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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. Sublingual technology is convenient for dosing in geriatric, pediatric and psychiatric patients with dysphagia. Sublingual drug delivery shows fast therapeutic action than orally ingested drugs with fewer side effects. This review highlights advantages, disadvantages, different sublingual Gland, sublingual formulation such as tablets, films drops, sprays etc, evaluation parameters.

KEYWORDS: Sublingual delivery, dysphagia, sublingual gland, improved bioavailability, evaluation.

INTRODUCTION

Sublingual Drug Delivery

Definition

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

The systemic drug delivery provide immediate onset of pharmacological effects through the sublingual route. Dysphasia (Difficulty in swallowing) is common problem of all age groups or on reduced liquid intake have difficulties in swallowing the solid dosage forms. Sublingual administration of the drug means placement of drug i.e. dosage form under the tongue & drug reaches directly into the systemic circulation.

Sublingual drug delivery is alternative approach to the enteral drug delivery. It avoids first pass metabolism in liver and gastric acid hydrolysis of drugs therefore shows in increase in oral bioavailability of drugs.

Principles

When a chemical comes in contact with mucous membrane beneath the tongue, it diffuse through it because of connective tissue beneath the epithelium contains a profusion of capillaries, the substance then diffuses into them and

enters the venous circulation. Drug solutes are rapidly absorbed into reticulated vein which is lies underneath the oral mucosa & transported through the facial veins, internal jugular vein & brachiocephalic vein & then enter in systemic circulation.

ADVANTAGES OF SUBLINGUAL DRUG DELIVERY

- It produces immediate systemic effect by enabling the drug absorbed quickly or directly through mucosal lining of the mouth beneath the tongue.
- Dose gets reduced.
- Onset of action is very fast.
- Improved bioavailability.
- Fewer side effects.
- Effective in disease like nausea, vomiting, migraine, schizophrenia.
- No need of water for administering tablet.
- Ease of drug administration gets increased.
- Sublingual area is much more permeable than buccal area.
- Bypass GI tract and hepatic portal system and avoid hepatic first pass metabolism due to this bioavailability of drug get increase.
- Rapid absorption due to high vascularization beneath the tongue.
- pH in the mouth is relatively neutral so drug will be more stable.
- Improved patient compliance

DISADVANTAGES OF SUBLINGUAL DRUG DELIVERY

- Unsuitable for uncooperative or unconscious patients.
- Unsuitable for bitter drugs.
- Poor Patient compliance.
- Eating, drinking, and smoking are not allowed.
- Administration of highly ionic drug is not allowed.
- Holding the dose in mouth is inconvenient, if any is swallowed that portion must be treated as an oral dose and subjected to first pass metabolism.

Characteristics of Sublingual Tablets

- Disintegration and dissolution play an important role in drug absorption when administrated sublingually, that is the reason to prepare a sublingual formulation because it disintegrate and dissolve rapidly in saliva without access of water.
- The physicochemical characteristics of tablets are size, hardness, disintegration time, porosity, friability.
- Smaller the tablet with low hardness and high porosity it means it rapidly disintegrate than larger size and harder the tablet.
- The amount and type of disintegrants also play an important role in rapid disintegration.
- The absorption of water-soluble excipients, such as saccharides, which helps in reaching rapid dissolution.

- Flavors, sweetener and taste masking agents which are important parameter for the formulation of bitter sublingual drugs with bitter taste.
- Sugar based excipient quickly dissolve in saliva, which create a sweet feeling in the mouth in sublingual formulation.

SUBLINGUAL GLAND

Salivary glands which are present in the floor of the mouth underneath 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. 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 occurs by transfer of the drug from its site of administration into systemic circulation, so it can be said that absorption is directly proportional layer thickness. 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.

SUBLINGUAL ABSORPTION

Mechanism of sublingual absorption

The absorption of sublingual mucosa is determined by lipid solubility, penetrable of the solution, ionization and molecular weight of the substance. The cells of oral epithelium and epidermis have able to absorb by endocyctosis. This mechanism is used in across the stratified epithelium. The active transport process is controlling the mucus membrane. The mouth is lined with a mucous membrane which is coated with squamous epithelium and produce mucous glands. The salivary glands are composed of lobules of cells in which saliva is released through the salivary ducts in the mouth. The three pairs of salivary glands are parotid, submandibular and sublingual which is present on the mouth. The sublingual drug is transferred across the sublingual mucosa is passive diffusion. Passive diffusion means the movement of a drug from the region of higher to the lower concentration across biological membrane and drug diffuses into the capillaries and then enters into the systemic circulation by the jugular vein.

Factors affecting on sublingual absorption

- **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.

DRUGS FOR SUBLINGUAL ADMINISTRATION

Sublingual drug administration is applied in the field of cardiovascular drugs, steroids, some barbiturates and enzymes. The drugs with dose less than 20 mg are suitable for sublingual drug delivery system. 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. 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

SUBLINGUAL FORMULATIONS

- Sublingual Tablets
- Sublingual Films
- Multipurpose tablets
- Sublingual drops
- Sublingual spray
- Lozenge
- Effervescent sublingual tablet

Sublingual Tablets

“Sublingual tablets are solid unit dosage form meant for placement under the tongue to produce immediate action by avoiding the first pass effect of drug by liver.”

The tablets are usually small and flat, compressed lightly to keep them soft. The tablet must dissolve quickly allowing the API to be absorbed quickly. It is designed to dissolve in small quantity of saliva. After the tablet is placed in the mouth below the tongue, the patient should avoid eating, drinking, smoking and possibly talking in order to keep the tablet in place. Swallowing of saliva should also be avoided since the saliva may contain dissolved drug. Bland excipients are used to avoid salivary stimulation. Nitroglycerine tablets and Ondansetron tablets (zopran) are the examples of sublingual tablets.

Sublingual Films

Mouth dissolving films or strip, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed

on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application.

It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. Sublingual strips are similar to tablets in that they easily melt in the mouth and dissolve rapidly. Suboxone is an example of medication that comes in a sublingual strip.

Multi-Purpose Tablets

Soluble tablets for either oral or sublingual administration, often also suitable for preparation of injections, Hydrostat (hydromorphone) and a number of brands of morphine tablets and cubes.

Sublingual Drops

Concentrated solutions to be dropped under the tongue, as with some nicocodeine cough preparatations.

Sublingual Spray

Spray for the tongue; certain human and veterinary drugs are dispensed as such.

Lozenge

Effects a metred and patient-controlled-rate combination of sublingual, buccal, and oral administration, as with the Actiq fentanyl lozenge-on-a-stick (lollipop).

Effervescent Sublingual Tablets

This method drives the drug through the mucous membranes much faster (this is the case in the stomach with carbonated or effervescent liquids as well) and is used in the Fentora fentanyl tablet.

EVALUATION PARAMETERS

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, color, presence or absence of an odor, 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.

Wetting Time

Using this test, the time required for moisture to penetrate the tablet completely is measured and possibly represents the time required to release drug in the presence of minute volumes of saliva.

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.

Table: Pharmaceutical limits for uniformity of weight (IP).

Average weight(mg)	Percentage deviation (%)
80mg or less	10
More than 80mg or less than 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. Friabilator 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.

Hardness was measured by various testers-

- Monsanto
- Pfizer
- Scheuniger
- Strong-Cob

5 tablets are randomly selected from each formulation is determined by hardness tester. Conventional tablet hardness: 2.5-5kg/cm

Dispersable or sublingual tablets hardness: 2- 2.5kg/cm

Extended release tablet hardness: 4-6kg/cm

In-Vitro Dispersion Time

In-vitro dispersion time can be measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8.

In-Vitro Disintegration Test

The test can be carry 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 measure in seconds.

Angle of repose

It is defined as a technique for determining the resistance to particle movement is an amount called the angle of repose of a powder and expressed by θ. It is determined by the fixed funnel method. It is the maximum angle that can be obtained between the surface of a powder heap and horizontal plane and measure the flow ability of powder.

In this the material was allowed to flow through a funnel to form a cone. Stop flowing the material when the pile reached a predetermined height. Then the equation is

$$Tan\theta=2h/Dt$$

$$D=2r$$

$$Tan\theta=h/r$$

H=height of pile

r=radius of pile

Table: Angle of repose.

Angle of repose	Flow properties
<25	Excellent
25-30	Good
30-40	Passable
>40	Poor

There is a relation between the angle of repose and the type of flow.

Carr's compressibility index

In this the powder has the ability to decrease the volume under pressure and it is determined by the density.

The Carr's compressibility Index was calculated from Bulk density and tapped density of the blend

%compressibility index=Tapped density-Bulk density/tapped x 100

Table: Carr's index.

Compressibility	Flow Properties
5-15	Excellent free flowing
12-16	Good free flowing
18-21	Fair
23-35	Poor
35-48	Very poor
>40	Extremely poor

Compressibility gives an idea about flow properties of the granules as per Carr's index

Hausner ratio

It is an important parameter which influences the mass of uniformity of the dose.

Hausner ratio=Tapped density/bulk density

Techniques used in preparation of sublingual tablets

Different techniques are used in preparation of sublingual tablets are as follows

- Direct compression
- Freeze drying technology
- Sublimation method
- Spray drying technology

Direct compression

This method is commonly used in the manufacture of sublingual tablet and show good mechanical power and has fast disintegration. The directly compressible sublingual formulation comprises soluble excipient, superdisintegrant and lubricant for achieving the fast tablet disintegration, it comprises microcrystalline cellulose, binder, sweeteners, flavoring, diluents and glidant.

This method no need of water is required in the formulation of sublingual tablets and it is an ideal method for heat-labile and moisture medication. Disintegration is affected by tablet size, hardness.

Large and hard tablet has more disintegration time than small tablet and less hardness. In present scenario sublingual tablet has aimed to enhance the patient compliance. Direct compression is the term in which tablets are directly compressed from powder-blend of active ingredient and soluble excipient which maintain the flow and uniformity in the die cavity.

This method is very popular because it reduces the number of steps involved and the material required. It is one of the best technique to produce a tablet for effective hardness. The choice of superdisintegrant in tablet for preparing the formulation and amount is important for achieving a fast disintegration and dissolution rate. It is simple and cost effective process and it is a cheaper and suitable technique.

Freeze Drying

In this method, it is used for drying, which is done at low temperature and water is removed and formed porous tablet and it is more breakable tablet and have good packaging.

Advantage

- Provide rapid dissolution.
- Increase absorption and bioavailability of drugs.
- Low disintegration time when the tablet is prepared by this method.

Disadvantage

- It is a slow process and forms a hygroscopic product.
- Expensive and time consuming method.
- Cost of production is high.
- Water soluble drugs with low dose.

Sublimation method

In this technique the active ingredient is easily evaporated substance, and other ingredients which are compressed by machine and form a tablet. Then sublimation of evaporated substance is done and creates pores in tablet and helps in reaching the rapid disintegration when tablet dissolves in saliva. Camphor, urea, ammonium bicarbonate, ammonium carbonate is used in evaporated substance.

Spray drying

It is a method in which there is an involvement of a blend containing drug, disintegrating agents, bulking agents. It shows a result which form a porous powder and it gets rapidly dissolve in water. Then a porous powder is compressed in a compression machine and forms a tablet.

4 Steps of spray drying are

- Feed preparation
- Atomization
- Drying particle shape formation
- Separation of dried products

Advantage

- Simple and rapid method
- It is effective in cost
- Reproducible
- Increase the dissolution release of drugs
- Control of particle size, porosity, shape.

Taste masking of sublingual tablets Taste

It is a very important parameter to improve the patient compliance. It is the brain's elucidation of chemicals that triggers receptors on the tongue, which are contained in the taste buds and give taste sensation on the tongue and dissolve in saliva. These taste buds contain sensitive nerve endings, which produce and transfer the electrical impulses via the 7th, 9th, 10th cranial nerves in the brain, which are constant to the perception of taste.

5 basic sensations are located on different receptors on the tongue area are

- Salty taste-located at the sides and tip of the tongue.
- Sweet taste-located at the tip of the tongue.
- Sour taste-located at the sides of the tongue.
- Bitter taste-located at the back of the tongue.
- Umami taste-self-determining sensations originate by monosodium glutamate involve mainly in seaweed and disodium inosinate in meat and fish.

Taste masking

It is defined as a clear reduction of a bitter taste by using taste masking agents. Taste masking technologies are very important for improving the organoleptic properties like taste, odor and patient compliance for geriatric and pediatric those have difficulty in swallowing a tablet.

2 aspects of taste masking technology

- Select a suitable taste masking agents like polymers, sweetener, flavors etc.
- Select suitable techniques.

Table: Agents for masking the basic taste.

Basic taste	Masking agents
Sweet	Vanilla, Grape
Sour	Lemon, Cherry, Orange
Metallic	Mint,Berries
Bitter	Liquorices, Coffee, Chocolate

These are 4 basic tastes- sweet, sour, metallic, and bitter and have various agents which mask the basic taste.

Sweeteners used in taste masking

- Natural Sweetener-Honey, Liquorices, Sucrose
- Artificial Sweetener-Saccharin, Aspartame
- Nutritive Sweeteners-Sucrose, Fructose, Glucose
- Non-Nutritive Sweeteners-Aspartame, Sucralose, Saccharin

FUTURE PROSPECTS

Sublingual tablets are one of the most suitable dosage forms for the oral delivery of drugs such as proteins and peptides that have limited bioavailability when administered by conventional tablet. Vaccines are generally not recommend for use by patients and facilitated by sophisticated auto injectors. The growths of enhanced oral protein delivery technologies by oral disintegrating tablets which may release these drugs in the oral cavity are very favorable for the delivery of high molecular Weight proteins and peptides.

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 few 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, sprays, Drops, Lozenge etc.

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