lot of advantages over oral drug delivery, as it provides with high patient compliance. It is non-invasive, avoids hepatic first -pass metabolism and provides faster absorption of the drug at the target site. As the drug delivery systems adheres to the mucosal surface,the concentration gradient of the drug increases at the site of absorption, therefore enhancing its bioavailibility in the systemic circulation Delivery of drugs through buccal mucosa have been explored extensively but description about the molecular interactions, safety and enhancement effect of permeates on mucosal absorption have to be further clarified. Oral mucosal route is considered better suited for biologics, however novel technologies for administration should be studied to overcome the drawbacks of this route

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