Chapter 8

STRUCTURE OF ORAL MUCOSA, ORO-MUCOSAL DRUG APPLICATION ROUTES, AND DRUG FORMS

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INTRODUCTION

The oro-mucosal route is an effective route of drug administration that allows the immediate onset of the systemic pharmacological action and is usually applied by the person himself for situations requiring immediate intervention or to obtain a sustained drug release profile. The drug is absorbed through the rich capillaries under the oral mucosa and rapidly enters systemic circulation. The main mechanism of oro-mucosal absorption is passive diffusion. In addition to a rapid onset of therapeutic effect, it is also a convenient route of administration in patients with dysphagia or where access to water is impossible. Dysphagia is a common problem in all age groups, especially in the elderly, children, the mentally disabled, those with stomach and intestinal issues, or those with difficulty swallowing solid forms of medication. Oro-mucosal drug administration also offers a significant advantage for this problem.

In this review, the structure and features of the oral mucosa, the principles of oro-mucosal drug absorption, the advantages and limitations of oro-mucosal drug absorption, the oro-mucosal pathways, the characteristics of the sublingual and buccal mucosa, the principles of drug transmission through the sublingual and buccal mucosa, oro-mucosal drug dosage forms and the future importance of oro-mucosal drug administration are mentioned.

ORAL MUCOSA AND DRUG ABSORPTION

Various approaches to the delivery of drugs throughout the body have now been described, including topical, IV and, oral. Many such strategies involve oral administration, including application to mucosal areas by spray, tablet, device, or similar dosage forms. The oral route still remains the most preferred

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route of drug administration due to the ease of drug administration and patient compliance. However, the oral route also has a hepatic first-pass effect that limits the uptake of some specific molecules, especially peptide and protein-structured molecules. Also, it has the risk of enzymatic degradation in the gastrointestinal tract. Therefore, mucous membranes are considered potential application areas for drug administration. Drug treatments through the mucosal membranes bring significant advantages over oral administration in creating a systemic effect (1). Some of these advantages are as follows: the absence of a first-pass effect through the liver, eliminating the risk of interaction with the gastrointestinal tract, increasing bioavailability, and providing a much more favorable enzymatic environment for the absorption of drugs (2, 3).

The oral cavity consists of parts such as the floor of the mouth, cheeks (buccal), tongue, lips, and soft and hard palate. The mucous membranes surround the cheeks, sublingual, palate, and labial parts. It is found in approximately 60% of the cheeks, tongue surface, and cheeks (4).

In the oro-mucosal cavity, the transport of drugs occurs in three parts: (i) the sublingual route covering the floor of the mouth, (ii) the buccal mucosal route in the mouth covering the palate and cheeks, and (iii) the local route by direct delivery of the drug into the intraoral cavity (1).

The sublingual area, cheeks, palate, and gums are the most efficient mucous membranes for administering oro-mucosal medications. Especially the sublingual and cheeks are the first choice because of the thickness of the epithelium and the high blood supply. Local and/or systemic ailments can be relieved by applying medication from these areas. In emergencies, the most commonly preferred method is the sublingual mucosa. However, this path is not always preferable. The main reasons for this are that the saliva and tongue activity is constantly variable, and the absorption of the dosage form is reduced, as a result of which it remains in contact with the mucosa. Compared to the sublingual area, the surface of the buccal mucosa is smoother and immobile. Patient compliance is advantageous due to its suitability for high and controlled release (5). The palatal mucosal epithelium is keratinized and relatively thick compared to the sublingual and buccal epithelium. Its permeability is also less in this respect. The epithelial surface is covered with mucus. Thanks to this mucus, the contact time of the drugs with the tissues is increased, and the therapeutic efficacy is increased (6).

Drug absorption for oro-mucosal administration is related to physicochemical properties of drugs as well as properties of mucosal membranes. For drugs to be delivered through mucosal membranes, they must have unique physicochemical properties, that is, a hydrophilic and lipophilic balance. In general, although the drug has a profile suitable for oro-mucosal administration, only a certain fraction of the drug penetrates the oral mucosa (7).

Structure of the Oral Mucosa

The mucosal membrane covering the mouth continues to the mucous lining at the edges of the lips and behind the pharynx. The permeability of the buccal mucosa for drugs has been reported to be 4 to 4000 times better than the skin's permeability (8). Considering the permeability of different regions of the oral mucosa, it was determined that the sublingual mucosa was more permeable than the buccal mucosa, and the buccal mucosa was more permeable than the palatal mucosa. The sublingual mucosa is highly vascularized and rapidly passes the active substances released from the drugs into the systemic circulation (1).

When the layers of the oral mucosa are examined, it has been reported that there is a stratified squamous epithelial layer on the outermost layer, a basement membrane underneath, connective tissue followed, and a submucosal layer on the inside. The buccal mucosal epithelium is 40-50 cell layers thick, while the sublingual epithelium is much thinner (6).

Permeability of the Oral Mucosa

The oral mucosa has an epithelial permeability between the skin and the intestinal mucosa. Due to the different functions of each region in the oral cavity, there are significant differences in mucosal permeability (9, 10).

The ease with which a drug can pass through the epithelium relates to its permeability coefficient. The partition coefficient of a drug is related to various physicochemical parameters such as the thickness of the membranes, particle size, molecular weight, and lipophilicity of the active substance. The permeability of the drug is most excellent in the sublingual region. The most negligible permeability is seen in the gingival area. Differences in oro-mucosal permeability result from a layer called membrane-coating granules (MCG). This layer is located in the outermost part of the superficial layer and differs between the mucous membranes (10).

Structures that make up MCG include glucosylceramides, sphingomyelins, ceramides, and other non-polar lipids. The main components of the non-keratinized mucosal epithelial structure are cholesterol, glycosphingolipids, and cholesterol-ester lipids. Although the basement membrane and MCGs show some resistance to permeability in mucosal absorption, the main limiting factor for mucosal permeability is the outer epithelial layer (9).

Principles of Absorption in Oro-mucosal Drug Administration

The primary function of the oro-mucosal epithelium is to protect the oral environment from potentially harmful substances and fluid loss. How vascularized it is is essential for drug absorption from the oral mucosa. However, the blood flow rate should not be ignored for the absorption of drugs. However, the blood flow rate is not a rate-limiting factor in the mucosal absorption of drugs (6).

Oral mucosal membranes are surrounded by hydrophilic and lipophilic barriers that must be overcome. The oro-mucosal permeability of drug molecules primarily depends on their passive diffusion through this lipophilic cell membrane and then their passage through the hydrophilic interior of oral epithelial cells. Secretions and enzymatic reactions in the oro-mucosal membranes cause rapid degradation of peptide and protein-structured molecules and limit their oro-mucosal transport. Although all of these limitations pose significant challenges to the delivery of drugs via the oro-mucosal route, different strategies are being developed to design appropriate drug dosage formulations (6).

Absorption of drugs through the oro-mucosal route occurs by passive diffusion. The surface area of the mucosal region, drug administration time, drug concentration, and dosage form is vital in this regard. Released drug concentration is essential for developing oro-mucosal drug delivery dosage forms (11). The unique structure of the oral mucosa presents significant challenges for formulators. Drugs with lipophilic character generally have higher permeability coefficients than hydrophilic ones. However, the water solubility of lipophilic drugs is generally much lower than that of hydrophilic drugs. Absorbed drugs require lipophilicity as well as hydrophilicity. Otherwise, the amount of bioavailable medications will decrease. Therefore, for a cure to be used by the oro-mucosal route, it must be in a balance between its partition coefficient and its solubility in water. To overcome these limitations, penetration enhancers are sometimes added to formulations. Generally, it is reported to increase the permeability of hydrophilic drugs by forming pores on cell surfaces (6, 12).

Advantages and Limitations of Oro-mucosal Drug Absorption

Orally administered drugs are exposed to chemical and enzymatic interactions in the gastrointestinal tract. With gastrointestinal absorption, drug molecules pass to the liver. Depending on the nature of the drug, extensive first-pass metabolism may occur, and the number of drug molecules bioavailable may be significantly affected (13). It is also common for the gastrointestinal mucosa to exhibit low permeability for macromolecular drugs (10).

In parenteral administration, degradation of the drug in the gastrointestinal tract is prevented and hepatic first pass is eliminated. However, injectable treatments are also one of the least patient-compliant drug administration methods (14). It needs to be done in a professional healthcare team and environment, and the production and equipment costs are also quite high.

As a result, the nasal, rectal, vaginal, ocular, and oral mucosa are prominent as potential sites for drug administration. These oro-mucosal drug delivery routes offer distinct advantages over oral and parenteral administrations. These include eliminating the first pass effect, high patient compliance, easy applicability, suitable for controlled release, and avoiding enzymatic reactions in the gastrointestinal tract (10, 15).

Oro-mucosal Drug Absorption Mechanisms

Oro-mucosal drug absorption is usually effective because, like the skin, the stratum corneum, the main barrier to absorption, is not found in this mucosa. Mucosal surfaces are generally rich in blood supply and provide rapid drug delivery to systemic circulation. The amount of drug absorbed depends on the concentration of the drug, the dosage form, the contact time of the drug with the mucosa, the vascularization of the mucosal tissues, the degree of ionization (pKa) of the drug and the pH of the absorption site, the molecular weight of the drug, the particle size of the drug, and the lipid solubility of the drug (16).

There are potentially two pathways for the absorption of drug molecules. The first is the transcellular pathway, and the other is the paracellular pathway. Paracellular drug transport involves the transport of molecules around or between cells (17). The tight junctions between cells are one of the biggest obstacles to the paracellular transport of macromolecules and polar compounds. Penetration enhancers added to drug formulations that cause the loosening of these tight junctions allow the passage of drugs through the transcellular

pathway by changing the cell membrane, lipid-protein interactions, and the lipid bilayer structure for a short time (18).

Oro-mucosal Passways

Excess vascular blood supply and absence of epidermis Stratum corneum in this mucosa cause a rapid increase in drug blood concentrations. Peak levels in the blood of most drugs are reached within 10 to 15 minutes, which is significantly faster than levels achieved by oral administration of the same drugs (19).

For oro-mucosal drug absorption, the drug must remain on the mucosal surface for a certain period (20). The ionization of drug molecules affects absorption. This route is preferred for drugs with a high pKa, as the pH of saliva is usually between 6.5 and 6.9 (21). Drug absorption from the sublingual mucosa is usually greater than from the buccal or oral mucosa (6, 12).

It has been reported that fentanyl-administered oro-mucosal increases the drug concentration in the blood rapidly. Still, when taken orally, the bioavailability of most of the drug after contact with stomach acid is very low. Another advantage of the oro-mucosal application of fentanyl is its ability to provide long-term analgesia. This is quite successful compared to analgesia induced by an IV dose of fentanyl (22).

The mucosa on the surface of the soft palate is rich in blood vessels. The soft palate continues along its border and is replaced by the nasal mucosa (23). This application also offers some advantages. It is a route of administration where direct drug absorption occurs and is suitable for low-dose drug administration, allowing increased drug bioavailability and reduced toxicity (24).

Buccal and Sublingual Drug Administration

Since saliva in the buccal and sublingual regions contains less mucin and enzymes (such as salivary amylase), it is an advantage in drug administration (25). Absorption of drugs from the sublingual region is relatively faster than the buccal mucosa due to the thinner epithelial cell line. In addition, the amount of drug absorbed from the blood vessels passes directly into the systemic circulation and eliminates the first-pass effect from the liver. This practice is beneficial for drugs sensitive to gastrointestinal disruption or subject to high hepatic first-pass effects. In addition, it is possible for drugs to remain more stable because the intraoral pH is relatively neutral compared to other parts of the gastrointestinal tract (26, 27). It is precious that the patients can easily

administer the doses themselves and that the drug can be removed with saliva immediately when the drug's effect needs to be stopped. It is also an ideal route of administration for patients with swallowing difficulties (25).

Sublingual and buccal formulations approved for clinical use today generally include solid dosage forms (tablets, strips, lozenges, wafers, etc.), liquid dosage forms (spray, drops, etc.), and semi-solid dosage forms (gel, paste, etc.) (28). Sublingual and buccal solid dosage forms are prepared to dissolve rapidly in a small amount of saliva to ensure rapid absorption from the mucosa without the need for water. Liquid dosage forms are formulated as a solution or suspension in a carrier system. Depending on the dose, it is administered orally as drops or as a spray with a metered valve (25).

Layered strips capable of controlled drug release have been developed for oro-mucosal administration, especially for buccal and sublingual administration. These layers are designed to release the drug over time (29, 30). This unique situation can sometimes lead to undesirable consequences. For example, formulations in prolonged contact with the mucosa may cause irritation and/or discomfort to patients in case of simultaneous eating and/or drinking. It is also possible that the dosage form may be detached from the mucosa and/or swallowed. This may cause it to attach to other parts of the gastrointestinal tract (25).

The following criteria are used for drug molecule selection for sublingual administration (26):

- Having a therapeutic requirement for rapid onset of action,
- Exposure to first-pass effects through the liver or low bioavailability in the gastrointestinal tract,
- Being highly effective (potent) at low doses,
- Having high permeability through mucous membranes,
- It should have a low molecular weight (<500 Da).

The main factors affecting sublingual absorption are as follows (31, 32):

- The thickness of the oral mucosal epithelium,
- The lipophilicity of the drug,
- pH of saliva,
- Oil/water distribution coefficient of the drug,
- The solubility of the drug in saliva,
- Binding of the drug to the oral mucosa.

Oro-mucosal Drug Delivery Systems

The factors in the drug selection and the mucosal site for oro-mucosal administration have been mentioned above. It is essential to consider these factors that influence drug release from a formulation. The release of a drug from a developed drug delivery system is controlled by the polymeric structures and excipients that make up the system. It is also essential that the decomposition products are non-toxic, non-irritating, and free of impurities in the prepared formulations (33).

The first prerequisite for a successful and effective oro-mucosal drug delivery system is its rapid adhesion to the mucosal surface and its ability to maintain it throughout use. The second prerequisite is that intraoral pH does not affect this adhesion performance (34). Some other desired properties of drug delivery systems are high drug encapsulation, drug release, and ease of administration (6).

Release of the drug from a polymeric carrier system occurs by diffusion or polymer degradation, or a combination of both. Polymer degradation may be enzymatic or hydrolysis. Here is the erosion of the polymer (35, 36). Advances in oro-mucosal drug release systems have focused on achieving the drug's therapeutic effect and overcoming environmental conditions in the oral cavity.

Solid Dosage Forms

Various solid dosage formulations have been developed and are commercially available, including sublingual tablets, lozenges, and buccal tablets. Although these formulations differ in shape and size, they share many standard features. Solid dosage forms are formulated to dissolve or disperse in the oral cavity. Depending on their size and formulation, they release drugs into the oral cavity in a short time (6). The patient usually controls the dissolution or disintegration of the drug from the dosage form. This period is variable, along with sucking and the production of salivary secretion. Ingestion of the drug also causes loss of effect. Therefore, absorption and bioavailability in solid dosage forms have a high inter-individual variability. The taste of the drug is another obstacle for these delivery systems. It is a fact that patient acceptance will not be possible unless the drug formulation can be masked with sufficient sweetening agents (6, 11).

Chewing Gum

Chewing gums are one of the modern approaches to oro-mucosal drug delivery and are useful for systemic drug administration. Gums have the potential to achieve controlled drug release over a long period. Other advantages

are that it is easy to use, the drug can be removed at any time, and controlled release can be changed by increasing or slowing the chewing power (9, 11).

Patches

Oro-mucosal patches offer unique properties, such as accelerating drug delivery, providing sustained or controlled release, and lowering plasma drug concentration when removed. In addition, patches are limited to the area to which they are attached, and the drug absorption profile exhibits less interindividual variability. The mucoadhesive layer of the patch prolongs the drug residence time in the adhered area. They also have an advantage over other oro-mucosal systems that use smaller areas because of their applicability to the oral cavity mucosa. Such patches can be used to treat fungal or mucosal infections and their applicability for systemic drug delivery (6, 11).

Fast Dissolving & Oral Disintegrating Tablets

Fast dissolving tablets (FDTs) or oral dissolving/disintegrating tablets (ODTs) can be prepared by direct compression, sublimation, or lyophilization techniques. Some of the production technologies of these tablets are patented (such as Zydis, Orasolve, Durasolv, Flashdose, Wowtab, and Flashtab). Increasing the bioavailability of drugs with low or insufficient water solubility through these tablets is possible. These tablets quickly dissolve or disintegrate in the patient's mouth in a short time. Thus, the active substance comes into contact with the oro-mucosal membranes, and absorption begins. They are also highly preferable in terms of patient compliance (9, 37).

Oral Dissolving Films and Strips

Oral fast-dissolving films (FDFs), also known as oral thin films (OTFs) or strips, contain all the advantages of tablets and instantly wet and dissolve with saliva, releasing the drug molecules hidden in the matrix. They are formulated using a film-forming polymer (such as PVA) or polymer group. Therefore, strips emerge as one of the oro-mucosal drug delivery strategies in clinical use and are frequently preferred in scientific studies (9, 37).

Liquid Dosage Forms

Viscous liquids, especially for coating the mucosa, are preferred as a preservative or drug delivery system for treating many local and systemic disorders. These bio-adhesive liquids are prepared with polymers and exhibit saliva-like behavior. These hydrogel-based systems are still being investigated today (6).

Novel Drug Delivery Systems

Designed as microparticles and nanoparticles, these systems show improved performance compared to conventional matrix tablets (38). With small particle sizes, they spread on the mucosa and exhibit long-term persistence. Recent studies have shown that size, structure, and shape are critical in oro-mucosal drug transport (6).

Nanoparticular dosage forms transport a drug or active compound by loading it into nanoparticles. For this reason, it is different from conventional drug forms. These differences can be listed as follows: Thanks to the nanoparticles, (i) drug permeability was increased throughout the epithelium; (ii) drug release kinetics could be altered; (iii) the passage of drugs with poor water solubility through the epithelium can be increased; and (iv) drugs that are easy to degrade while passing through the gastrointestinal tract or have a high first-pass effect through the liver are maintained (39, 40).

For sublingual or buccal nanoparticular drug delivery, nanoparticles' size, zeta potential, composition, and surface properties should be determined. The design and structure of nanoparticles are configurable, including therapeutic activity, mucoadhesion, mucosal permeability, and controlled release (41). It has been reported that a hydrophilic coating (such as PEG) on nanoparticles reduces interaction with mucus components and increases mucosal transmission (42, 43).

Most nanoparticle studies have used nanoparticles with a particle size of about 100 to 300 nm for drug delivery to the sublingual or buccal mucosa (25). In studies, it has been proven that nanoparticles, especially 200 nm in size, can penetrate deep into the mucosa (44). Few studies have yet examined the effect of nanoparticle size on permeability (45).

The surface charges of nanoparticles, namely zeta potentials, significantly affect the transport of drugs in nanoparticle form to the oral mucosa. Studies have reported that cationic and anionic-charged nanoparticles pass through the epithelium (46). Differences were also detected in the interaction of the oral mucosa with oppositely charged nanoparticles. It has been reported that positively charged nanoparticles interact more with mucus and exhibit lower mucosal permeability than negatively charged nanoparticles (47, 48). This indicates the existence of an electrostatic interaction between positively charged nanoparticles and negatively charged mucin. Anionic nanoparticles were found to interact less electrostatically with mucus (49).

The residence time in the sublingual or buccal region should be increased to optimize drug permeability and systemic absorption of nanoparticulate drug delivery systems. Most studies have reported sustained drug release from nanoparticles in the mucosa, where the drug diffuses and adheres to the formulation base (25).

Although most oro-mucosal studies on nanoparticulate drug delivery systems are in vitro and ex vivo studies, there are few in vivo studies. In vivo studies provide better information for drug absorption. However, there are significant anatomical differences in the sublingual and buccal mucosa among experimental animals. Although porcine mucosal epithelium was used in ex vivo studies because of its similarity to human mucosa, rodents with keratinized mucosa were used in in vivo studies. This does not make it possible to elucidate the absorption mechanisms of nanoparticles in real-time. It has also been seen in recent studies that more comprehensive in vitro, ex vivo, and preclinical studies are needed to ensure the reproducibility of nanoparticle drug delivery systems to sublingual and buccal mucosa in terms of efficacy and safety (25).

The Future of Oro-mucosal Drug Delivery

Many dosage forms have been developed for oro-mucosal administration in the recent past. These dosage forms include toothpaste, mouthwashes, lozenges, gels, chewing gums, lollipops, films, patches, tablets, and special devices (6). These formulations, which prolong the drug release in the oral mucosa, offer great convenience in the prevention and treatment of local and systemic diseases (50). Especially for drugs prone to high degradation in the gastrointestinal tract, the buccal mucosa will continue to be the preferred route of administration for drug release, for which systemic effects are desired. Various buccal applications have been commercialized or proposed, especially in treating many systemic and chronic diseases (51-53). These dosage forms and routes of administration will continue to attract attention in the future in treating local diseases affecting the oral cavity.

CONCLUSION

The oro-mucosal drug delivery route has several advantages for systemic drug delivery. It offers an alternative application for drugs subject to high first-pass effects in the liver or degradation in the gastrointestinal tract. In this way, drugs' side and toxic effects are reduced, and their bioavailability is increased.

The buccal and sublingual route of administration also has very high patient compliance for patients with swallowing difficulties. Today, the expectation of rapid therapeutic effect and the development of drug release technologies have increased the preference for the oro-mucosal route, especially the sublingual or buccal route, in treating many diseases.

The oro-mucosal route is becoming increasingly popular for systemic drug administration as it has significant advantages over the oral route. Even in situations requiring rapid onset of therapeutic effect, it is more convenient and comfortable than intravenous drug administration; Costs are also significantly lower as it does not require specialized personnel or equipment. For these reasons, it is evident that oro-mucosal drug delivery systems will occupy more space in our lives as an ideal drug delivery route in the future.

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