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Review Article

A REVIEW: SUBLINGUAL ROUTE FOR SYSTEMIC DRUG DELIVERY

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ABSTRACT

Drug delivery via the oral mucous membrane is considered to be a promising alternative to the oral route. Sublingual route is a rapid onset of action and better patient compliance than orally ingested tablets. Sublingual literally meaning is "under the tongue", administrating substance via mouth in such a way that the substance is rapidly absorbed via blood vessels under tongue. The portion of drug absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes giving acceptable bioavailability. Different techniques are used to formulate the sublingual dosage forms. New sublingual technologies for patient needs enhanced life-cycle management to convenient dosing for geriatric, paediatric and psychiatric patients with dysphagia. This review highlights advantages, disadvantages and different sublingual formulation such as tablets and films, evaluation.

Keywords: Sublingual delivery, Oral cavity, Dysphagia, Improved bioavailability, Evaluation.

INTRODUCTION

Systemic drug delivery provide immediate onset of pharmacological effect through the sublingual route. Dysphagia (difficulty in swallowing) is a common problem of all age groups, children, elderly, uncooperative or on reduced liquid intake have difficulties in swallowing these dosage forms.[1,2] Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and brachiocephalic vein and then drained in to systemic circulation. Within the oral cavity, delivery of drugs via the membranes of the oral cavity is classified into three categories.

Sublingual Delivery

Systemic delivery of drugs through the mucosal membranes lining the floor of the mouth to the systemic circulation.

Buccal Delivery

Drug administration through the mucosal membranes lining the cheeks and the area between the gums and upper and lower lips to the systemic circulation.

Local Delivery

Drug delivery to periodontal, gingival, delivery for the local treatment of ulcers, bacterial and fungal infections and periodontal disease.

Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly into the blood stream through ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and brachiocephalic vein and then drained in to systemic circulation.[3] The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed

through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes.[4-6]

ADVANTAGES OF SUBLINGUAL DRUG DELIVERY SYSTEM

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric patients and psychiatric patients.
- A relatively rapid onset of action can be achieved compared to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
- Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

DISADVANTAGES OF SUBLINGUAL DRUG DELIVERY SYSTEM

- Although this site is not well suited to sustained delivery Systems.
- Sublingual medication can not be used when a patient is uncooperative or unconscious.
- Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.

SUITABILITY OF DRUG FOR PREPARATION OF SUBLINGUAL TABLET

No bitter taste. Dose lowers than 20 mg, e.g. nifedipine. Small to moderate molecular weight. Good stability in water and saliva. Partially no ionized at the oral cavities pH. Under going first pass effect e.g. ketotifen fumarate. Many drug properties could potentially affect the performance of sublingual tablets like solubility, crystal morphology, particle size, hygroscopicity, compressibility and bulk density of drug. Some drugs undergoes extensive first pass metabolism which results in poor bioavailability of its oral dosage forms, that kind of drugs are suitable for sublingual dosage form. Drugs that are unstable in parenteral preparation are suitable for sublingual dosage form. Many pharmaceuticals are designed for sublingual administration, including cardiovascular drugs, steroids, barbiturates, enzymes, antiemetics, vitamins, minerals and vaccines.

SUBLINGUAL GLANDS

Salivary glands which are present in the floor of the mouth under neath the tongue. They are also known as sublingual glands. They produce mucin in turn produces saliva. The interior area of the mouth remains lubricated due to production of the saliva by the glands, which is necessary for chewing and food swallowing. The fluid which is produced by the glands gets mix with the food, so the food gets easily chewed. Due to low secretion of the saliva it can create problem in swallowing the food and potential for food lodge in the throat increases. The absorption is transfer of the drug from its site of administration into systemic circulation, so it can be said that absorption is directly proportional layer thickness. The absorption of the drug following this way Sublingual > Buccal > Gingival >Palatal. Due to high permeability and rich blood supply, the sublingual route can produce rapid onset of action so the drug with short delivery period can be delivered and dose regimen is frequent. The drug gets diluted in the saliva and from there the drug is adsorbed across the oral cavity. For example: Glyceryl nitrate-a potent coronary vasodilator which is used for rapid symptomatic relief of angina. After administration, its gets pharmacologically active after 1-2 minutes. Oral spray was found to provide rapid relief of symptom with first class metabolism. The extent of first class metabolism when compared to the sublingual spray decreased to 48% with sublingual tablets and 28% with the oral dose. Nitrate which appears in

the plasma concentration can be maintained for 24 hours when administrated sublingually.

THE MECHANISM OF SUBLINGUAL ABSORPTION

The absorption potential of the buccal mucosa is influenced by the lipid solubility and therefore the permeability of the solution (osmosis), the ionization (pH), and the molecular weight of the substances. For example, absorption of some drugs via the buccal mucosa is shown to increase when carrier pH is lowering (more acidic) and decrease with a lowering of pH (more alkaline).[7,9] The cells of the oral epithelium and epidermis are also capable of absorbing by endocytosis (the uptake of particles by a cell as if by hollowly wrapping itself around it. These engulfed particles are usually too large to diffuse through its wall). It is unlikely that this mechanism is used across the entire stratified epithelium. It is also unlikely that active transport processes operate within the oral mucosa. However, it is believed that acidic stimulation and uptake into the circulatory system.

DRUGS FOR SUBLINGUAL ADMINISTRATION

Sublingual drug administration is applied in the field of cardiovascular drugs, steroids, some barbiturates and enzymes. It has been a developing field in the administration of many vitamins and minerals which are found to be readily and thoroughly absorbed by this method. Sublingually absorbed nutrition, which avoids exposure to the gastric system and liver, means direct nutritional benefits, particularly important for sufferers of gastro-intestinal difficulties such as ulcers, hyperactive gut, coeliac disease, those with compromised digestion, the elderly and invalids the nutritional benefit is independent of gastro-intestinal influences.[10,11] Examples of drugs administered by this route include antianginal like nitrites and nitrates, anti hypertensive like nifedipine, analgesics like morphine and bronchodilators like fenoterol. Certain steroids like estradiol and peptides like oxytocin can also be administered e.g. fentanyl citrate, apomorphine, prochlorperazine dimaleate (PRO), and hydrazine HCl (HYD).

FACTORS AFFECTING THE SUBLINGUAL ABSORPTION[12]

Solubility in Salivary Secretion

In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of drug is necessary for absorption.

Binding to Oral Mucosa

Systemic availability of drugs that bind to oral mucosa is poor.

pH and pKa of The Saliva

As the mean pH of the saliva is 6.0, this pH favors the absorption of drugs which remain unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.

Lipophilicity of Drug

For a drug to be absorbed completely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.

Thickness of Oral Epithelium

As the thickness of sublingual epithelium is 100-200 µm which is less as compared to buccal thickness. So the absorption of drugs is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva.

METHOD OF PREPARATION OF SUBLINGUAL FORMULATIONS

Sublingual Tablets

Various techniques can be used to formulate sublingual tablets. Direct compression is one of the techniques which require the incorporation of a super disintegrant into the formulation, or the use of highly water-soluble excipients to achieve fast tablet disintegration. Direct compression does not require the use of water or heat during the formulation procedure and is the ideal method for moisture and heat-labile medications. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final

weight of tablet can easily exceed that of other production methods. Directly compressible tablet's disintegration and solubilization depends on single or combined action of disintegrates, water soluble excipients and effervescent agent. Disintegration efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and /or high friability and low hardnes.[13,14]

Films

Solvent casting is a process which comprises of casting a dope from a casting die onto a casting support, drying the cast dope on the casting support form film, stripping off the film from the casting support, and further drying the film while conveying the film with carrying it at both side edges of the film by a pin tenter, wherein residual volatile component content of both side edges of the film being carried by the pin tenter is from 30 mass % to 320 mass % of solid matter at the beginning of being cared by the pin tenter.[17] Solvent Evaporation technique can also be used instead of solvent casting for the preparation of sublingual films. Sublingual sprays are also in trend which improves the time to reach maximum plasma concentration as compared to other types of sublingual dosage forms. E.g. in case of oxycodone, maximum plasma concentrations is reached within 20 minutes when compare with immediate release oral tablets (1.3 hours), intramuscular (1 hour), and intranasal oxycodone (0.42 hour) in healthy volunteers.[8]

EVALUATION[15-25]

General Appearance

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet Thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as accounting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Wetting Time

A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petri dish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

Uniformity of Weight

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The limit for weight variation.

Table 1: IP limit for weight variation

Avg Weight of Tablet	% Variation Allowed
80mg or less	10
60mg but < 250mg	7.5
250mg or more	5

Friability

It is measured of mechanical strength of tablets. Roche friabilator can be used to determine the friability by following procedure. A preweighed tablet was placed in the friabilator. Fribaiator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the

measure of friability and is expressed in percentage as %Friability = loss in weight / Initial weight x 100.

Tablet Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

In-Vitro Dispersion Time

In-vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

In-Vitro Disintegration Test

The test was carried out on 6 tablets using the apparatus specified in I.P. 1996 distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

CONCLUSION

Sublingual drug delivery has been used for formulation of many drugs with view point of rapid drug release and quick onset of action. Sublingual products were developed to overcome the difficulty in swallowing conventional tablet, among pediatric, geriatric and psychiatric patients with dysphagia. The potential for such dosage forms is promising because strong market acceptance and patient demand. Peak blood levels of most products administered sublingually are achieved within 10-15 minutes, which is generally much faster than when those same drugs are ingested orally. Sublingual absorption is efficient. The percent of each dose absorbed is generally higher than that achieved by means of oral ingestion. Various types of sublingual dosage forms are available in market like tablets, films and sprays.

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