International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

Systemic Drug Delivery via Oral Mucosa - A Review

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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. This article aims at discussing the various drugs and the methods of delivery used to administer them through the oral mucosa.***

Keywords: Transmucosal, drug delivery, oral mucosa

1. Introduction

The oral cavity can be used for local as well as systemic therapy. Examples of local therapy would be the treatment of oral infections, dental caries, mouth ulcers, and stomatitis. The buccal route is of particular interest with regard to the systemic delivery of small molecules that are subjected to first-pass metabolism, or for the administration of proteins and peptides. The multilayered structure and mainly protective role of the mucosa within the oral cavity would imply that it would not be as good a site for drug absorption as other single cell layer mucosae, e.g. those found in the small and large intestines. Of the non-keratinised mucosae, the buccal mucosa, being comparatively thicker, is a poorer site for drug absorption than other, thinner mucous membranes, e.g. the sublingual mucosa [1]. It has been suggested that these physiological features explain the comparatively few reports to date (relative to other non-parenteral routes) of peptide absorption across the buccal mucosa [2,3]. For absorption to occur the drug has to be in solution, therefore in the case of a dry dosage form the drug will have to dissolve in the saliva. It is therefore possible that much of the drug may be "washed out" from the oral cavity and swallowed. One other important factor to consider is the organoleptic property of the drug, and it may be necessary to chemically modify or microencapsulate the drug to reduce any unpleasant taste [4].

2. Permiability of Oral Mucosa

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 keratinisation 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 200μm 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, keratinisation 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.

3. Physiological Bariers for Transmucosal Drug Delivery

The environment of the oral cavity presents some significant challenges for systemic drug delivery. The drug needs to be released from the formulation to the delivery site (e.g. buccal or sublingual area) and pass through the mucosal layers to enter the systemic circulation. Certain physiological aspects of the oral cavity play significant roles in this process, including pH, fluid volume, enzyme activity

and the permeability of oral mucosa. For drug delivery systems designed for extended release in the oral cavity (e.g. mucodhesive systems), the structure and turnover of the mucosal surface is also a determinant of performance. Table 1 provides a comparison of the physiological characteristics of the buccal mucosa with the mucosa of the GI tract.

The principle physiological environment of the oral cavity, in terms of pH, fluid volume and composition, is shaped by the secretion of saliva. Saliva is secreted by three major salivary glands (parotid, submaxillary and sublingual) and minor salivary or buccal glands situated in or immediately below the mucosa. The parotid and submaxillary glands produce watery secretion, whereas the sublingual glands produce mainly viscous saliva with limited enzymatic activity. The main functions of saliva are to lubricate the oral cavity, facilitate swallowing and to prevent demineralisation of the teeth. It also allows carbohydrate digestion and regulates oral microbial flora by maintaining the oral pH and enzyme activity [10, 11]. The daily total salivary volume is between 0.5 and 2.0 L. However, the volume of saliva constantly available is around 1.1 ml, thus providing a relatively low fluid volume available for drug release from delivery systems compared to the GI tract. Compared to the GI fluid, saliva is relatively less viscous containing 1% organic and inorganic materials. In addition, saliva is a weak buffer with a pH around 5.5-7.0. Ultimately the pH and salivary compositions are dependent on the flow rate of saliva which in turn depends upon three factors: the time of day, the type of stimulus and the degree of stimulation [12]. For example, at high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the pH.

Saliva provides a water rich environment of the oral cavity which can be favourable for drug release from delivery systems especially those based on hydrophilic polymers. However, saliva flow decides the time span of the released drug at the delivery site. This flow can lead to premature swallowing of the drug before effective absorption occurs through the oral mucosa and is a well accepted concept as "saliva wash out". However, there is little research on to what extent this phenomenon affects the efficiency of oral transmucosal delivery from different drug delivery systems and thus further research needs to be conducted to better understand this effect.

The cells of the oral epithelia are surrounded by an intercellular ground substance called mucus, the principle components of which are complexes made up of proteins and carbohydrates; its thickness ranging from 40 to 300μm [13]. In the oral mucosa; mucus is secreted by the major and minor salivary glands as part of saliva. Although most of the 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 20MDa and contain large amounts of carbohydrate. Mucins are made up of basic units (≈400–500kDa) linked together into linear arrays. These big molecules are able to join together to form extended three-dimensional network [14] which acts as a lubricant allowing cells to move relative to one another, and may also contribute to cell-cell adhesion [11]. At physiological pH, the mucus network carries a negative charge due to the sialic acid and sulfate residues and forms a strongly cohesive gels structure that will bind to the epithelial cell surface as a gelatinous layer [15,16,17]. This gel layer is believed to play a role in mucoadhesion for drug delivery systems which work on the principle of adhesion to the mucosal membrane and thus extend the dosage form retention time at the delivery site.

Another factor of the buccal epithelium that can affect mucoadhesion of drug delivery systems is the turnover time. The turnover time for the buccal epithelium has been estimated 3-8 days compared to about 30 days for the skin [18] which may change permeability characteristics frequently.

4. Drug Absorption

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 (equations 1 and 2): where P is permeability coefficient, A is the amount of drug absorbed, D is the diffusion coefficient of the drug in the oral mucosa, Kp is the partition coefficient of the drug between delivery medium and the oral mucosa, h is the thickness of the oral mucosa, C is the free drug concentration in the delivery medium, S is the surface area of the delivery site on the oral mucosa and t is the duration of drug contacting the oral mucosa. 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. 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 solubilities 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. [19]

5. Drug Forms

To improve oral transmucosal delivery of drugs, several new dosage forms have been developed: solutions, tablets/lozenges (including lyophilised and bioadhesive), chewing gum, solution sprays, laminated systems and patches, hydrogels, adhesive films, hollow fibres and microspheres. 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 unfavourable 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.

6. Solid Forms

Several solid lozenge 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 oesophageal mucosa. As shown in equation 2, the amount of drug delivered is directly proportional to the surface area. 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 minutes, 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 oesophagus and into 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 flavouring agents, it is difficult to achieve high patient acceptability of this type of product.

7. Gum

Chewing gum is one of the more 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.

8. 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 dose form. The mucoadhesive layer, either in the drug matrix or attached to drug matrix as an additional layer, prolongs the duration of drug matrixing 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 up to 10 to 15 hours. 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. Nonetheless, 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.

9. Mucosal Adhesive Materials

Mucosal-adhesive materials have been investigated and identified in previous work [20,21,22]. These are generally hydrophilic macromolecules that contain numerous hydrogen-bond-forming groups. The presence of carboxyl groups and a molecular size greater than 100kDa favour adhesion. In most cases these materials require moisture to become adhesive but may excessively hydrate to form a slippery mucilage, and lose their adhesive properties. Several strategies (i.e. the inclusion of a hydrophobic component or a cross-linking agent) have been used to

prevent excess hydration [23]. Some of the most extensively studied mucosal adhesives are the poly(acrylic acids), e.g. Carbopol 934 and polycarbophil. The high concentration of carboxyl groups in a dry tablet of poly(acrylic acid) would be predicted to generate a low surface pH on moistening, and pH values of between 2 and 3 have been detected in our laboratories. A low pH would be expected to damage a contacting mucosal surface, and this has been reported in an in vivo study [24]. Salts and bases have been included in poly(acrylic acid)-containing formulations to raise the pH [25], but the presence of predominantly ionised carboxyl groups would result in a loss of the adhesive properties [26]. Thus the ultimate suitability of poly(acrylic acid) for use as a bioadhesive component in a pharmaceutical formulation may be questioned. Other anionic mucosal-adhesive materials include sodium carboxymethylcellulose, sodium alginate, and maleic anhydride copolymers. Non-ionic polymers on the whole tend to be weaker adhesives, and these include hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, poly (ethylene oxide), poly(vinyl alcohol), and starch. Chitosan [27] and diethylaminoethyl-dextran [28] are examples of cationic materials that have been proposed as mucosal-adhesive polymers.

10. Conclusion

Transmucosal dosages are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. Peak blood levels of most products administered are achieved within 10-15 minutes, which is generally much faster than when those same drugs are ingested orally. The absorption is efficient and percent of each dose absorbed is generally higher than that achieved by means of oral ingestion. Fentanyl Citrate, Lorazepam, Zolpidem tartrate, Isosorbide dinitate, Nicotine bitartrate, Buprenorphine hydrochloride, naloxone, Melatonin Hormone and most importantly Nitroglycerine are the few drugs that are delivered through oral mucosal route, especially sublingual. More such drugs for respiratory and cardiovascular disorders should be developed in future.

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