Journal of Controlled Release 140 (2009) 2–11

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review

Orotransmucosal drug delivery systems: A review

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ARTICLE INFO

Article history:
Received 18 May 2009
Accepted 27 July 2009
Available online 6 August 2009

Keywords:
Transmucosal
Soft palate
Paracellular
Transcellular
Drug delivery

ABSTRACT

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods and also enhances drug bioavailability because the mucosal surfaces are usually rich in blood supply, providing the means for rapid drug transport to the systemic circulation and avoiding, in most cases, degradation by first-pass hepatic metabolism. The systems contact with the absorption surface resulting in a better absorption, and also prolong residence time at the site of application to permit once or twice daily dosing. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route than the intravenous route. Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug. Although many drugs have been evaluated for oral transmucosal delivery, few are commercially available. The clinical need for oral transmucosal delivery of a drug must be high enough to offset the high costs associated with developing this type of product. Transmucosal products are a relatively new drug delivery strategy. Transmucosal drug delivery promises four times the absorption rate of skin. Drugs considered for oral transmucosal delivery are limited to existing products, and until there is a change in the selection and development process for new drugs, candidates for oral transmucosal delivery will be limited. The present papers intend to overview a wide range of orotransmucosal routes being potentially useful for transmucosal drug delivery and remind us of the success achieved with these systems and the latest advancement in the field.

Contents

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doi:10.1016/j.jconrel.2009.07.016

1. Introduction

Oral administration of pharmaceutical compositions has some drawbacks. For instance, it is difficult to keep the medicament at the desired location so that it can be absorbed, distributed and metabolized easily. Accordingly, there has been much interest in the use of the mucosal lining of body cavities. Regions in the oral cavity where effective drug delivery can be achieved are buccal, sublingual, palatal and gingival. 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 permeability of the oral mucosa is probably related to the physical characteristics of the tissues. The sublingual mucosa is more permeable and thinner than the buccal mucosa and because of the considerable surface area and high blood flow; it is a feasible site when a rapid onset is desired. The sublingual route is generally used for drug delivery in the treatment of acute disorders, but it is not always useful. It is because its surface is constantly washed by saliva and tongue activity which makes it difficult to keep the dosage form in contact with the mucosa. Unlike the sublingual mucosa, the buccal mucosa offers many advantages because of its smooth and relatively immobile surface and its suitability for the placement of controlled-release system which is well accepted by patients. The buccal mucosa is a useful route for the treatment of either local or systemic therapies overcoming the drawbacks of conventional administration routes. The buccal mucosa is relatively permeable, robust in comparison to the other mucosal tissues and is more tolerant to potential allergens which have a reduced tendency to irreversible irritation or damage. So, it has been largely investigated as a potential site for controlled drug delivery in various chronic systemic therapies. However, salivary production and composition may contribute to chemical modification of certain drugs [1]. Moreover; involuntary swallowing can result in drug loss from the site of absorption. Furthermore, constant salivary scavenging within the oral cavity makes it very difficult for dosage forms to be retained for an extended period of time in order to facilitate absorption in this site. The relatively small absorption area and the barrier property of the buccal mucosa contribute to the inherent limitations of this delivery route. Both the buccal and sublingual membranes offer advantages over other routes for administration. For example, drugs administered through the buccal and sublingual routes have a rapid onset of action and improved bioavailability of certain drugs. These routes can bypass the first-pass effect and exposure of the drugs to the gastrointestinal fluids. Additional advantages include easy access to the membrane sites so that the delivery system can be applied, localized, and removed easily. Further, there is good potential for prolonged delivery through the mucosal membrane within the oral mucosal cavity [2]. The palatal mucosa is intermediate in thickness and keratinized thus lessening its permeability. All of these epithelia are coated with a layer of mucus. Bioadhesive polymer can significantly improve the performance of many drugs, as they are having prolonged contact time with these tissues. These patient compliance controlled drug delivery products have improved drug bioavailability at suitable cost.

Drug selection for oral transmucosal delivery is limited by the physicochemical properties of the drugs themselves. To be delivered transmucosally, drugs must have unique physicochemical properties, i.e. a proper balance between solubility and lipophilicity. Generally only a few milligrams of drug can cross the oral mucosa, even if the drug has a favorable profile for oral mucosal delivery. Presently, new classes of drugs are typically not developed specifically for oral transmucosal delivery. Therefore, drugs considered for oral transmucosal delivery are limited to the existing products. Until there is a drastic change in the selection and development process of new drugs, candidates for oral transmucosal delivery will continue to be limited. Many products on the market, however, have shown unique properties and advantages of this delivery route. The key in the future will be to involve drug delivery and formulation scientists early in the drug selection process, so that more drugs that are suitable for delivery routes other than oral and parental can be developed [3].

2. Overview of the oral mucosa

2.1. Structure

The oral mucosa is composed of an outermost layer of stratified squamous epithelium below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium [4]. The epithelium of the buccal mucosa is about 40–50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.

2.2. Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4–4000 times greater than that of the skin [5]. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeability of the oral mucosae decrease in the order of, sublingual greater than buccal, and buccal greater than palatal [6]. This ranking is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized. Intercellular spaces at the upper one-third of the epithelium. This barrier exists in the outermost 200 μm of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase and lanthanum nitrate. When applied to the outer surface of the epithelium, these tracers can only penetrate through outermost layer or two of cells. When applied to the submucosal surface, they permeate up to, but not into, the outermost cell layers of the epithelium. According to these results, it seems apparent that flattened surface cell layers present are the main barrier to permeation, while the more isodiametric cell layers

are relatively permeable. In both keratinized and non-keratinized epithelia, the limit of penetration coincided with the level where the membrane coating granules could be seen adjacent to the superficial plasma membranes of the epithelial cells. Since the same result was obtained in both keratinized and non-keratinized epithelia, keratinization by itself is not expected to play a significant role in the barrier function [7]. The components of the membrane coating granules in keratinized and non-keratinized epithelia are however different [8]. The membrane coating granules of keratinized epithelium are composed of lamellar lipid stacks, whereas the non-keratinized epithelium contains membrane coating granules that are non-lamellar. The membrane coating granule lipids of keratinized epithelia include sphingomyelin, glucosylceramides, ceramides, and other non-polar lipids, however for non-keratinized epithelia, the major membrane coating granule lipid components are cholesterol esters, cholesterol, and glycosphingolipids [9]. Aside from the membrane coating granules the basement membrane may present some resistance to permeation as well, however the outer epithelium is still considered to be the rate-limiting step to mucosal penetration. The structure of the basement membrane is not dense enough to exclude even relatively large molecules.

2.3. Environment

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some may be attached to certain regions on the cell surfaces. This matrix may actually play a role in cell–cell adhesion, as well as act as a lubricant, allowing cells to move relative to one another [10]. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems [11]. In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized mucus secreting cells like the goblet cells, however in the oral mucosa; mucus is secreted by the major and minor salivary glands as part of saliva. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands [12]. At physiological pH, the mucus network carries a negative charge (due to the sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer. It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called 'membrane coating granules' [13]. The turnover time for the buccal epithelium has been estimated 5–6 days, and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500–800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100–200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosa of areas subject to mechanical stress (the gingivae and hard palate) is keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and only have small amounts of ceramides [14].They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia [15,16]. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals. It allows for the continuous mineralization of the tooth enamel after eruption and helps in demineralization of the enamel in the early stages of dental caries [17]. Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus, and the degree of stimulation [18]. The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the pH. The daily salivary volume is between 0.5 and 2 l and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

3. Mucus

3.1. Structure, function and composition

The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness ranging from 40 μm to 300 μm [19]. Although most of mucus is water (≈95–99% by weight) the key macromolecular components are a class of glycoprotein known as mucins (1–5%). Mucins are large molecules with molecular masses ranging from 0.5 to over 20 MDa. They contain large amounts of carbohydrate (for gastrointestinal mucins 70–80% carbohydrate, 12–25% protein and up to ≈5% ester sulfate). Undegraded mucins from a variety of sources are made up of multiples of a basic unit (≈400–500 kDa), linked together into linear arrays to give the macroscopic mucins with molecular masses claimed to be as high as ≈50 MDa [20]. It serves as an effective delivery vehicle by acting as a lubricant allowing cells to move relative to one another and is believed to play a major role in adhesion of mucoadhesive drug delivery systems [21]. At buccal pH, mucus can form a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer. Mucus molecules are able to join together to make polymers or an extended three-dimensional network. Different types of mucus are produced, for example G, L, S, P and mucus, which form different network of gels.

4. Transmucosal drug absorption

4.1. Principles of drug absorption via the oral transmucosa

A thorough description of the oral mucosa and its function is available elsewhere [22]. We have only included those details relevant to the oral mucosal delivery of drugs. The oral cavity comprises the lips, cheek (buccal), tongue, hard palate, soft palate and floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosae. The mucosal tissues in the cheeks (buccal), the floor of the mouth (sublingual) and the ventral surface of the tongue account for about 60% of the oral mucosal surface area. 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)[23] is relatively small compared with the gastrointestinal tract (350 000 cm^2) and skin (20 000 cm^2)[24]. However, the oral mucosa is highly vascularized, and therefore any drug diffusing into the oral mucosa membranes has direct access to the systemic circulation via capillaries and venous drainage. Thus, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the gastrointestinal tract 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 [25]. The oral mucosa is made up of closely compacted epithelial cells, which comprise the top quarter to one-third of the epithelium [26–28]. The primary function of the oral epithelium is to protect the underlying tissue against potential harmful agents in the oral environment and from fluid loss [29]. In order for a drug to pass through the oral mucosa, it must first diffuse through the lipophilic cell membrane, and then

pass through the hydrophilic interior of the cells of the oral epithelium. Thus, the oral mucosa provides both hydrophilic and hydrophobic barriers that must be overcome for efficient mucosal delivery. An enzymatic barrier also exists at the mucosa, which causes rapid degradation of peptides and proteins, limiting their transport across the oral mucosa. Although these layers provide a unique challenge for drug delivery via the oral mucosa, several different approaches in the design and formulation of suitable delivery systems have been developed to circumvent these barriers.

4.2. Transmucosal drug absorption mechanisms (Fig. 1)

Drug absorption through a mucosal surface is generally efficient because the stratum corneum epidermis, the major barrier to absorption across the skin, is absent. Mucosal surfaces are usually rich in blood supply, providing the means for rapid drug transport to the systemic circulation and avoiding, in most cases, degradation by first-pass hepatic metabolism. 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. Tight junctions or similar interconnections exist between cells. The intercellular tight junction is one of the major barriers to paracellular transport of macromolecules and polar compounds. Tight junction structure and permeability can be regulated by many potential physicochemical factors, including the concentration of cAMP and intracellular calcium concentrations. The mechanism of absorption enhancement of hydrophilic drugs by methylated cyclodextrins may be related to a temporary change in mucosal permeability and opening of the tight junctions [30,31]. Poly-(acrylic acid) derivatives such as Carbomer 934® and Chitosans have been extensively studied for their possible uses as absorption enhancers that cause the loosening of tight junctions [32,33]. Absorption enhancer alters membrane, lipid–proteins interactions and lipid bilayer and facilitates transcellular routes while in the paracellular route the absorption enhancer disrupts intracellular occluding junctional complexes and opens the paracellular route [34]. The structure of the epithelial membrane is frequently simplified to consist of a lipid pathway and an aqueous pore pathway, in which the absorption of a drug is determined by the magnitude of its partition coefficient and molecular size until the diffusion through the aqueous diffusion layer (P_a) becomes a rate-limiting steps in the course of transmembrane permeation. Transmucosal permeation of polar molecules (such as peptide based pharmaceuticals), may be by way of paracellular route, however several barriers exist during the course of paracellular permeation [35].

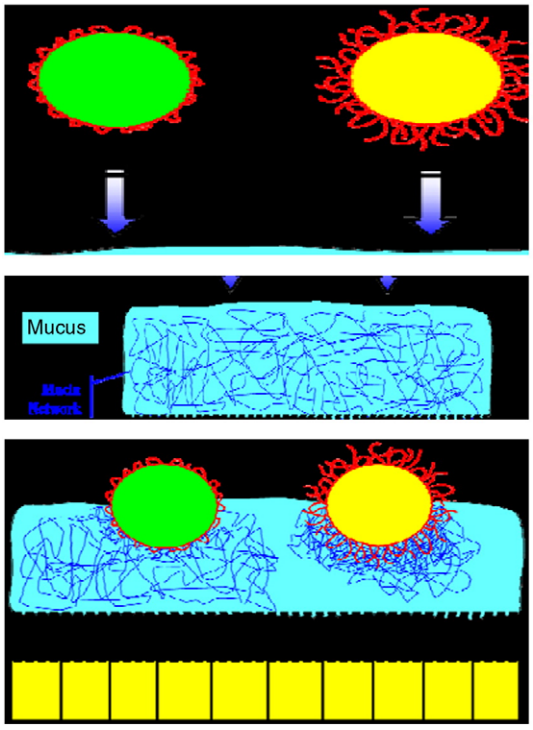

Fig. 1. Mucus interaction with drug delivery systems.

1) Basal lamina, whose barrier function is dependent upon the molecular weight of the permeant molecule and its reactivity with the barrier as well as the structural and functional factors of the barrier.
2) Membrane coating granules, which extrudes into the intercellular region of both keratinized and non-keratinized oral epithelium and prevent the transmucosal penetration of water-soluble peptide or protein, such as horse radish peroxidase.
3) The keratin layer, whose barrier function in oral mucosa is not as well as defined as in the skin. Although the rate of permeation of water was shown to be greater in non-keratinized than in keratinized oral epithelium.

Drug absorption via the oral mucosa is a passive diffusion process. By simplifying the oral mucosa into a hydrophobic membrane, Fick's first law can be used to describe the drug absorption process. 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]. The effective formulation must not only release the drug to the mucosal surface, but do so with the drug in its free form. If the drug is bound to other components in the formulation, it is not available for transmucosal delivery and the bioavailability will be greatly reduced. The unique properties of the oral mucosa have also imposed unique drug delivery challenges for formulation scientists. In general, lipophilic compounds have much higher permeability coefficients than hydrophilic compounds. However, the aqueous solubility's of lipophilic compounds are usually much lower than those of hydrophilic compounds. Thus, the amount of drug absorbed may not be high for lipophilic compounds if their hydrophobicity is too high. There is a fine balance between partition coefficient and solubility for a drug to be suitable for oral mucosal delivery. Due to these constraints, the potency of the drug is important for selecting appropriate candidates. The amount of drug that can be delivered via the oral mucosa is limited to a few milligrams. Occasionally, permeation enhancers are used to promote drug absorption, especially for hydrophilic drugs. Their exact mechanism of action is unknown, and may be different for different types of enhancers. It is believed that the enhancers form aqueous pores on the cell surfaces, thereby increasing the permeability of hydrophilic compounds. The use of permeation enhancers, however, must consider issues such as local tissue irritation, long term tissue toxicity and enhanced permeability to pathological micro-organisms. Despite considerable research on oral mucosal permeation with enhancers, no product has yet to be commercially developed using a permeation enhancer.

4.3. Enhancement of transmucosal agent transport

Non-enhanced drug delivery is based solely on diffusion. Hydrophilic, ionic drugs usually diffuse through the intercellular space, while hydrophobic are able to pass through cellular membranes. Depending on physicochemical properties of the drug, the mucosa may have insufficient permeability and could represent a major limitation in the

development of a transmucosal drug delivery system. In addition, the limitation of the available absorption area and the short time of exposure, because of the washing effect of saliva, can decrease absorption efficiency even more. Permeation of drugs throughout epithelial barriers could be promoted by 'penetration enhancers' utilizing different techniques, usually subdivided into chemical or physical methods. Penetration enhancers are capable of decreasing the barrier properties of the mucosa by increasing cell membrane fluidity, extracting the structural intercellular and/or intracellular lipids, altering cellular proteins, or altering the mucus structure and rheology [37–39]. Chemical enhancers could be added to a pharmaceutical formulation, alone or in combination, in order to increase the permeation rate, without damage to, or irritation of, the mucosa. Enhancer efficacy depends on the physicochemical properties of the drug, the administration site and the nature of the vehicle. Penetration enhancers are thought to improve mucosal absorption by different mechanisms, for example, reducing the viscosity and/or elasticity of the mucus layer, or by transiently altering the lipid bilayer membrane, or overcoming the enzymatic barrier, or increasing the thermodynamic activity of the permeant. Various chemicals have been used as permeation enhancers across the epithelial tissues; among them chelators (e.g. sodium EDTA or salicylates), surfactants (e.g. sodium dodecyl sulfate, polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether and benzalkonium chloride), bile salts (e.g. sodium deoxycholate, sodium glycocholate, sodium taurocholate and sodium glycodeoxycholate), fatty acids (e.g. oleic acid, capric acid and lauric acid) and non-surfactants (e.g. cyclodextrins and azones1). Recently, chitosan and its derivates have been extensively used to enhance permeation across either monostratified or pluristratified epithelia of small polar molecules and hydrophilic large molecules either in animal models or in human beings [40].Through the mechanical penetration enhancers, drug absorption can also be enhanced mechanically, for example, by removing the outermost layers from epithelium to decrease the barrier thickness, or electrically, for example, by application of electric fields or by sonophoresis. The latter acts by reducing, temporarily, the density of lipids in the intercellular domain of the membrane. This 'disruption' occurs due to a combination of micromechanical, thermic and cavitation effects that effectively 'open up' the intracellular pathways, allowing substances to penetrate. After chemical enhancement, the most efficient permeation enhancement methods for intraoral applications are probably the electrical mechanisms, such as electrophoresis (iontophoresis), electro-osmosis and electroporation. Electrophoretic enhancement in the oral cavity has been reported for a number of applications [41]. It is most effective for water-soluble, ionized compounds. The rate of migration is limited by the maximum electric current which can be applied across the mucosa; generally, currents below 0.5 mA/cm^2 can be applied without adverse effects [42]. Another means of increasing the drug transport rate is by utilizing electro-osmosis. Human tissue possesses fixed negative charge, and binds mobile, positive, counter ions, forming an electrically charged double layer in the tissue capillaries. When an electric field is applied across the tissue, there is a net flow of water through the tissue through the migration of the mobile solvated counter ion, a process known as electro-osmosis. Drugs dissolved in the interstitial water are, hence, transported into the tissue by bulk flow. In electroporation, high potential (20–100 V) pulses are applied across the tissue. Due to electrostriction forces, cellular membranes are temporarily perforated or even micro channels in the tissue are formed. Those channels serve as a drug transport route and are closed within few minutes without any lasting damage to the tissue [37,40].

5. Oral transmucosal routes

5.1. Oral transmucosal (sublingual, buccal, soft palatal) administration

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 a rapid rise in blood concentrations. The drug appears in blood within 1 min, and peak blood levels of most medications are achieved within 10 to 15 min, which is substantially faster than when the same drugs are administered by the orogastric route. The fentanyl oralet™ was developed to take advantage of oral transmucosal absorption for the painless administration of an opioid in a formulation acceptable to children [43,44]. The administration of other medications by this route and with similar delivery systems is being investigated [45]. Most pediatric patients swallow medications, administered orally, potentially leading to drug degradation in the gastrointestinal system. 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. For significant drug absorption to occur across the oral mucosa, the drug must have a prolonged exposure to the mucosal surface. Taste is one of the major determinants of contact time with the buccal or oral mucosa [46]. Drug ionization also affects drug uptake. Because the pH of saliva is usually 6.5 to 6.9, absorption is favored for drugs with a high pK_a [47]. 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 [48]. Drug absorption is generally greater from the buccal or oral mucosa [49] than from the tongue and gingiva. The fentanyl oralet™ is the first FDA-approved formulation of this type for children. Current approval is for preoperative sedation and for painful procedures in a hospital setting [50]. Because the pK_a of fentanyl is 8.4, absorption through the oral mucosa is favored. The fentanyl oralet™ has been used successfully in oncology patients undergoing painful procedures such as bone marrow aspiration or lumbar punctures. Oral transmucosal administration of morphine (by a buccal tablet) has been considerably less reliable than administration of fentanyl; this is not surprising as because of the relatively low lipid solubility of this drug [51]. Absorption of buprenorphine is better than that of morphine, but the utility of this drug is limited by the slow onset of effect. The oral transmucosal 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 [52]. Glottic rigidity has been demonstrated to be an important cause of ventilatory difficulty due to fentanyl-induced muscle rigidity. Chest wall or glottic rigidity has occurred in adults with an intravenous fentanyl dose as small as 75 μg; however, no dose response studies have systematically addressed this issue in adults or children. Fentanyl administered by oral transmucosal 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 glottic or chest wall rigidity has been reported during the induction of anesthesia [53]. An additional possible safety factor is that a large proportion of swallowed drug is destroyed by gastric acid, which reduces the potential for later drug uptake. Another possible advantage of oral transmucosal administration of fentanyl is that the sustained therapeutic blood levels achieved may offer analgesia for painful procedures that last an hour or more. This contrasts with the extremely short duration of analgesia (minutes) with single low doses of intravenous fentanyl. As with any narcotic, the potential exists for respiratory depression and oxygen desaturation with the moderately rapid absorption through the oral mucosa; pharmacodynamic studies have demonstrated a small but clinically important incidence of oxygen desaturation with the fentanyl oralet™ [54]. In response to these findings, the recommended dosage was lowered from 15 to 20 μg/kg to the currently approved dose of 5 to 15 μg/kg. The importance of pulse oximetry and careful vigilance must be emphasized. The advantages of relatively rapid absorption offered by this

drug delivery system make it a reasonable alternative to intravenous therapy. Some have argued that narcotics administered to children have a disagreeable taste, precluding the use of this oral transmucosal drug delivery system. No evidence exists to suggest that appropriate narcotic therapy in children increases the risk of addiction in later life. Furthermore, this rationale has never been used to prevent the palatable delivery of other potentially harmful drugs, such as children's vitamins. Because the relief of pain and anxiety is an important part of the daily practice of many pediatric care givers, it is appropriate to encourage the development of these innovative, non-painful, and non-threatening techniques of drug administration. Each drug must pass rigorous scientific evaluation to ensure safe usage and to define the precise role of the drug in pediatric health care. It would be wrong to reject this route of drug administration simply because of the concern that children would think that it is pleasurable to take narcotics or sedatives via this route or modality of drug delivery. The soft palate is a mobile flap suspended from the posterior border of the hard palate, sloping down the back between the oral and nasal parts of the pharynx. The soft palate is a thick fold of mucosa enclosing an aponeurosis, muscular tissue, vessels, nerves, lymphoid tissue and mucous glands and two small pits, the fovea palatine, one on each side of the midline are present they represents the orifices of ducts from some of the minor mucous glands of the palate [55]. The mucous membrane on the oral surface of the soft palate is highly vascularized. The papillae of the connective tissue are few and short, the stratified squamous epithelium is non-keratinized, the lamina propria shows distinctive layer of elastic fibres separating it from the submucosa. The latter is relatively loose and contains almost a continuous layer of mucous glands. Typical oral mucosa continues around the free border of the soft palate for a variable distance and is then replaced by nasal mucosa with its pseudostratified, ciliated columnar epithelium [56]. This route of administration is advantageous 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, 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 [57] (Fig. 2).

6. Transmucosal drug delivery system

6.1. Pharmaceutical consideration and formulation design for successful transmucosal drug delivery system

Drug selection for oral transmucosal delivery is limited by the physicochemical properties of the drugs themselves. To be delivered transmucosally, drugs must have unique physicochemical properties, i.e. a proper balance between solubility and lipophilicity. Moreover, generally only a few milligrams of drug can cross the oral mucosa, even if the drug has a favorable profile for oral mucosal delivery. Presently, new classes of drugs are typically not developed specifically for oral transmucosal delivery. It is also important to consider factors influencing drug release from a system. The release kinetics of a given drug from a system could be governed predominantly by the polymer morphology and excipients present in the system. Finally, ideal formulation and its degradation products should be non-toxic, non irritant and free from leachable impurities. It should not aid in development of secondary infections and prevent the effects of local drug irritation at the site of application. An ideal transmucosal drug delivery system must meet several prerequisites to be successful. The first prerequisite for a transmucosal drug delivery system is that it should rapidly attach to the mucosal surface and maintain a strong interaction to prevent displacement. Spontaneous adhesion of the system at the target site is critical and can be achieved through bioadhesion promoters that use tethered polymers. Contact time should also be sufficiently long at the target site, normally longer than that needed for complete drug release. The second prerequisite for a successful and effective transmucosal drug delivery system is that the bioadhesion performance should not be impacted by surrounding environmental pH. Other desirable characteristics of a 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. This may happen in the form of bulk erosion or surface erosion [58,59]. It is also important to consider factors influencing drug release from a polymer. The release kinetics of a given drug from a polymeric matrix could be governed predominantly by the polymer morphology and excipients present in the system [60].

Fig. 2. Oral transmucosal technology.

6.2. Oral transmucosal dosage forms

To improve oral transmucosal delivery of drugs, several new dosage forms have been developed: solutions, tablets/lozenges (including lyophilized and bioadhesive), chewing gum, solution sprays, laminated systems and patches, hydrogels, adhesive films, hollow fibres and microspheres [61]. Advances in oral mucosal 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. Mucoadhesive carrier is a viable option to develop a non-invasive carrier platform for the controlled release of bioactive.

6.2.1. Solid forms

Several solid lozenges formulations have been developed and are commercially available, including nitroglycerin sublingual tablet, fentanyl lozenge on a handle and prochlorperazine buccal tablets. Although these formulations vary in shape and size, they share many common characteristics. This method of delivery is simple for patients to use. The solid formulations dissolve in the oral cavity. The drugs are released and exposed to the entire mucosa and the top third of the esophageal mucosa. The limitation of this delivery form is the short residence time. Depending on the size and formulation, the lozenge or tablet is usually dissolved within 30 min, thus limiting the total amount of drug that can be delivered. The dissolution or disintegration is usually controlled by the patient, i.e. how hard they suck the unit. Increased sucking and saliva production causes swallowing and loss of drug down the esophagus and the gastrointestinal tract. Thus, solid dosage forms generally have a much higher inter- and intra-individual variation in absorption and bioavailability. In addition, since these formulations are open systems, the delivery medium is not well controlled. Although the formulation offers some control, it is difficult to control drug or other ingredient concentrations because

the media is constantly diluted by saliva. This makes it difficult to effectively use permeation enhancers in this type of system. Taste of the drug is another hurdle for this delivery system. Unless the drug is tasteless or the taste can be masked by sweetening and flavorings agents, it is difficult to achieve high patient acceptability of this type of product.

6.2.2. Gum

Chewing gum is one of the modern approaches to oral transmucosal drug delivery and is a useful means for systemic drug delivery. The advantages of chewing gum over other oral mucosal drug delivery systems are the possibility of controlled drug release over an extended time and the potential to improve the variability in drug release and retention times. One of the advantages of chewing gum is convenience. Furthermore, an individual may be able to control the drug intake by simply changing the rate and vigour of chewing, or expelling the gum altogether. Since chewing gum is also an open system, it shares many of the same limitations of the other solid formulations.

6.2.3. Patches

Flexible adhesive patches have been developed in an effort to overcome some of the drawbacks of other dosage forms. Transmucosal delivery patches have unique characteristics, including relatively rapid onset of drug delivery, sustained drug release and rapid decline in the serum drug concentration when the patch is removed. Also, a buccal patch is confined to the buccal area over which it is attached and therefore the absorption profile may have less inter- and intra-individual variability. In general, oral mucosal patches can be classified into three categories: patches with a dissolvable matrix, patches with a non-dissolvable backing, and patches with a dissolvable backing. Patches with a dissolvable matrix are designed to release drug into the oral cavity. They work similarly to, and share many of the limitations of, the solid dos e form. The mucoadhesive layer, either in the drug matrix or attached to drug matrix as an additional layer, prolongs the duration of drug matrix in the oral cavity. Therefore, compared with other open dosage forms, these types of patches are longer acting and can potentially deliver more drug. They also use the entire oral cavity mucosa as compared with other closed systems that typically use smaller areas. These types of patches are also suitable for treating local diseases such as candidiasis or mucositis. Patches with non-dissolvable backing are usually designed for systemic delivery. Since they are closed systems and the formulations are protected from saliva, the drug concentrations are controlled and drug is continuously delivered for 10 to 15 h. The disadvantages of these systems are that they use only a small mucosal area and the backings have to be removed by the patient after drug administration. Patches with dissolvable backing share many characteristics of patches with non-dissolvable backing, but they have the advantage of the entire patch dissolving in the oral cavity. Patches with dissolvable backings are shorter acting than patches with non-dissolvable backing. Oral mucosal dosage forms are convenient, easy to use, and have the potential to offer a low-cost and painless alternative to more invasive routes of administration. Each delivery form offers very distinct delivery characteristics that can be used in a broad range of therapies. The majority of patches provide a longer period over which to deliver the formulated as either solvent-cast mucoadhesive polymer discs or drug to and through the buccal mucosa.

6.2.4. Solution, suspension, and gel-forming liquids

Viscous 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. Using sodium alginate suspension as a novel bioadhesive liquid, researchers showed that the esophageal surface can be coated to protect against reflux and can deliver therapeutic agents to the damaged mucosa [62,63]. The retention behavior of various bioadhesive formulations was evaluated on the esophageal surface under conditions mimicking the salivary flow. Both polycarbophil and xanthum gum demonstrated excellent bioadhesive potential, and carmellose sodium and theromosensitive poloxamer (Lutrol 407) demonstrated poor retention. A thermosensitive hydrogel of poloxamer covalently linked to polyacrylic acid and carbopol. This “esophageal bandage”, upon oral administration, demonstrated significant retention within the esophagus.

6.2.5. Multiparticulates, microparticles, and nanoparticles

Oral delivery systems based on multiparticulates, microparticles, and nanoparticles often exhibit improved performance in comparison with monolithic matrix tablets [64]. By diffusing into the mucous gel layer by virtue of their relatively small size, these small immobilized carriers show a prolonged gastrointestinal residence time [65]. Recent work has shown that, in addition to size and chemistry, shape is also a critical feature of transmucosal drug delivery particles and can dictate particle velocity, diffusion and adhesion to the mucus surface in a complex manner.

7. Current and future development of transmucosal drug delivery

Many dosage forms have been developed and include toothpastes, mouthwashes, lozenges, gels, chewing gums, lollipops, films, patches, tablets and some specialized devices [66]. Conventional dosage forms, however, exhibit some drawbacks, for example, low bioavailability, because of the washing effect of saliva and mechanical stresses. Formulations that prolong the drug release in the mouth offer great advantages in preventing and treating local diseases or in promoting transmucosal delivery of drugs for systemic therapies [67]. Despite these obstacles for transmucosal drug delivery mentioned above, the buccal mucosa remains an attractive site for the delivery of systemic drugs, in particular for those who are prone to a high level of degradation inside the gastrointestinal tract. Various buccal delivery applications have thus been marketed or proposed in treatment of systemic and chronic diseases — among them are trigeminal neuralgia, Meiniere's disease, diabetes, addiction and so on [68–74]. Similar to the treatment of diseases affecting the oral cavity, intraoral systemic drug delivery would benefit from sustained drug release, without the need for the patient to intervene. This would raise the patient's compliance particularly of chronically ill. Acharya et al. [3] patented a device and method for oral transmucosal delivery of drugs or any other constituents via the inner buccal cavity. The device is applied and adheres to the mucosa of the oral cavity without causing adverse effects. It consists of a bilayer tablet: a mucoadhesive layer and an overlying active substance containing layer. The mucoadhesive layer can contain polyvinylpyrrolidone (PVP) as the only adhesive or can be combined with other hydrophilic polymeric substances. It was claimed that this non-plasticized PVP mucoadhesive has sufficient adhesion not only for mucosal membranes but also to a variety of materials, such as polyacrylic denture material. The active layer also contains a hydrophilic polymer carrier. The layers in the device dissolve and release the active substance into the oral cavity and are particularly suitable for delivering substances active in the oral cavity such as breath fresheners and substances to combat dry mouth. It is also useful for the delivery of ionic drugs such as peptides. Krumme et al. patented a device and a method of multi-layer transmucosal therapeutic film, comprising at least two layers connected with each other, for transmucosal administration of active substances [75]. The therapeutic systems which are suitable, in particular, for transmucosal administration (entering through or across the mucous membrane) of active substances have a structure of at least two layers that are connected with each other. The mucoadhesive layer is capable of swelling in an aqueous medium, although it is insoluble or only poorly soluble in such media. One of the two sides of the inventive system is limited by a mucoadhesive layer which optionally contains active

substance or is free of active substance. The mucoadhesive layer of the system is connected with a backing layer that is monolayered or double-layered and which may serve as an active substance reservoir. The insolubility or reduced solubility of the adhesive layer increases the period of adhesion to the mucosa, thereby enabling an active substance release that lasts for a prolonged period. Since the inventive systems are film-shaped and may have a thickness of less than 1 mm, they do not cause a foreign body sensation and are not unpleasant for patients thus contributing to improved compliance.

7.1. Clinical application of oral transmucosal drug delivery

Oral transmucosal delivery of analgesics has received considerable attention. Oral transmucosal fentanyl is designed to deliver rapid analgesia for breakthrough pain, providing patients with a non-invasive, easy to use and non-intimidating option. For analgesics that are used to treat mild to moderate pain, rapid onset has relatively little benefit and oral mucosal delivery is a poor option. Oral mucosal deliveries of sedatives such as midazolam, triazolam and etomidate have shown favorable results with clinical advantages over other routes of administration. Oral mucosal delivery of the antinausea drugs scopolamine and prochlorperazine has received some attention, as has oral mucosal delivery of drugs for erectile dysfunction. Oral transmucosal formulations of testosterone and estrogen have been developed. In clinical studies, sublingual testosterone has been shown to result in increase in the lean muscle mass and muscle strength, improvement in positive mood parameters, and increases in genital responsiveness in women. Short-term administration of estrogen to menopausal women with cardiovascular disease has been shown to produce coronary and peripheral vasodilatation, reduction of vascular resistance and improvement in endothelial function. Studies of sublingual administration of estrogen are needed to clarify the most beneficial regimen. Although many drugs have been evaluated for oral transmucosal delivery, few are commercially available. The clinical need for oral transmucosal delivery of a drug must be high enough to offset the high costs associated with developing this type of product. Several cardiovascular drugs administered transmucosally have been studied extensively. Nitroglycerin is one of the most common drugs delivered through the oral mucosa. Transmucosal absorption of nitroglycerin from solutions through the oral cavity was demonstrated in the mid-nineteenth century. Research on other cardiovascular drugs, such as captopril, verapamil and propafenone, has proven promising. Oral transmucosal delivery of analgesics has received considerable attention. These drugs include potent analgesics such as oral transmucosal fentanyl citrate and buprenorphine. Oral transmucosal fentanyl is designed to deliver rapid analgesia for breakthrough pain, providing patients with a non-invasive, easy to use and non-intimidating option. For analgesics that are used to treat mild to moderate pain, rapid onset has relatively little benefit and oral mucosal delivery is a poor option. Oral mucosal delivery of sedatives such as midazolam, triazolam and etomidate has shown favorable results with clinical advantages over other routes of administration. Oral mucosal drug delivery offers several advantages over both injectable and enteral delivery. Drugs absorbed via the oral mucosa to avoid the fate of enterically administered drugs: low gastric pH and proteases, and first-pass hepatic degradation. One early study of the hypoglycaemic effects of sublingual insulin indicated that absorption of human insulin through the oral mucosa is possible [76]. Oral transmucosal fentanyl is one such example. The initial use of fentanyl was primarily in operating rooms as an anaesthetic agent and as a transdermal patch form to control chronic baseline pain. The use of fentanyl to treat breakthrough cancer pain is a new indication for which there are no other approved alternatives that offer the advantages of oral transmucosal delivery. The unique characteristics of oral transmucosal delivery combined with the pharmacokinetic and pharmacodynamic properties of fentanyl make OTFC a favorable option for pain management in cancer patients. Recently, an oral aerosol rectal, system (Oralin), was developed [69]. This system delivers accurate insulin doses into the mouth by use of a metered-dose aerosol. Mouth deposition is dramatically increased compared with that of conventional technology. This oral aerosol formulation is rapidly absorbed through the buccal mucosal lining and in the oropharynx regions, and it provides the plasma insulin levels necessary to control postprandial glucose rise in patients with diabetes mellitus [77]. The challenge now is to synthesize drug moieties that exhibit increased absorption across the oral mucosa and are more potent in their action [78].

7.1.1. Recent advances in transmucosal drug delivery systems

Vaccination against debilitating infectious diseases has proven remarkable in prevention of these diseases and has contributed significantly to an increase in life expectancy, especially in children, in many parts of the world. In order to have adequate mucosal protection, there are several factors that can influence the effectiveness of vaccines. The most critical factor in mucosal vaccine effectiveness is the route of administration and potential for the antigen to be processed by the antigen-presenting immune cells, such as macrophages and dendritic cells. Presently, most vaccines are administered via the parenteral route or via other invasive routes. Invasive mode of vaccine administration can trigger the systemic immune response, but may not essentially provide adequate mucosal immune protection. On the other hand, effective mucosal vaccines will not only elicit superior local immune protection, but has been shown to trigger systemic response analogous as that of parenterally-delivered vaccine. As such, it is critically important to examine the development of mucosal vaccination strategies that can effectively trigger systemic as well as mucosal immunity [79]. Mucosal vaccines have currently been investigated using a broad spectrum of nanocarrier systems such as multiple emulsions, liposomes, polymeric nanoparticles, dendrimers, ISCOMs etc. More importantly, mucosal delivery of nanocarrier antigens and vaccines can trigger immunization at different mucosal barriers which is body's imperative first line defense in addition to systemic immune response. From the future perspective, development of vaccines using combined strategic approach like nanocarriers delivered by mucosal route of delivery can play a major role in the treatment of infectious diseases.

8. Advantages and limitations of oral transmucosal drug delivery

Absorption of certain drugs across the oral mucosa provides patients with a rapid onset of action, approaching that seen with intravenous administration. Additionally, oral mucosal drug delivery offers an alternative when enteral administration is impractical (e.g. in patients who have 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 (e.g. intravenous, intramuscular). Finally, drugs administered via the oral mucosa do not require technical equipment (e.g. infusion pumps) and expertise and thus are more cost-effective than invasive therapies. Not all drugs, however, can be efficiently absorbed through the oral mucosa. For example, the systemic bioavailability of peptides and proteins are typically less than 5% of administered dose with transmucosal delivery due to the physicochemical barrier of the oral mucosa, which contains enzymes that break down peptides. Recent technological advances, however, have resulted in the development of absorption enhancers that may allow successful mucosal delivery of these and other molecules. Limitation of oral mucosal delivery is that absorption may be more variable than with other routes. 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. Therefore, oral mucosal delivery is suitable only for drugs with a high potency. Finally, oral mucosal delivery may be difficult in certain pathological conditions that affect the integrity of the mucosa, such as blisters or mucositis (Table 1).

Table 1
Recently marketed and under research oral mucosal drug delivery systems [18,80,81].

Mucosa	Drug	Proprietary name	Dosage forms
Sublingual	Nitroglycerin	Nitrostat	Tablet
	Isosorbide dinitrate	Linitral spray	Spray
	Nifedipine	Suladrin	Bioadhesive tablet
	Buprinorphine	Sorbitrate	Chewable tablet
		Isocard spray	Spray
		Adalat	Tablet
		Tengerin	Tablet
Buccal	Prochloperazine	Buccastem	Bioadhesive tablet
	Nicotine	Tementill	Solution
	Fentanyl	Nicorette	Chewing gum
	Metronidazole	BEMA™ System	Buccal adhesive disk
	Doxycycline	Elyzol®	Gel
	Peptides	Atridox®	Gel
			Hydrogels
			Hollow fibres
Gingival	Buprinorphine	Cydot	Patch
	Melatonin		
Soft palatal	Amikacin	–	Smart flexiplate
	Gentamycin	–	Bioplate

9. Conclusions

The oral cavity for long has been a site of medicinal application in order to treat diseases in the mouth itself. Here, considerable improvements have been made in long-sustained delivery. The oral transmucosal route is becoming more and more popular for systemic drug delivery because it does have significant advantages compared to the peroral route. The grand majority of devices utilize solely chemical/physical released control to adjust the release rate. Oral transmucosal technology offers an alternative means of administering drugs. It allows more rapid absorption into the bloodstream than is possible with oral administration to the gastrointestinal tract. Oral transmucosal administration is non-invasive, no technical and convenient for patients. In patient populations requiring rapid onset of action for therapeutic drugs, this route is more comfortable and convenient than intravenous drug administration, and costs may be significantly lower because no specialized care or equipments are necessary. In addition to the many potential advantages of oral transmucosal drug delivery, there are several limitations that must be considered. Numerous drugs have been investigated for oral transmucosal delivery, yet few have become commercially available. The primary reason for this bias has to do with the economic incentives driving the development of new drug formulations. For a product to be a viable candidate for oral transmucosal delivery, the drug must not only possess the necessary physicochemical properties, but there must also be a significant clinical advantage. Because the cost of the drug substance is only a fraction of the cost of a drug product, increase in bioavailability alone is not a strong enough incentive to develop a new dosage form. Clinical need, and in many cases new indications, is often the driving force for developing an alternative drug delivery form. It thus belongs to a new class of oral delivery systems that have the promise, in the future, of providing an ideal drug delivery system.

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