Oral local drug delivery: An overview

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ABSTRACT

Oral cavity is a site where both local and systemic delivery of drugs can take place. Oral route has been the most convenient and commonly employed route of drug delivery. Oral mucosal drug delivery is an alternative and promising method of systemic drug delivery which offers several advantages. Local delivery allows topical treatment of various oral mucosal diseases. However, treatment can be made effective if the drugs can be targeted directly to the site of lesion, thereby reducing the systemic side effects. This review mainly focuses on the oral mucosa, its structure and permeability features, various routes of drug delivery and important aspects of oral mucoadhesive drug delivery, drug dosage forms for various oral lesions.

Keywords: Oral mucosa, mucoadhesive, dosage forms.

INTRODUCTION

The oral mucosa is the "skin" inside the mouth, and it covers most of the oral cavity apart from the teeth. It has several functions. Its main purpose is to act as a barrier. It protects the deeper tissues such as fat, muscle, nerve and blood supplies from mechanical insults, such as trauma during chewing, and also prevents the entry of bacteria and some toxic substances into the body.

Oral mucosal diseases are the most common diseases affecting humans. These diseases can be effectively treated by various topical therapeutic approaches. But there are various drawbacks that result in the short retention time of the drugs. Herewith we are listing few drawbacks that might be the reasons for low therapeutic efficacy, which should be overcome (Paderni et al., 2012):

2. Inadequate distribution of drugs within the areas of oral cavity.
3. Patient discomfort due to unpleasant taste sensations.
4. Barrier effect of oral mucosa.

Structure of oral mucosa

The oral mucosa has several properties which make it an attractive site for drug delivery. It has a total surface area of about 200 cm². It consists of 2 layers: a thick, stratified squamous avascular epithelium, and an underlying, vascular layer of mesodermal origin (Collins and Dawes, 1987). Its epithelium is approximately 40 to 50 cell layers thick (Shojaei, 1998). Oral squamous stratified epithelium can be divided into two, namely non-keratinized and keratinized epithelium. Non-keratinized mucosae include buccal and sublingual mucosae; whereas keratinized mucosae include the gingival and the palatal mucosae. There is regional variation in epithelial thickness (depending on the site) within the oral mucosa. The epithelial thicknesses of buccal, sublingual, gingival and palatal mucosae are 500, 100, 200 and 250 µm, respectively.

In addition there are three types of oral mucosa within the oral cavity. They are:

1. Masticatory mucosa which includes gingiva and the hard palate (25%).
2. Specialized mucosa which includes the dorsum of the tongue (15%), and
3. Lining mucosa which includes buccal mucosa and the floor of the mouth (60%) (Collins and Dawes, 1987).

Permeability of oral mucosa

The surface of the oral mucosa is permeable for certain
drugs which help in its absorption and initiation of its effects. This permeability feature of the oral mucosa is the most important factor that determines the appropriate drug formulations so that the drug gets absorbed and reaches the deeper layers of the oral mucosa. The movement of drug molecules mainly depends on the following features – local variations in mucosal thickness, epithelial keratinization and lipid composition. These features are collectively known as the barrier region of the oral mucosa. The permeability of oral mucosa is attributed to intercellular materials derived from membrane coating granules, which are found in the intermediate cell layers of both keratinized and non-keratinized epithelia (Shojaei, 1998). As there is a regional difference in the epithelial thickness of oral mucosa, it has been suggested that the permeability pattern decreases gradually from the sublingual mucosa to the buccal mucosa and palatal mucosa.

Routes of drug transport

Compounds or molecules with different chemical properties penetrate the barrier region of the oral mucosa via different routes. There are two main pathways that are involved in the passive diffusion of drug molecules across the membranous tissues. They are intracellular or transcellular pathway and intercellular or paracellular pathway.

Targeted drug delivery in the oral cavity is highly desirable for local treatment of a variety of oral diseases such as recurrent apthous stomatitis, potentially malignant lesions, oral mucositis, periodontitis and certain oral infections. The target sites for local drug delivery in the oral cavity include the buccal, sublingual and periodontal region (Figure 1). Delivery of drugs via the membranes of the oral cavity is classified into three categories (Nibha and Pancholi, 2012):

1. **Buccal delivery**: is drug administration through the mucosal membranes lining the cheeks and the area between the gums and upper and lower lips to the systemic circulation.
2. **Sublingual delivery**: is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth to the systemic circulation.
3. **Local delivery**: is drug delivery to periodontal, gingival, delivery for the local treatment of ulcers, bacterial and fungal infections and periodontal disease.

**SUBLINGUAL DRUG DELIVERY**

Sublingual administration of the drug involves the placement of the drug under the tongue and the drug reaches directly into the blood stream through ventral surface of the tongue and floor of the mouth. The drug molecules are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and then transported and drained into the systemic circulation. When compared to the oral ingestion of tablets, the sublingual route usually produces a faster onset of action. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route (Nibha and Pancholi, 2012). Sublingual absorption is mostly rapid in action, but also is short acting in duration.

**Advantages**

1. Ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric and psychiatric patients.
2. Convenience in administration of drug and accurate dosing as compared to liquid formulations.
3. Water is not required for swallowing the dosage form, which is a convenient feature for patients who are traveling and do not have immediate access to water.
4. Fast dissolution of medicament and absorption which will leads to rapid onset of action.
5. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased. (Narang and Sharma, 2011; Nibha and Pancholi, 2012)

**Disadvantages**

1. Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
2. This site is not well suited for sustained-delivery systems.
3. Sublingual medication cannot be used when a patient is uncooperative or unconscious.
4. The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the blood vessels. This will decrease the absorption of the medication. (Narang and Sharma, 2011; Nibha and Pancholi, 2012)

**BUCCAL DRUG DELIVERY**

Buccal administration of the drug involves the delivery of the drug via the buccal mucosa lining the cheeks, including systemic and/or local delivery. The buccal mucosa is less permeable when compared to the sublingual mucosa, because of which it constitutes a preferred route for the systemic treatment of chronic disorders especially when a sustained delivery of systemically acting drugs is required (Gandhi et al., 2011).
Advantages

1. Improved patient compliance
2. Sustained drug delivery.
3. Rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.
4. Increased ease of drug administration
5. Large contact surface of the oral cavity contributes to rapid and extensive drug absorption (Gandhi et al., 2011).

Disadvantages

1. For local action, the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequently increasing the dose.
2. Non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.
3. For both local and systemic action, patient acceptability in terms of taste, irritancy and ‘mouth feel’ is an issue (Gandhi et al., 2011).

MUCOADHESIVE DRUG DELIVERY

The dosage forms previously used were not able to release medication at a fixed rate to a specific site of action. That is, these dosage forms are constantly washed away resulting in less retention time and unpredictable distribution of the drug on the site of action. To overcome these drawbacks, a new dosage system namely the mucoadhesive drug delivery system has been introduced. These dosage system offer several advantages over the previous drug delivery systems. They include:

a) Intimate contact between the drug and the oral mucosa
b) Increased retention time
c) Fixed rate of drug release to the specific site of action (Paderni et al., 2012)

Mechanism of mucoadhesion

Mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. It is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. There are several steps suggested in the process of mucoadhesive bond formation. They are as follows:

1. The first step is the spreading, wetting, and dissolution of mucoadhesive polymer at the interface (Tangri and Satheesh Madhav, 2011).
2. The second step is the mechanical or physical entanglement between the polymer and the tissue surface mucus layer, resulting in an interpenetration layer.
3. The next step is the result of chemical interactions, such as covalent and ionic bonds, hydrogen bonding, and Van der Waals' interactions.

Advantages of mucoadhesive drug delivery

1. Increases the retention time of the dosage form at the site of absorption.
2. Due to an increased retention time, it enhances absorption and hence the therapeutic efficacy of the drug.
3. Excellent accessibility.
4. Improved patient compliance - ease of drug administration.
5. Faster onset of action is achieved due to mucosal surface (Latheeshjla et al., 2011). (Figure 2)

Mucoadhesive dosage forms can be broadly classified into two, according to the mechanism by which the drug molecule is released from the delivery device (Paderni et
Figure 2. Mechanism of transmucosal permeation.

al., 2012). They are as follows:

1. **Monolithic or matrix type:** In which the drug is uniformly dispersed or dissolved in the polymer matrix and drug release is affected by diffusion through the polymer network.

2. **Reservoir or membrane controlled type:** A drug reservoir is entrapped between an impermeable backing layer and a polymeric membrane that controls the rate of drug release.

The desirable features of oral adhesive system include:

(a) High drug loading capacity
(b) Nonirritant to the tissues
(c) Good mucoadhesiion
(d) Patient comfort
(e) Sustained drug delivery

There are several mucoadhesive systems available for the purpose of oral local drug delivery mainly for the local treatment of variety of oral lesions. These systems include:

i) Tablets
ii) Patches
iii) Films
iv) Gel or ointment
v) Sprays
vi) Oral rinses

**MUCOADHESIVE TABLETS**

Mucoadhesive tablets are small, flat and oval shaped with a diameter of 5 to 8 mm. These tablets adhere to the oromucosal surface until the release of drug is complete. These types of tablets can be applied to different areas within the oral cavity including the palatal mucosa and cheek mucosa (Hooda et al., 2012).

**Advantages**

1. Prevent leakage of drug into the oral cavity.
2. Treatment of localized oral lesions.

**Disadvantages**

1. Lack of physical flexibility of the material applied to the mucosa.
2. Patient discomfort
3. Poor compliance in cases of long term therapy.

**MUCOADHESIVE PATCHES**

Mucoadhesive patches are the most recently developed dosage form. These patches can be of two types, dissolvable form which are long acting and can produce sustained drug release especially for treating oral candidiasis and mucositis whereas non dissolvable form which can deliver a more concentrated dose of the drug. Non-dissolvable form offer protection from saliva that can retain the drug molecules for about 10 to 15 h.

**Advantages**

1. High flexibility, thus good retention time for the drug
2. Patient comfort and compliance
3. Accurate dosing of drug delivery (Patel et al., 2011).
Disadvantages

1. Can only deliver the drug to a small area of the mucosa
2. Significant amount of drug will be lost into the oral cavity
3. Non dissolvable patches have to be removed by the patient after use (Patel et al., 2011).

MUCAADHESIVE FILMS

Mucoadhesive films are laminates mainly consisting of a polymeric drug-loaded layer which is an impermeable backing layer. This backing layer is used to promote unidirectional drug release. Thin strips of these adhesive films are capable of loading up to 20 mg of drug that can be rapidly delivered to treat certain oral conditions.

Advantages

1. Long term treatment
2. Rapid drug delivery
3. Patient comfort

Disadvantages

1. Deliver drug molecules only to a smaller area

MUCAADHESIVE GEL OR OINTMENT

Mucoadhesive gel or ointments are the semisolid form of drug dosage mainly introduced for the easy dispersion of drug through the mucosa. These drug systems form an intimate contact with the oral mucosal membrane and facilitate the rapid release of drug molecules at the site of absorption (Paderni et al., 2012). Major application of mucoadhesive gels is in the treatment of oral conditions such as periodontitis, recurrent aphthous stomatitis, traumatic ulcers, oral mucositis, chronic immunologically mediated oral lesions and to some extent salivary hypofunction.

Advantages

1. Rapid onset of action
2. Ease of use

Disadvantages

1. Inaccurate drug dosing
2. Less retention time of the drug

MUCAADHESIVE SPRAYS AND ORAL RINSES

Mucoadhesive sprays and oral rinses are adhesive liquid forms that form a thin coat over the entire oral mucosa when applied. This type of dosage form increases the total surface area through which the drug molecules can be absorbed. These liquid drug dosage forms has been proposed for the treatment of some oral diseases, such as oral lichen planus and other immunologically mediated diseases, recurrent aphthous stomatitis, oral mucositis, hyposalivation and potentially malignant disorders, such as leukoplakia and erythroplakia (Gandhi et al., 2011).

Advantages

1. Good mucoadhesion and viscoelasticity
2. Increased patient compliance

Disadvantages

1. Drug dosage may not be accurate
2. Unintended administration through the gastrointestinal tract by swallowing.

MOST COMMON OROMUCOSAL LESIONS AND SUITABLE DRUG FORMULATIONS

1. Recurrent aphthous stomatitis:
   a) Amlexanox (mucoadhesive tablets, patches)
      i) Reduce recurrent aphthous ulcer pain and lesion size
      ii) Patch forms are more flexible increasing patient comfort (Liu et al., 2006)
   2. Hydroxyapatite (mucoadhesive gel)
      i) Reduces the size, number and symptoms of oral ulcers
      a) Doxycycline (mucoadhesive gel)
         i) fast reduction in pain
      3. Oral lichen planus
         a) Tacrolimus (oral rinse)
            i) symptomatic relief
         b) Cyclosporine (mucoadhesive gel)
         c) Clobetasol (mucoadhesive gel)
   4. Xerostomia
      a) Phystostigmine (mucoadhesive gel)
i) relief in the feeling of dryness

b. Interferon alpha (mucoadhesive tablets) (von Bultzingslowen et al., 2007)

5. Oral mucositis

a) Gelclair, MuGaurd (mucoadhesive covering agents)
   i) protection for the ulcerated oral mucosa

b) Tumor growth factor – TGF-β3 (mucoadhesive gel)
   i) Protection against candida infection
   ii) Acts as a protective barrier to reduce discomfort

6. Oral infections

a) Metronidazole (mucoadhesive tablets) (Das et al., 2011)
   i) Sustained release for treatment of periodontal disease

b) Tetracycline (mucoadhesive patch)
   i) Excellent activity against candida albicans
   ii) Good mucoadhesion and stability

CONCLUSION

Oral local drug delivery is a most efficient drug delivery approach than systemic drug delivery system. Oral mucosa accessibility and rich blood supply makes it a more attractive site for topical drug delivery. The salient features of oral mucosa which makes it a preferred site for drug application, into which more targeted delivery of drug molecules can be made for the treatment of various oromucosal diseases thereby reducing systemic side effects. Since only a small quantity of drug is delivered by means of oral local drug delivery, it should be considered a delivery route appropriate for drugs exhibiting high therapeutic potency.

REFERENCES


