Recent trends in oral transmucosal drug delivery systems: an emphasis on the soft palatal route

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Introduction: The oral mucosa is an appropriate route for drug delivery systems, as it evades first-pass metabolism, enhances drug bioavailability and provides the means for rapid drug transport to the systematic circulation. This delivery system offers a more comfortable and convenient delivery route compared with the intravenous route. Although numerous drugs have been evaluated for oral mucosal delivery, few of them are available commercially. This is due to limitations such as the high costs associated with developing such drug delivery systems.

Areas covered: The present review covers recent developments and applications of oral transmucosal drug delivery systems. More specifically, the review focuses on the suitability of the oral soft palatal site as a new route for drug delivery systems.

Expert opinion: The novelistic oral soft palatal platform is a promising mucoadhesive site for delivering active pharmaceuticals, both systemically and locally, and it can also serve as a smart route for the targeting of drugs to the brain.

Keywords: bio-polymer, buccal route, drug delivery, soft palates, sublingual route, transmucosa

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1. Introduction

Transmucosal routes of drug delivery include mucosal linings of the nasal, rectal, vaginal, ocular and oral cavity, and offer distinct advantages over peroral administration for systemic drug delivery. The advantages of this route include possible bypass of first-pass effect, avoidance of presystemic elimination within the gastrointestinal tract (GIT) and depending on the particular drug, a better enzymatic flora for drug absorption [1]. Drug delivery via the oral cavity is highly acceptable by patients, as the mucosa is relatively permeable and has a rich blood supply, it is robust and shows short recovery times after stress or damage and the virtual lack of Langerhan cells makes the oral mucosa tolerant to potential allergens. Furthermore, these factors make the oral mucosal cavity a very attractive and feasible site for local and systemic drug delivery [2,3]. The oral cavity comprises the lips, cheeks, tongue, hard palate, soft palate and the floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa, which includes the buccal, sublingual, gingival, palatal and labial mucosae. Local therapy is used to treat conditions such as gingivitis, oral candidosis, oral lesions, dental caries and xerostoma while systemic delivery delivers drugs into the circulation by avoiding the effects of hepatic 'first-pass metabolism'. The drug delivery systems used for the oral cavity include mouthwashes, aerosol sprays, chewing gums, bioadhesive tablets, gels and patches [4].

The buccal and sublingual sectors are the most commonly used routes for drug delivery and they may be used for the treatment of local or systemic diseases. The sublingual mucosa is more permeable and thinner than the buccal mucosa and

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Article highlights.

- Oral transmucosal system allows a more rapid absorption into the blood stream as compared with oral administration to the gastrointestinal tract (GIT) and consequently offering an alternative means of drug administration, which is more comfortable and convenient for patients than intravenous drug administration.
- Soft palate has a promising non-keratinized histology with a unique thickness when compared with the buccal mucosa.
- The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosae.
- Natural mucoadhesive polymers are generally linear polymers with high molecular weight, contain a substantial number of hydrophilic, negatively charged functional groups and form three-dimensional expanded networks which make these biopolymers suitable for mucoadhesive formulations.

This box summarizes key points contained in the article.

because of the considerable surface area and high blood flow, it is a suitable site when a rapid onset is desired. The buccal mucosa is relatively permeable, is robust in comparison with the other mucosal tissues and is more tolerant to potential allergens that have a reduced tendency to cause irreversible irritation or damage [5]. There are few major problems associated with drug therapy within the oral cavity, which include the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs. This may lead to the requirement of frequent dosing the non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system, which could result in some areas of the oral cavity not receiving therapeutic levels of drug and affect patient acceptability in terms of taste and 'mouth feel' [6-10].

The soft palatal mucosa is intermediate in thickness and non-keratinized thus lessening its permeability. This route has various advantages over the buccal and sublingual route such as tongue activity and salivary secretion does not affect the performance of drug delivery via soft palatal mucosa [11].

2. Advantages and limitations of oral mucosal drug delivery

The oral transmucosal drug delivery system has various advantages which include more patient compliance as compared with the injectable delivery of drugs. Absorption of certain drugs across the oral mucosa provides patients with a rapid onset of action. Additionally, oral transmucosal drug delivery offers an alternative when enteral administration causes difficulty in swallowing, nausea or vomiting or intestinal failure. Oral mucosal delivery is non-invasive and less intimidating for many patients compared with other routes of administration such as intravenous and intramuscular route, as it can be removed in case of unwanted effects. The variable absorption compared with the other routes is the biggest limitation of oral mucosal delivery. In addition, the barrier properties of the epithelium result in the oral mucosa being an efficient barrier to drug penetration, allowing only small quantities of a drug to penetrate.

3. Overview of oral mucosa

The oral mucosa is composed of the lamina propria followed by the submucosa as the innermost layer covered by an outermost layer of stratified squamous epithelium. The epithelium has a mitotically active basal cell layer that advances through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. The epithelial cells become flat as they travel from the basal layers to the superficial layers.

The permeability of the buccal mucosa is 4 – 4000 times greater in comparison with the skin [12]. The permeability of different regions of the oral cavity is considerably different because of the diverse structures and functions of the different oral mucosae. In general, the permeability of the oral mucosae decreases in the order of sublingual > buccal > palatal, which is based on the relative thickness and degree of keratinization of these tissues [13]. The sublingual mucosa is relatively thin and non-keratinized, the buccal mucosa is thicker and non-keratinized, whereas the palatal mucosa is intermediate in thickness but keratinized.

The oral epithelia are enclosed by mucus, an intercellular ground substance, made up of proteins and carbohydrates. The mucus may be free of association or may be attached to certain regions on the cell surfaces and play a role in cell–cell adhesion, in addition to acting as a lubricant, allowing cells to move relative to one another and playing a role in the bioadhesion of mucoadhesive drug delivery systems [14,15]. The mucus is generally synthesized by specialized mucus secreting cells like the goblet cells but in the oral mucosa it is secreted by the major and minor salivary glands as part of saliva. Approximately 70% of the total mucin found in saliva is contributed by the minor salivary glands [10]. The mucus network contains sialic acid and sulfate residues that generate a negative charge on the mucus at physiological pH, which may play a role in mucoadhesion by forming a strong cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer. Saliva is an aqueous fluid with 1% organic and inorganic materials; its pH ranges from 5.5 to 7 depending on the flow rate [16]. Saliva enhances the wettability of formulations where the water content of saliva is absorbed the dosage form and helps in to significant enhancement of the bidirectional drug delivery system than with the unidirectional drug delivery system.

4. Soft palate

The soft palate is a flexible, muscular flap which extends postero-interiorly from the posterior edge of the hard palate into the pharyngeal cavity (**Figure 1**) [17,18]. When the soft

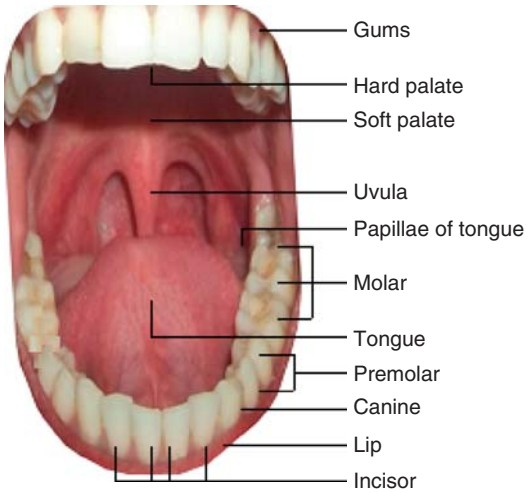


Figure 1. Overview of oral cavity.

palate is pulled interiorly against the posterior part of the tongue, it cuts off the mouth from the pharynx, thus permitting respiration to continue during sucking or chewing without danger of inhalation of food or fluid.

The soft palate is made up of a fold of mucous membrane which encloses parts of five pairs of muscles of which only the uvular muscles are intrinsic. The uvular muscles lie on the superior surface of the aponeurosis, and run side by side in the midline from the posterior nasal spine of the palatine bones to the mucous membrane of the uvula. It makes the anterior part of the soft palate rigid. The levator palati muscle arises from the medical side of the auditory tube and the adjacent part of the petrous temporal bone. It descends behind the auditory tube inside the free upper border of the superior constrictor muscle, and curves medically to join the opposite muscle and be partially attached to the superior surface of the palatal aponeurosis. Palatoglossus is a small counterpart of the levator palate on the inferior surface of the palate. It is attached to the inferior surface of the palatal aponeurosis and meets the opposite muscle in the midline. Palatopharyngeus muscle arises from the superior surface of the soft palate and the posterior margin of the hard palate. Salpingopharyngeus slender muscle arises by one or two slips from the inferior border of the cartilage of the auditory tube at its pharyngeal and it descends in the salpingopharyngeal fold to join palatopharyngeus. The lesser palatine and glossopharyngeal nerves supply the mucous membrane. The tensor palate is supplied by the mandibular nerve through the otic ganglion; all the other muscles are supplied by the pharyngeal plexus, a glossopharyngeal/vagal complex. These nerves and muscles play vital role in the absorption and distribution of drug given by soft palatal route [17].

Soft palate has a promising non-keratinized histology with a unique thickness as compared with the buccal mucosa. The soft palatal mucosa possesses inbuilt properties that do not interfere when the patient performs his/her regular activities like talking, eating, drinking, etc. Apart from this, the soft palatal region is flexible and mobile tissue can be easily accessed for placing the dosage form. Once the dosage form is placed at the site with mucoadhesive properties, the dosage form will remain at the site for a long period in order to achieve a controlled drug release [19].

5. Glycoproteins (mucins)

Glycoproteins are the most important components of mucus and are responsible for its gelatinous structure, cohesion and antiadhesive properties [20,21]. Despite the various body sites at which mucus is secreted, glycoproteins usually have similar structure (**Figure 2**) and are highly glycosylated protein molecules with molecular weights reaching 5 – 105 [22]. In space, glycoproteins form a branched three-dimensional network with large number of loops (**Figure 3**) [23-25]. The polypeptide chain consists of 800 – 4500 amino acid residues and is characterized by two types of areas: strongly glycosylated areas and areas lacking carbohydrate side chains. Glycosylation increases the resistance of the molecules to proteolytic hydrolysis. The terminal domains of the glycoprotein (C- and N-) are areas containing more than 10% cysteine. These parts of the domains are responsible for the formation of large mucin oligomers due to the formation of disulfide bonds. The greater part of the protein carcass consists of a repeating sequence of serine, threonine and proline residues [26]. Oligosaccharide sequences are attached to 63% of the protein core, at every third residue within the glycosylated areas, with the result that there are more than 200 carbohydrate chains per glycoprotein molecule [27]. The main functions of the mucus are to protect and lubricate the supporting epithelial layer.

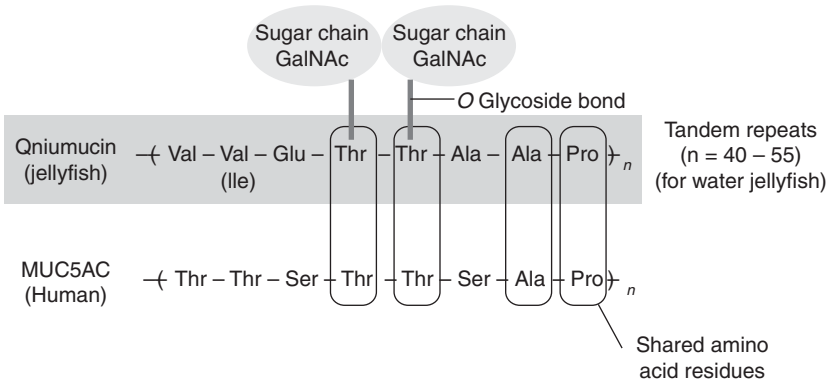
The glycoprotein of mucus forms a complex with the functional group of either polymer or the drug containing a reacting functional group thereby forming a complex which promotes and sustains action by increasing the site-specific residence time [28].

6. Transmucosal drug absorption

The novelistic transsoft palatal route possesses a smart inbuilt advantage over other transmucosal routes like buccal, sublingual, gastric, colon mucosa, etc. because it is devoid of non-keratinized, less salivary secretion which leads to minimum drug loss into the saliva. The soft palatal tissue is devoid of proteolytic enzyme which avoids the drug degradation and reduction of the drug dose. The cellular turnover of soft palate is less when compared with other mucosa.

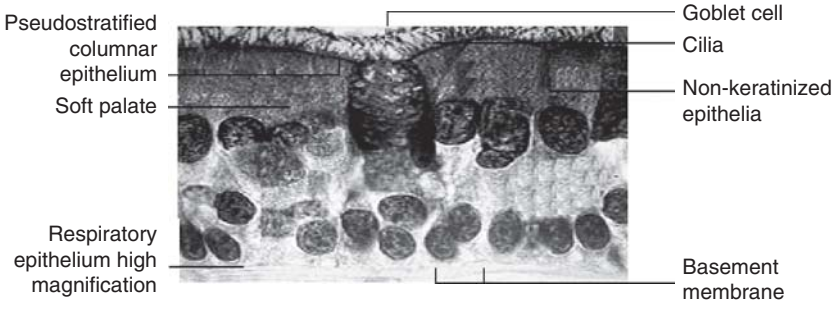
6.1 Principles and mechanisms of drug absorption via oral transmucosa

The administration of active principles on the buccal mucosa with the aim of achieving a systemic and reservoir effect has led to pharmaceutical development of a new form of dosage. There are some methods by which penetration of compounds through the oral mucosa can be improved: by the use of



Val: valine; Ile; isolucine; Glu: glutamic acid; Thr: threonine; Ala: alanine; Pro: proline; Ser: serine

Figure 2. Structure of mucus.



Ventrally: covered by oral epithelium (stratifiedsquamous epithelium)
Dorsally: covered by respiratory epithelium (pseudostratified columnar epithelium with goblet cells)

Figure 3. Human soft palate.

prodrug, co-administration of enzyme inhibitors, delivery systems, enhancers or physical methods [29]. The buccal and sublingual tissues are the primary focus for drug delivery via the oral mucosa because they are more permeable than the tissues in other regions of the mouth. The surface area of the oral mucosa (200 cm^2) is relatively small compared with the GIT (350,000 cm^2) and skin (20,000 cm^2) [30,31]. The drugs that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the GIT and first-pass metabolism in the liver. The rate of blood flow through the oral mucosa is substantial, and is generally not considered to be the rate-limiting factor in the absorption of drugs by this route [32]. Drug absorption through a mucosal surface is generally efficient because the stratum corneum epidermis, the major barrier to absorption across the skin, is absent. The amount of drug absorbed depends on the drug concentration, vehicle of drug delivery, mucosal contact time, venous drainage of the mucosal tissues, degree of the drug's ionization and the pH of the absorption site, size of the drug molecule and relative lipid solubility. There are two routes potentially involved in drug permeation across epithelial membranes: transcellular route and paracellular route. Paracellular transport is the transport of molecules around or between cells. The mechanism of absorption of hydrophilic drugs by methylated cyclodextrins may be related to a temporary change in mucosal permeability and opening of the tight junctions [33,34]. Transmucosal permeation of polar molecules (such as peptide-based pharmaceuticals) may be via paracellular route, however, several barriers such as basal lamina, membrane coating granules and keratin layer exist during the course of paracellular permeation [35]. Parameters such as diffusion coefficient, partition coefficient and thickness of the tissue are inherent properties of the drug and the mucosa. Other parameters, such as surface area, duration of drug delivery and concentration are controlled by the dosage form and formulation. Free drug concentration is a key issue in terms of developing transmucosal drug delivery dosage forms [36].

6.2 Enhancement of transmucosal agent transport

Most of drugs follow diffusion controlled mechanism for their absorption through oral mucosa. However; hydrophilic, ionic drugs usually diffuse through the intercellular space, while

hydrophobic drugs are able to pass through cellular membranes. The mucosa may have insufficient permeability for maximum drug due to its interaction with mucus, limitation of the available absorption area and the short time of exposure, because of the washing effect of saliva. Permeation of drugs throughout epithelial barriers could be promoted by 'penetration enhancers' utilizing different techniques, usually subdivided into chemical or physical methods. Penetration enhancers alter the barrier properties of the mucosa as they increase cell membrane fluidity, extract the structural intercellular and/or intracellular lipids and alter cellular proteins, or mucus structure and rheology [37-39]. The efficacy of penetration enhancer depends on the physicochemical properties of the drug, the administration site and the nature of the vehicle. There is a marked variation in molecular weight as well as physicochemical properties of various drugs. Hence, a large of drugs have been investigated for buccal transmucosal delivery using various permeation enhancers.

7. Experimental methodology for buccal permeation studies

Before an oral transmucosal drug delivery system can be formulated, the permeation studies must be conducted to determine the feasibility of this route of administration for the candidate drug. At present, many accurate *in vitro* and *in vivo* methods are available for these studies.

7.1 *In vitro* methods

At the present time, most of the *in vitro* studies examining drug transport across buccal mucosa have used buccal tissues from animal models. Animals are sacrificed immediately before the start of an experiment. Buccal mucosa with underlying connective tissue is surgically removed from the oral cavity, the connective tissue is then carefully removed and the buccal mucosal membrane is isolated. The membranes are then placed and stored in ice-cold (4°C) buffers (usually Krebs buffer) until mounted between side-by-side diffusion cells for the *in vitro* permeation experiments [40]. Buccal cell cultures have also been recommended as useful *in vitro* models for buccal drug permeation and metabolism [41,42]. Nielsen and Rassing conducted a study to investigate and compare the effect of pH and drug concentration on nicotine permeability across the TR146 cell culture model and porcine buccal mucosa *in vitro*. Nicotine concentrations between 10 (-5) and 10 (-2) M were applied to the apical side of the TR146 cell culture model or the mucosal side of porcine buccal mucosa. Buffers with pH values of 5.5, 7.4 and 8.1 were used to obtain different fractions of non- and mono-ionized nicotine. The apparent permeability (P(app)) of nicotine across both models increased significantly with increasing pH, and the P(app) values obtained with the two models could be correlated in a linear manner [43]. Obradovic and Hidalgo used freshly isolated animal buccal mucosa as well as human buccal tissue cultures to check the absorption of drug through buccal mucosa [44].

7.2 *In vivo* methods

In vivo buccal absorption test was first described by Beckett and Triggs to measure the kinetics of drug absorption [45]. The methodology involves the swirling of a 25 ml sample of the test solution for up to 15 min by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined in order to assess the amount of drug absorbed. This method suffered from lot of drawbacks which includes drug dilution by saliva, accidental swallowing of a portion of the sample solution and the inability to localize the drug solution within a specific target site (buccal, sublingual, gingival or palatal) of the oral cavity. To overcome these limitations, various modifications of the buccal absorption test have been carried out [46,47], but these modifications also suffer from the inability of site localization. The site localization to retain the drug is feasible by using a mucoadhesive system [48,49]. Other *in vivo* methods have been used for same purpose and carried out using a small perfusion chamber attached to the upper lip of anesthetized dogs by cyanoacrylate cement [50,51]. Koland *et al.* performed *in vivo* buccal permeation studies of ondansetron hydrochloride from mucoadhesive sustained release films in New Zealand white rabbits of 2.5 – 3.0 kg of either sex [52].

7.3 Experimental animal species

There are number of animals available for the oral absorption study and choice of experimental animal species for such experiments depends on individual itself. Many researchers have used small animals such as rats [53-55] and hamsters [56-58] for *in vivo* permeability studies. The rabbit has been extensively utilized in experimental studies because rabbit is the only laboratory rodent that has non-keratinized mucosal lining similar to human tissue [59-61]. Larger experimental animals such as monkeys [62], dogs [63,64] and pigs [65-67] have also been used for permeability and drug delivery studies. For *in vitro* studies, porcine tissue is more suited as compared with dog buccal tissue due to its easy availability and cost-effectiveness.

8. Oral transmucosal routes

The oral transmucosal route includes mostly the sublingual, buccal and soft palatal route for drug delivery. Oral transmucosal absorption is generally rapid because of the rich vascular supply to the mucosa and the lack of a stratum corneum epidermis. This minimal barrier to drug transport results in rapid rise in blood concentration. The drug appears in blood within 1 min, and peak blood levels of most medications are achieved within 10 – 15 min, which is substantially faster than when the same drugs are administered by the orogastric route.

8.1 Buccal route

The buccal route of drug delivery offers several advantages for controlled drug delivery for extended periods of time. The mucosa of buccal is well supplied with vascular and lymphatic

drainage and first-pass metabolism in the liver and presystemic elimination in the GIT are avoided. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. However, the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery. Drug absorption is generally greater from the buccal or oral mucosa [68] than from the tongue and gingiva. Oral transmucosal administration has the advantage of avoiding the enterohepatic circulation and immediate destruction by gastric acid or partial first-pass effects of hepatic metabolism. The Fentanyl Oralet™ (Abbott Laboratories, Abbott Park, IL, USA), the first Food and Drug Administration (FDA)-approved formulation, was developed to take advantage of buccal absorption for the painless administration of an opioid in a formulation acceptable to children [69,70]. The buccal route of administration may offer some protection from the adverse effects of intravenous fentanyl. Peak respiratory depression and the development of glottic and chest wall rigidity are related to the dose and rate of administration; this effect may be attenuated by pretreatment with thiopental or benzodiazepine [71]. Fentanyl administered by buccal route results in relatively rapid elevation of the drug concentration in the blood, but this rate of increase is less likely to result in glottic or chest wall rigidity than when fentanyl is given intravenously. However, one possible case of glottis or chest wall rigidity has been reported during the induction of anesthesia [72].

8.2 Sublingual route

The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailabilities of many drugs, and is convenient, accessible and generally well accepted. The sublingual route is by far the most widely studied of these routes. Sublingual dosage forms are of two different designs, those composed of rapidly disintegrating tablets and those consisting of soft gelatin capsules filled with liquid drug. Such systems create a very high drug concentration in the sublingual region before they are systemically absorbed across the mucosa. The sublingual region lacks an expanse of smooth muscle or immobile mucosa and is constantly washed by a considerable amount of saliva making it difficult for device placement. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action making it appropriate for drugs with short delivery period requirements with infrequent dosing regimen [73]. Prolonged exposure to the oral sublingual mucosal surface may be accomplished by repeated placement of small aliquots of drug directly beneath the tongue of a cooperative child or incorporation of the drug into a sustained-release lozenge [74].

8.3 Soft palatal route

Soft palatal route is also a successful route for drug delivery systems and offers all the advantages proposed by buccal and sublingual routes but this route of drug administration is beneficial because the combined effects of the direct drug absorption and the decrease in excretion rate allow for an increased bioavailability of the drug with a smaller dosage and less frequent administration. Additionally, decrease toxicity and wastage of expensive drug because of reduction in initial drug loading concentration, inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site [19].

9. Oral transmucosal drug delivery systems

The unique physicochemical characteristics of drug such as molecular weight, size of molecule, degree of ionization and partition coefficient, demand careful attention for the development of effective oral transmucosal formulation. An ideal oral transmucosal drug delivery system must meet several prerequisites to be successful. First, it should rapidly attach to the mucosal surface and maintain a strong interaction to prevent displacement. Second prerequisite is that the bioadhesion performance should not be impacted by surrounding environmental pH. Other desirable characteristics of an oral transmucosal drug delivery system include high drug loading, complete drug release and convenient administration. Drug release from a polymeric material takes place either by the diffusion or by polymer degradation or by their combination. Polymer degradation usually takes place by the enzymes or hydrolysis and may happen in the form of bulk erosion or surface erosion [75]. A multitude of dosage forms are available or are being investigated for drug delivery from the oral mucosa (**Table 1**). Advances in oral transmucosal drug delivery have focused on the development of drug delivery systems that not only achieve the therapeutic aims of delivery but also overcome the unfavorable environmental conditions found in the oral cavity. Modern formulations have used creative approaches that incorporate a combination of these strategies to create a balance between patient convenience and clinical benefits.

9.1 Aqueous solutions

Aqueous solutions are oldest and most widely used delivery system for local delivery which includes simple solutions (mouthwashes and gargles), suspension and gel-forming liquids. Recently, gel-forming liquids have been investigated primarily to coat the mucosa to act as a protectant or a vehicle for drug delivery for the treatment of local disorders, including motility dysfunction, fungal infections. The sodium alginate suspension as a novel bioadhesive liquid is recently investigated by researchers, which showed that the esophageal surface can be coated to protect against reflux and can deliver therapeutic agents to the damaged mucosa [76,77].

9.2 Lozenges

Lozenges are solid preparations, containing one or more medicaments, usually in a flavored sweetened hard candy or compressed base. They are intended to gradually dissolve on the back surface of the tongue and to provide drug delivery

Table 1. List of investigated oral transmucosal formulations.

Active ingredient	Polymers used	Dosage form	Targeted site	Ref.
Benzydamine hydrochloride	HPMC types (E5, E15, E50 and K100M	Gel	Buccal drug delivery	[126]
Calcitonin and teriparatide	Biodegradable and biocompatible polymers	Nanoparticles	Buccal and nasal drug delivery	[127]
Valdecoxib	Chitosan and HPMC K4M	Films	Buccal drug delivery	[84]
LDC	Chitosan glutam	Hydrogel	Buccal drug delivery	[86]
Tizanidine hydrochloride	HPMC K4M, sodium carboxymethyl cellulose	Tablets	Buccal drug delivery	[80]
Carvedilol	HPMC, CP 934, eudragit RS 100 and EC	Patches	Buccal drug delivery	[82]
Propranolol hydrochloride	Locust bean gum and chitosan	Tablets	Buccal drug delivery	[128]
Insulin	Chitosan-EDTA, ethylcellose	Hydrogel films	Buccal drug delivery	[129]
Progesterone	Chitosan	Films	Buccal drug delivery	[130]
CPM	HEC	Patches	Buccal drug delivery	[83]
Ciclopiroxolamine	60% (w/w) of carbomer	Tablets	Buccal drug delivery	[131]
Flurbiprofen	Cellulose derivative and polyacrylic derivative blend	Tablets	Buccal drug delivery	[79]
Propranolol hydrochloride	Eudragit L100	Patches	Buccal drug delivery	[132]
LDC	CP	Patches	Buccal drug delivery	[133]
Carvedilol	HPMC K4M, HPMC K15M and CP 934	Tablets	Buccal drug delivery	[134]
Propranolol hydrochloride	SCMC and CP 934	Tablets	Buccal drug delivery	[135]
Carvedilol	AC5 (HPMC E 15)	Patches	Buccal drug delivery	[136]
Propranolol hydrochloride	Chitosan	Patches	Buccal drug delivery	[137]
PACAP	Thiolated chitosans	Flat-faced discs	Buccal drug delivery	[138]
Mucoadhesive polymers	Mucoadhesive polymers	Tablets	Buccal drug delivery	[26]
Prednisolone	HPMC	Tablets	Buccal drug delivery	[139]
Salbutamol sulfate	PVA, chitosan	Patches	Buccal drug delivery	[140]
Ibuprofen	Containing PVP, NaCMC	Patches	Buccal drug delivery	[141]
Nicotine	Xanthan gum, karaya gum, guar gum and glycol chitosan	Tablets	Buccal drug delivery	[142]
Metronidazole	HEC and carbomer 940 2:2 ratio	Tablets	Buccal drug delivery	[143]
Cetylpyridinium chloride	PVA, HEC and chitosan	Tablets	Buccal drug delivery	[144]
Piroxicam	HPMC and CP	Tablets	Buccal drug delivery	[145]
Miconazole nitrate	Ionic polymers, SCMC and chitosan, or non-ionic polymers, PVA, HEC and HPMC	Tablets	Buccal drug delivery	[146]
Danazol	PC and HPMC	Tablets	Buccal drug delivery	[147]
HCA	HPMC (Methocel K4M), carboxyvinyl polymer (CP 974P) and PC (Noveon AA1)	Tablets	Buccal drug delivery	[148]
Isosorbide dinitrate	Grafted starch	Microsphers	Buccal drug delivery	[149]
Acyclovir	Copolymers of acrylic acid and poly (ethylene glycol) monomethylether monomethacrylate	Patches	Buccal drug delivery	[150]
CPM	Gum from *Hakea gibbosa* (Hakea)	Tablets	Buccal drug delivery	[151]
Amikacin	Gum exudates of *Arachis hypogea*	Smart flexiplates	Soft palatal drug delivery	[28]
Gentamicin	Polymer from *Cordia dichotoma*	Bioplates	Soft palatal drug delivery	[152]

CP: Carbopol; CPM: Chlorpheniramine maleate; EDTA: Ethylenediaminetetraacetic acid; HCA: Hydrocortisone acetate; HEC: Hydroxyethylcellulose; HPMC: Hydroxypropylmethylcellulose; LDC: Lidocaine hydrochloride; NaCMC: Carboxymethylcellulose sodium salt; PACAP: Pituitary adenylate cyclase-activating polypeptide; PC: Polycarbophil; PVA: Polyvinyl alcohol; PVP: Polyvinylpyrrolidone; SCMC: Sodium carboxymethylcellulose.

locally to the mouth, tongue, throat, etc., to minimize systemic and maximize local drug activity [78].

9.3 Transmucosal tablets

The transmucosal tables are intended to be held in the mouth, where they release their drug contents for absorption directly through the oral mucosa. The nitroglycerin sublingual and prochlorperazine buccal tablets are most commonly used formulations, available in market. The limitation of this delivery form is the short residence time and usually dissolved within 30 min, thus limiting the total amount of drug that can be delivered. These delivery systems have some limitations such as, inter- and intra-individual variation in absorption and bioavailability because it is difficult to control drug or other ingredient concentrations, as the media is constantly diluted by saliva. Taste of the drug is another problem for this delivery system if the drug is unpleasant in taste. In this condition, the taste can be masked by sweetening and flavorings agents. Perioli *et al.* designed a sustained release mucoadhesive bilayered tablet, using mixtures of mucoadhesive polymers and an inorganic matrix (hydrotalcite), for the topical administration of flurbiprofen in the oral cavity [79]. Shanker *et al.* studied the formulation and

evaluation of bioadhesive buccal drug delivery of tizanidine hydrochloride tablets, which is extensively metabolized by liver. The tablets were prepared by direct compression using bioadhesive polymers such as hydroxylpropyl methylcellulose K4M, sodium carboxymethyl cellulose alone and a combination of these two polymers [80].

9.4 Chewing gum

Chewing gum as oral transmucosal drug delivery is gaining popularity in recent days and is a useful means for systemic drug delivery. The advantages of chewing gum over other oral transmucosal drug delivery system include the patient convenience and compliance, possibility of sustained drug release over an extended period of time and the potential to improve the variability in terms of drug release and retention times. However, it requires continuous chewing for drug release so not suitable for geriatric patient. It shares many of the same limitations of the other solid formulations because it is also an open system. Chlorhexidine chewing gum can be used to treat gingivitis, periodontitis, oral and pharyngeal infections. It can also be used for inhibition of plaque growth. Chlorhexidine chewing gum offers numerous flexibility in its formulation as it gives less staining of the teeth and is distributed evenly in the oral cavity. The bitter taste of chlorhexidine can be masked quite well in a chewing gum formulation [35]. The formulation nicorette available as mint and classic with different flavor and dosage, is developed with ion-exchange resin, and releases 90% of drug after 30 min chewing [37]. The release rate is controlled by the rate and vigor of chewing. Thus, the patient can control the drug intake to match his/her needs [81].

9.5 Mucoadhesive patches/films

Transmucosal patches/films systems have several unique features, which include relatively rapid onset of drug delivery, sustained drug release, rapid decline in the serum drug concentration when the patch is removed and less inter- and intra-individual variability. Since they are closed systems and the formulations are protected from saliva, the drug concentrations are controlled and drug is continuously delivered for 10 – 15 h. These systems have some limitations such as, they use only a small mucosal area and the backings have to be removed by the patient after drug administration. Thimmasetty *et al.* prepared the carvedilol (β-adrenergic antagonist) patches using hydroxypropylmethylcellulose (HPMC), carbopol (CP) 934, eudragit RS 100 and ethylcellulose (EC) [82]. Sekhar *et al.* described buccal permeation of chlorpheniramine maleate (CPM) and its transbuccal delivery using mucoadhesive buccal patches. Bioavailability from optimized buccal patch was found 1.46 times higher than the oral dosage form [83]. Averineni *et al.* developed the mucoadhesive buccal film of valdecoxib for the treatment of oral submucous fibrosis, a localized buccal disease. The films were made out of chitosan and HPMC K4M as polymers. Sodium taurocholate was used as a permeation enhancer. Pharmacokinetic studies of the buccal mucoadhesive film showed that the drug was released locally at the target site of action, and a very small amount might have absorbed systemically [84].

9.6 Gels

Gels are usually clear, transparent semisolid containing solubilized active substances. Due to their plastic rheological behavior they can cling to the surface of application for reasonable duration before they are washed or warn off. Karavana *et al.* developed and examined the characterization of benzidamine hydrochloride (BNZ) bioadhesive gels as platforms for oral ulcer treatments. Bioadhesive gels were prepared with four different HPMC types (E5, E15, E50 and K100M) with different ratios [85]. Hydrogels for the buccal application of the anesthetic drug lidocaine hydrochloride (LDC) were prepared by Pignatello, *et al.* using chitosan glutamate (CHG), a soluble salt of chitosan, or a binary mixture of CHG and glycerin, at different weight ratios. LDC-loaded hydrogels can be proposed for the symptom relief of aphthosis or other painful mouth diseases [86].

9.7 Multiparticulates, microparticles and nanoparticles

The use of multiparticulates for transmucosal delivery is not popular in present scenario because these are quite difficult to formulate. But in near future, this type of drug delivery will be developed to overcome the limitations of other dosage forms. Oral delivery systems based on multiparticulates, microparticles and nanoparticles often exhibit improved performance in comparison with monolithic matrix tablets [87]. By diffusing into the mucous gel layer by virtue of their relatively small size, these small immobilized carriers show a prolonged gastrointestinal residence time [88].

9.8 Bioplate/flexiplate

Bioplates and flexiplates are recently developed drug delivery devices for soft palatal route. Satheesh Madhav and collaborators developed and standardized the smart bioplate and flexiplate using the polymers from *Lallimantia royalena* seeds, *Prunus amygdalis* and *Bosweillia serrata*, for the delivery of amikacin and gentamicin via oro-soft palatal route [28,89,90].

10. Mucoadhesive polymers used in the oral cavity

The ideal mucoadhesive polymers should posses some necessary structural characteristics for bioadhesion such as strong hydrogen bonding groups, strong anionic or cationic charges, high molecular weight, chain flexibility and surface energy properties favoring spreading on mucus layer [91]. In general, mucoadhesive polymers can be classified as synthetic versus natural, water-soluble versus water insoluble and charged versus uncharged polymers [26]. Examples of the recent polymers classified in these categories are listed in **Table 2**. Natural mucoadhesive polymers are generally linear polymers with

Table 2. Polymers in oral transmucosal drug delivery system.

Principle	Categories	Subcategories	Examples [153]
Source	Natural		Agarose, chitosan, guar gum, Hakea gum, xanthan gum, gellan gum, carragenan gum, pectin
	Semi-natural		Gelatin, hyaluronic acid and sodium alginate
	Synthetic	Cellulose derivatives	CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methylhydroxyethylcellulose
		Poly(acrylic acid)-based polymers	Copolymer of acrylic acid and PEG CP, PC, PAA, poly (methylvinylether-comethacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acid-coethylhexylacrylate), poly (methacrylate), poly(alkylcyanoacrylate), poly (isohexylcyanoacrylate), poly(isobutylcyanoacrylate)
		Others	PHPMAm, polyoxyethylene, PVA, PVP, thiolated polymers
Solubility	Water-soluble		CP, HEC, HPC (waterb38 8C), HPMC (cold water), PAA, sodium alginate, PVP, MC, SCMC and other cellulose derivatives
	Water-insoluble		Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic		Aminodextran, DEAE dextran, trimethylated chitosan
	Anionic		Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum, CP, polyacrylates and their cross-linked modifications
	Non-ionic		Eudragit-NE30D, hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan
Potential bioadhesive forces	Covalent		Cyanoacrylate
	Hydrogen bond		Acrylate, hydroxylated methacrylate, poly(methacrylic acid), CP, PC, PVA
	Electrostatic interaction		Chitosan

CP: Carbopol; CMC: Carboxymethylcellulose; DEAE: Dimethylaminoethyl; EC: Ethylcellulose; EDTA: Ethylenediaminetetraacetic acid; HEC: Hydroxyethylcellulose; HPC: Hydroxypropylcellulose; HPMC: Hydroxypropylmethylcellulose; MC: Methyl cellulose; PAA: Poly(acrylic acid); PC: Polycarbophil; PEG: Poly(ethylene glycol); PHPMAm: Poly(*N*-2-hydroxypropyl methacrylamide); PVA: Polyvinyl alcohol; PVP: Polyvinylpyrrolidone; SCMC: Sodium carboxymethylcellulose.

high molecular weight, contain a substantial number of hydrophilic, negatively charged functional groups and form three-dimensional expanded networks [92]. The polymers like poly(acrylic acid), cellulose ester derivatives and polymethacrylate derivatives come under the class of synthetic polymers. Chitosan, guar gum and Hakea gum (gum from *Hakea gibbosa*) are classified as semi-natural/natural mucoadhesive polymers. The charged polymers are classified into cationic and anionic polymers, such as chitosan and polycarbophil, respectively, while hydroxypropylcellulose (HPC) is non-ionic polymer [93].

10.1 Novel mucoadhesive polymers

The novel polymers are capable of forming covalent bonds with the mucus and the underlying cell layers, and hence, exhibit improved chemical interactions. The new generation of mucoadhesives, except thiolated polymers, can adhere directly to the cell surface, rather than to mucus. They interact with the cell surface by means of specific receptors or covalent bonding instead of non-specific mechanisms, which are characteristic of the previous polymers.

10.1.1 Thiolated mucoadhesive polymers

Recently, it has been shown that polymers with thiol groups provide much higher adhesive properties than polymers generally considered to be mucoadhesive. The enhancement of mucoadhesion can be explained by the formation of covalent bonds between the polymer and the mucus layer which are stronger than non-covalent bonds. These thiolated polymers, known as thiomers, interact with cysteine-rich subdomains of mucus glycoproteins via disulfide exchange reactions or via simple oxidation process [94]. The modified polymers, which contain a carbodiimide-mediated thiol bond, exhibit much-improved mucoadhesive properties [95]. Some improved mucoadhesive properties such as tensile strength, high cohesive properties, rapid swelling and water uptake behavior, of the thiolated polymers, have made them an attractive new generation of mucoadhesive polymers [96]. Langoth *et al.* developed a model for buccal mucosal delivery of pentapeptide (Leu-enkephalin), taking advantage of the improved adhesion time due to the specific interaction of a polycarbophil–cysteine conjugated polymer with the buccal mucosa, as well as its enzyme inhibitory effect [97].

10.1.2 Target-specific mucoadhesive polymers

The development of mucoadhesive polymer, which is able to selectively create specific molecular interactions with a particular target, such as a receptor on the cell membrane of a specific tissue, is a very attractive potential for targeted delivery. Specific proteins or glycoproteins, such as lectins, which are able to bind certain sugars on the cell membrane, can increase bioadhesion and potentially improve drug delivery via specific binding and increase the residence time of the dosage form [98]. Woodley and Naisbett [99] demonstrated the

Table 3. List of biopolymers useful in oral transmucosal drug delivery system.

Biopolymer	Ref.
Biopolymer from extract of *Ocimum basilicum*	[89]
Biopolymer from *Sesamum indicum* seeds	[154]
Biopolymer from *Psidium gaujava*	[155]
Sodium salt of *Musa paradisiaca* biopolymer	[156]
Biopolymer from *Cocos nucifera*	[157]
Biopolymer from the leaves of *Bombax malabaricum*	[158]
Biopolymer from kernels of *Helianthus annus*	[159]
Biopolymer from fruit pulp of *Cordia dichotoma*	[152]
Biopolymer from *Mangifera indica*	[160]
Biopolymer from *Lotus corniculatus*	[161]
Biopolymer from *Cajanus indicus*	[162]
Biopolymer from *Logelaria siceraria*	[163]
Biopolymer from *Arahcis hypogea* seeds	[164]
Biopolymer from *Lallimantia royalena* seeds	[165]
Biopolymer from *Annona squamosa* fruit pulp	[166]
Biopolymer from *Gravia oppositifolia*	[167]
Biopolymer from *Cucurbita maxima* fruit pulp	[168]
Biopolymer from *Psidium guajava*	[169]
Biopolymer from *Artocarpus heterophyllus*	[170]

application of tomato lectin in oral drug delivery for the first time. It has been shown that tomato lectin can bind rat intestinal epithelium safely without inducing any harmful effects on the membrane [100]. Nevertheless, lectin-mediated mucoadhesive polymers, as second-generation mucoadhesives, contain an enormous potential for future use in drug delivery which, unfortunately, have not yet been fully explored. The recent idea of developing blectinomimetics Q (lectin-like molecules) based on lectins, and even biotechnologically generated derivatives of such molecules, holds an interesting future for this class of bioadhesion molecules [101].

10.1.3 Bacterial adhesion

The adhesive properties of bacterial cells, as a more complicated adhesion system, have recently been investigated. The ability of bacteria to adhere to a specific target is rooted from particular cell-surface components or appendages, known as fimbriae, which facilitate adhesion to other cells or inanimate surfaces. The attractiveness of this approach lies in the potential increase in the residence time of the drug on the mucus and its receptor-specific interaction, similar to those of the plant lectins. As an example, *Escherichia coli* have been reported to specifically adhere to the lymphoid follicle epithelium of the ileal Peyer's patch in rabbits [102]. Additionally, different staphylococci possess the ability to adhere to the surface of mucus gel layers and not to the mucus-free surface [103].

10.1.4 Mucoadhesive polymers as enzyme inhibitor and permeation enhancer

Some mucoadhesive polymers such as polyacrylates, cellulose derivatives and chitosan can act as an enzyme inhibitor and penetration enhancer themselves and prove to be successful strategies in oral mucoadhesive drug delivery [104].

10.1.5 Biopolymers

In recent years, the use of polymers from natural sources in drug delivery systems has become a very popular field of research; however, the oral transmucosal drug delivery system is most common among all other delivery systems. Recently, more than 50 biopolymers have been identified and isolated by Satheesh Madhav for oral transmucosal drug delivery system and most of them are used frequently in various drug delivery systems. Some of the polymers identified and isolated by Satheesh Madhav are assembled in **Table 3**.

11. Evaluation of mucoadhesive properties

Oral mucoadhesive drug delivery is used to evaluate the measurement of the effectiveness of mucoadhesive polymer. Various *in vivo*, *ex vivo* and *in vitro* methods are used for testing the efficacy of the mucoadhesive nature of test dosage form. Commonly used *in vitro*/*ex vivo* methods include tensile strength measurement, shear strength measurement and chip-based systems, whereas various imaging techniques are used for the evaluation of the delivery systems under *in vivo* conditions.

In vitro tensile strength measurement is done by dipping a filter paper in 8% mucin dispersion. Thereafter, the mucin-coated filter paper is placed in contact with the hydrated polymeric samples, in physiological solutions, for a definite period of time, followed by the determination of the maximum force required to detach the filter paper and polymer surfaces after the mucoadhesive bonding [105]. Similarly, *ex vivo* experimentations are also done with the exception that the mucin-coated filter paper is replaced with excised mucosal tissues [106,107]. The mucoadhesive properties can also be determined by incubating the hydrated polymer matrix surface kept in contact with a viscoelastic 30% (w/w) mucin solution in water with the subsequent determination of the maximum detachment force required to separate the polymer matrix and mucin solution surfaces after the adhesion [108]. The mucosal tissue is attached to two blocks and the adhesion force of the mucoadhesive system is measured. The weight required to detach the two blocks is considered the detachment force. *Wash-off test* may also be used to determine the mucoadhesive property of delivery systems. In the test, the mucosal tissue is attached onto a glass slide with the help of a double-sided cyanoacrylate tape. The operation of the equipment gives an up-and-down movement to the tissue-delivery matrix system. In this study, the time for the complete detachment of the delivery system from the mucosal layer is determined [109]. The shear stress measures the force that causes a mucoadhesive to slide with respect to the mucus layer in a direction parallel to the plane of contact [110]. Adhesion tests based on the shear stress measurement involve two glass slides coated with polymer and a film of mucus. Mucus forms a thin film between the two polymer-coated slides, and the test measures the force required to separate the two surfaces. For the relative measurement of mucoadhesive nature of powder polymer samples, modified Du Noüy tensiometer may be used [111].

Table 4. Patented formulations of oral transmucosal system.

Inventor	Title	Patent number	Year of patent
Abeer M. Al-ghananeem	Compositions and methods for transmucosal delivery of lofexidine	US12410114	2009
Hao Zhang	Oral transmucosal drug dosage using solid solution	US6264981	1999
Michael S. Balkin	Oral transmucosal delivery tablet and method of making it	US5656284	1995
Brian Hague	Sugar-free oral transmucosal solid dosage forms and uses thereof	US10771046	2004
Hao Zhang	Dissolvable backing layer for use with a transmucosal delivery device	US7276246	2007
Kazuyoshi Furusawa	Fentanyl compound-containing edible patch to be applied to oral mucosa	US10668284	2003
Janet Anne Halliday	Oral transmucosal delivery	US6488953	2001
Christopher N. Jobdevairakkam *et al.*	Composition of fentanyl citrate oral solid transmucosal dosage form	US11271767	2005
Roy L. Mcquinn *et al.*	Transmucosal drug delivery device	US5780045	1996
Stelios Tzannis *et al.*	Bioadhesive drug formulations for oral transmucosal delivery	US11650227	2007
Vikas Agarwal *et al.*	Oral transmucosal nicotine dosage form	US11986097	2007
Mirja Huhtinen *et al.*	Transmucosal veterinary composition comprising detomidine	US1667100	1993
Matthew T. Scholz *et al.*	Bioadhesive composition and patch	US5750136	1995
Kauko Kurkela *et al.*	Transmucosal formulations of levosimendan	US6399610	2000
Roy L. Mcquinn	Non-invasive transmucosal drug monitoring method	US5113860	1991
Adel Pinhasi *et al.*	Solid composition for intra-oral delivery of insulin	US11887653	2006
Paul C. Wilhelmsen	Tablet giving rapid release of nicotine for transmucosal administration	US6248760	1999
James E. Biegajski *et al.*	Water-soluble pressure-sensitive mucoadhesive and devices provided therewith	US5700478	1995
John M. Pinney *et al.*	Two-stage transmucosal medicine delivery system for symptom relief	US6358060	2002
Katsumi Ihara *et al.*	Phentanyl-containing adhesive patch for application to oral-cavity mucosa	US10524024	2006
Leah M. Lehman *et al.*	Method and apparatus for transdermal or transmucosal application of testosterone	US11441311	2005
Sonia J. Heiber *et al.*	Buccal delivery of glucagon-like insulinotropic peptide	US5766620	1998

Recently, mucoadhesion studies have been reported by using BIACORE® integrated chip (IC) systems. The method involves immobilization of the polymer (powder) on to the surface of the IC with the subsequent passage of the mucin solution over the same. This results in the interaction of the mucin with that of the polymer surface. The polymer–mucin interaction is measured by an optical phenomenon called surface plasmon resonance (SPR), which measures the change in the refractive index when mucin binds to the polymer surface [112]. Recently, adhesive bonds, formed between drug delivery device and mucin, are characterized and estimated by various spectroscopic methods such as ultraviolet (UV), Fourier transform infra-red (FTIR) and nuclear magnetic resonance (NMR) spectrometers.

12. Recent advances in oral transmucosal drug delivery system

Extensive efforts have recently been focused on targeting a drug or delivery system in a particular region of the oral cavity such as soft palate, for extended period of time, not only for local targeting of drugs but also for the better control of systemic drug delivery. Administration of vaccine antigens directly to various mucosal sites for the effective protection of mucosal surfaces against colonization and invasion of infectious agents have recently come into focus. Additionally, suboptimal immune responses are frequently induced by mucosal immunization and the use of mucosal adjuvants is commonly required. As a result, development of successful mucosal vaccines depends largely on the improvement of mucosal antigen delivery and on the discovery of new and effective mucosal adjuvants [112]. Chitosan easily forms microparticles and nanoparticles which encapsulate large amounts of antigens such as ovalbumin, diphtheria toxoid or tetanus toxoid. It has been shown that ovalbumin-loaded chitosan microparticles are taken up by the Peyer's patches of the gut-associated lymphoid tissue (GALT). This unique uptake demonstrates that chitosan particulate drug carrier systems are promising candidates for oral vaccination [113]. The identification of an increasing array of highly potent, endogenous peptide and protein factors termed cytokines, which can be efficiently synthesized using recombinant DNA technology, offers exciting new approaches for drug therapy via oral mucosa to avoid degradation of proteins and peptides that occurs as a result of oral administration, gastrointestinal absorption and first-pass hepatic metabolism [114]. Recently,

Table 5. List of oral transmucosal dosage forms available in market.

Brand name	Active drugs	Uses	Manufacturer	Dosage form
Loramyc	Miconazole lauriad	Oropharyngeal candidiasis	Bioalliance Pharma	Buccal tablet
Lauriad	Acyclovir	Herpes labialis	Bioalliance Pharma	Buccal tablet
Onsolis	Fentanyl citrate	Opioid analgesic	Meda Pharmaceuticals, Inc.	Buccal soluble film
BEMA	Buprenorphine	Opioid analgesic	Biodelivery Sciences International, Inc.	Buccal soluble film
Actiq	Fentanyl citrate	Opioid analgesic	Wolters Kluwer Health	Lozenge on a stick
Fentora	Fentanyl citrate	Opioid analgesic	Wolters Kluwer Health	Buccal tablet
Sublimaze	Fentanyl citrate	Opioid analgesic	Wolters Kluwer Health	Injection
ACT fluoride rinse	Fluoride topical	Anticavity	Cerner Multum, Inc.	Oral solution
Amantadine oral solution USP	Amantadine hydrochloride	Antiviral	Qualitest Pharmaceuticals	Oral solution
Rapamune	Sirolimus	Hepatic impairment	Wyeth Pharmaceuticals	Oral solution
Nicoderm CQ	Nicotine	Smoking cessation agent	Pfizer	Oral patch
Anadrol-50	Androgen	Hormonal agent	Thomson Healthcare Products	Oral patch
Nitrocot	Nitroglycerin	Anti-angina	Thomson Healthcare Products	Sublingual tablet
Buprenorphine HCl sublingual tablets (CIII)	Buprenorphine hydrochloride	Opioid analgesic	Roxane Laboratories	Sublingual tablet
Saphris	Asenapine maleate	Schizophrenia, bipolar disorder	Catalent UK Swindon Zydis Ltd.	Sublingual tablet
Gelclair	Glycyrrhetinic acid/povidone/ sodium hyaluronate	Relieve mouth pain and irritation	Wolters Kluwer Health	Oral gel
Gel-kam	Fluoride	Anticavities	Cerner Multum, Inc.	Oral gel

Table 6. Permeability enhancers used in transmucosal drug delivery.

Permeability enhancer	Active drug	Attributes	Ref.
n-Butyric acid and *n*-butanol	Acyclovir	Increase the permeability of acyclovir through buccal mucosa	[55]
n-Butyric acid and *n*-butanol	Propranolol	Increase the permeation of propranolol through buccal mucosa	[171]
Dextran	Octreotide, LHRH insulin and IFN	Large molecular weight hydrophilic polymers significantly increase the permeation of hormones	[172-175]
Sodium deoxycholate and sodium lauryl sulfate	Salicylic acid	Increase the permeability of salicylic acid across rabbit buccal mucosa	[176]
Sodium glycocholate, Sodium lauryl sulfate	Insulin	Increase in insulin bioavailability from about 0.7% (without permeation enhancer) to 26 – 27% in the presence of sodium glycocholate (5% w/v) and sodium lauryl sulfate (5% w/v)	[53,177]
Sodium deoxycholate and sodium glycocholate	Insulin	Increase the buccal absorption of insulin	[155]

LHRH: Leutinizing hormone releasing hormone.

with the availability of *in vitro* cell live culture (e.g., cell line TR14 derived from human buccal carcinoma), a new method for studying buccal drug permeability has been developed. The *in vitro* permeation experiments are also carried by using reconstituted human oral non-keratinized epithelium and transwell diffusion cells system. Such studies can provide initial leads to suitable drug candidates for oral mucosal drug delivery. Recent works on such studies and their implication on new opportunities for improving therapeutic modality, for example, to achieve better bioavailability, rapid onset of action and convenient drug administration from oral transmucosal drug delivery have been performed [115]. The palatal implant method originally designed to reduce snoring can significantly reduce the apnea–hypopnea index (AHI) in some patients with mild to moderate obstructive sleep apnea (OSA) in a single office-based procedure [116].

Various oral mucosal dosage forms that have been developed till date include toothpastes, mouthwashes, lozenges, gels, chewing gums, lollipops, films, patches, tablets and some other specialized devices [117]. Most of them are patents (**Table 4**) and very few are available in market (**Table 5**). However, conventional oral mucosal dosage forms, due to their washing

effect of ingredients because of salivary secretion and breakdown of formulation due to mechanical stresses encountered inside oral cavity exhibit some drawbacks, especially lower bioavailability. Therefore, attempts have been made by various researchers to develop formulations that prolong drug release in oral cavity which offers greater advantages in the prevention and treatment of local diseases or in promoting oral mucosal delivery of drugs for systemic therapies [118]. Despite these obstacles, the buccal delivery applications have been marketed or proposed in treatment of systemic and chronic diseases, few of them are trigeminal neuralgia, Meiniere's disease, diabetes, drug addiction and drug dependence [119-124]. Oral transmucosal drug delivery through oral cavity, apart from treatment of local disease is very much beneficial to systemic drug delivery through sustained drug release, without the need for the patient to intervene and hence better patient acceptability. This would raise the patient's compliance particularly in case of chronic illness. A few examples of smaller non-ionizable molecules that enhance the permeability in transmucosal drug delivery are summarized in **Table 6**. Cooke *et al*. patented a device and a method of multi-layer transmucosal therapeutic film, comprising at least two layers, one impregnated above the other for transmucosal administration of active substances [125]. Very recently, Satheesh Madhav and Uma Shankar got a patent on formulation of amikacin-loaded bioplates by using smart biopolymeric material from *Arachis hypogea* seeds and they tested their formulation in goat soft palatal mucosa and found very attractive results [28].

13. Conclusion

The oral transmucosal drug delivery method has been found most suitable as compared with other systematic drug delivery systems. Over the past years, the oral cavity has been known as a site for therapeutic application in order to treat diseases in the mouth. Nowadays, a significant development has been done in long-sustained delivery systems for systemic therapy. Oral transmucosal system allows a more rapid absorption into the blood stream as compared with oral administration to the GIT and consequently offering an alternative means of drug administration, which is more comfortable and convenient for patients than intravenous drug administration. The drugs for oro-trans mucosal delivery must have the necessary physicochemical properties together with a significant clinical advantage. On the basis of applications and advantages of oral transmucosal drug delivery method, it may be concluded that the oro-trans mucosal route is a significant alternative for other drug delivery forms.

14. Expert opinion

Oral transmucosal products are relatively new drug delivery strategy. Apart from other oro-trans mucosal drug delivery systems, the soft palatal drug delivery system may be considered as a new class of drug delivery systems. The reason behind this approach is that the soft palate tissue consists of non-keratinized tissues thus delaying the absorption and sustaining the drug release. Moreover, the site is not affected by salivary secretion and tongue activity and can be used as an ideal route for drug delivery in the near future. It can also serve as a smart route for the targeting of drugs to the brain.

The key finding in the research done on soft palatal drug delivery system is the soft palatal mucosa which is used as a primary drug delivery site for various APIs (active pharmaceutical ingredients) like amikacin, rosiglitazone, pioglitazone, gentamicin, etc. by suitably formulating mucoadhesive-loaded plates. The results are encouraging and significant in delivering a drug for a long period of time but this platform has a limitation that the dose of API should be less and dosage form must have significant mucoadhesivity with soft palatal mucosa for achieving prolonged release dosage form. This novelistic approach can also be used as a platform for brain targeting which has been scientifically confirmed by suitably formulating insulin-loaded bioadhesive films and same has been evaluated for its mucoadhesibility; *in vitro* and *in vivo* study findings have revealed that the significant amount of drug reaches the brain via neural pathway for eliciting its pharmacological response. The soft palatal drug delivery research has shown an innovative finding and inbuilt properties of soft palatal mucosa for delivering API through systemic targeting to the brain. The ultimate goal in this field is to explore this mucosal platform as a transmucosal drug delivery site for delivering API through systemic or site-specific targeting to the brain in order to prolong the drug release and to minimize the dose of the drug.

The scientists who are interested to do work in this area should acquire a knowledge about the anatomy, physiology, nerve supply and basic concept of the mucoadhesion and factors to be considered for selection of suitable excipient to designing mucoadhesive dosage forms. The biggest challenge is to have a soft palatal platform that has a potential mucosal layer that can serve as a targeting site for drug delivery and also has unique mucosal features than buccal and sublingual mucosae in order to achieve good patient compliance. Currently, some mucodhesive formulations are available in the market, in near future majority of APIs will be formulated as mucoadhesive formulations. This concept can be used for optimizing the dose of drug and minimizing its undesirable effects. The transmucosal drug delivery system uses soft palatal mucosa, lingual mucosa, nasal mucosa, oral aural mucosa, intestinal mucosa, lung mucosa, vaginal mucosa and sublingual platforms for delivering various APIs to produce its prolongability and sustainability of drug to reduce the dosing frequency and improve patient compliance.

Declaration of interest

The authors declare no conflict of interest. DK Semwal and RB Semwal have received Post Doctoral Fellowships sponsored by UGC. NV Satheesh Madhav and R Semwal are employed by the Dehradun Institute of Technology.

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