Available online on 30.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Sublingual Drug Delivery Systems- Faster Therapeutic Action Dosage Forms

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ABSTRACT

Sublingual means "under the tongue" refers to administrating substances through mouth such that the substance is absorbed rapidly via blood vessels under the tongue. It outweighs orally ingested tablets in rapid onset of action and better patient compliances. The amount of drug absorbed through sublingual blood vessels bypasses hepatic first pass metabolic process giving more bioavailability. These days people lead short period of action so sublingual is the most suitable form of administration. New sublingual technologies address many pharmaceutical and patient desires and convenient dosing for all age groups.

Keywords: Sublingual route and patient compliance, dysphagia, sublingual technologies.

Article Info: Received 14 July 2019; Review Completed 16 Aug 2019; Accepted 22 Aug 2019; Available online 30 Aug 2019

Cite this article as:

Santosh Kumar R, Sarath Chandra T, Sublingual Drug Delivery Systems- Faster Therapeutic Action Dosage Forms, Journal of Drug Delivery and Therapeutics. 2019; 9(4-A):838-831 http://dx.doi.org/10.22270/jddt.v9i4-A.3672

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Introduction:

The sublingual administration of the drug means placing a drug under the tongue and when the drug reaches directly into the blood flow through the surface of the tongue and floor of the mouth. Systemic drug delivery offers immediate onset of action. The drug solutes are rapidly absorbed through passive mechanism into the reticulated vein of sublingual which lies underneath the oral mucosa and transported brachiocephalic vein then finally into the systemic circulation [1].

The absorption of drugs through the sublingual route is 3-10 times faster than that of the oral route of administration. Sublingual administration of drug is applicable in the field of cardiovascular drugs, steroids, barbiturates and enzymes. It tends to a way of development of the drugs in the administration of minerals and vitamins which are readily absorbed [2].

Mechanism of sublingual administration:

The lining of mucosa consists of three distinct layers. They are namely:

- The outermost layer: epithelial membrane
- The innermost layer: basement membrane
- The lamina propria

The outermost layer is the epithelial membrane that consists of stratified squamous epithelial cells which has a protective barrier function. The basement membrane is the innermost layer of the epithelial membrane which restore (to a former level/condition) of the epithelium. The lamina propria which is a less dense layer of connective tissue that consists of collagen and elastic fibres. The mouth is lined with the mucous membrane which is covered by squamous epithelium containing mucous glands. The sublingual mucosa is quite similar to that of the buccal mucosa [3].

The absorption potential of oral mucosa have an effect on the lipid solubility and the permeability of the solution, ionization and the molecular eight of the substances. When the carrier pH is more acidic, the absorption of some drugs through oral mucosa varies with a higher pH (more alkaline) [4].

The sublingual absorption is the most rapid in action, but short acting in duration. For example, Nitroglycerine is an effective anti-anginal drug when taken orally which is extensively metabolized. It is absorbed rapidly through the sublingual mucosa because of its short biological half-life (3-5 min). Systemic circulation enhances the availability of the drug and rapid onset of action. Note: smoking causes vasoconstriction may affect drug absorption [5].

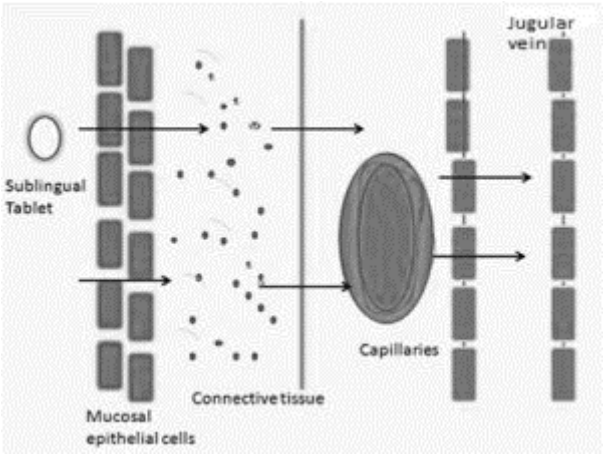

Fig 1. Mechanism of absorption through sublingual mucosa

Drugs for Sublingual administration:

Sublingually absorbed nutrition, which avoids subjection to the gastric system and liver, means direct nutritional benefits, specifically influential for the sufferers of the gastrointestinal struggling such as ulcers, hyperactive gut, coeliac disease, those with the settled digestion, the elderly and the ailing nutritional benefit is unconventional of gastro-intestinal influences.

Examples of drugs administered by this route include antianginal like nitrites and nitrates(example: isosorbide dinitrate, isosorbide mononitrate, nitroglycerine), antihypertensive like nifedipine, analgesics like morphine, codeine, fentanyl and bronchodilators like fenoterol. Certain steroids like estradiol and peptides like oxytocin can also be delivered eg. fentanyl citrate, Apomorphine, prochlorperazine dimaleate and hydrazine HCl [6].

Factors affecting the sublingual absorption [7]

Thickness of oral epithelium:

- The thickness of sublingual epithelium is bout 100-200µm which is less than as compared with buccal epithelium.
- The sublingual epithelium is thinner, so the absorption of drugs is faster and the immersion of drug in smaller volume of saliva.

Lipophilicity of drug:

- The complete absorption of a drug through the sublingual route, the drug should possess slightly higher lipid solubility than that is required for GI absorption which is necessary for passive permeation.

pH and pka of saliva:

- The mean pH of saliva is 6.0, which favours the durg absorption which remain unionized. Also, the drug absorption through the oral mucosa occurs only if the pka is more than 2 for an acid and less than 10 for a base.

Oil to water partition coefficient:

- Compounds of favourable oil to water partition coefficients are instantly absorbed through the oral mucosa. The range of oil-water partition coefficient is 40-2000 which is considered optimal for the drugs to be absorbed sublingually.

Solubility in salivary secretion:

- Besides high lipid solubility, the drug must be soluble in aqueous buccal fluids i.e, biphasic solubility of the drug is essential for absorption.

Binding to oral mucosa:

- Systemic availability of drugs which bind to oral mucosa is less/poor.

Ideal properties of drug in sublingual drug delivery system:

- Drug should not be bitter to taste.
- Dose must be lower than 20mg-Nifedipine.
- Small to moderate molecular weight.
- Good stability in water and saliva.
- Undergoing first pass metabolism eg: Ketotifen fumarate.
- Drug should not be ionized t the pH of oral cavities.
- Some drugs undergo extensive first pass metabolism, that results in poor bioavailability in its oral dosage forms.

Advantages [8]

- 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.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.
- The large contact surface area of the oral cavity contributes to rapid and extensive drug absorption.
- Liver is bypassed and also drug is protected from degradation to pH and digestive enzymes of the GIT.
- Low dosage forms gives high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects.
- Improved drug compliance.
- Rapid absorption due to high vascularization.

Disadvantages [9]

- Although this site is not well suited to the sustained drug delivery systems.
- Sublingual medication cannot be used when patient is uncooperative or unconscious.

Method of preparation of sublingual tablet formulations [10]

Sublingual tablets:

It is the ideal method for moisture and heat-labile medications. Directly compressible tablet's disintegration and solubilisation depends on single or combined action of disintegrates. Disintegration efficacy is strongly effected by tablet size, low hardness and high friability. Large and hard tablets have disintegration time more than that usually required.

Molded Sublingual Tablets:

Molded sublingual tablets are generally prepared from the soluble ingredients so that the tablet re rapidly soluble. In addition to the drug, they contain an excipient namely lactose, dextrose, mannitol or rapidly soluble materials of these ingredients. Tablets which consists of insoluble excipients may be formulated from finely divided kaolin, calcium carbonate, calcium phosphate. A fine screen or #120 mesh boiling cloth is used to pass the soluble tablets for the rapid solubility. Volatile solvents, such as acetone may also be used. Antioxidants like sodium bisulphate and other ingredients also may be added to improve the physical and chemical stability of the product [11-12].

Compressed sublingual tablets:

The compressed sublingual tablet formulation contain directly soluble excipients, a lubricant and a super disintegrant. Mostly all sublingual formulations incorporate some saccharide based material. Effervescent agents are also used to increase the disintegration and dissolution of sublingual tablets. Sublingual tablets of sumatriptan succinate were prepared by direct compression. All the tablet particles were weighed and mixed in geometrical order and compressed into tablets of 110mg by direct compression method [13]

In vitro evaluation:

Physical evaluation:

- All batches of sublingual formulations like tablets and films were evaluated for weight variation and drug content. But the hardness and friability were calculated for tablets.
- As the hardness of sublingual tablet is an essential factor because if the sublingual tablet is too hard, the solvent-borne drug attenuation may not occur into the interior portion of the tablet and therefore remain on a surface portion of the tablet, where the drug attenuation may not adhere to the sublingual tablets [17].
- If the sublingual tablet is too soft, then the sublingual tablet may be disintegrated by the solvent of the drug attenuation. If possible, the sovent-borne drug attenuation should be absorbed into the interior of the sublingual tablet.
- Sublingual films were also evaluated for thickness using tensile strength [19], folding endurance [20], surface pH [21], and swelling index [22].

Disintegration time:

A relatively simple method with rigorous conditions has been developed to evaluate the DT of sublingual tablets. Each individual tablet is dropped into 10-mL glass test tube (1.5-cm diameter) containing 2 ml distilled water, and the time required for complete tablet disintegration is observed by visually and recorded using a stop watch. The visual inspection can be inflated by gently rotating the test tube at a 45^0 angle, without any agitation, to disseminate any tablet particles that might mask any remaining undisintegrated portion of the tablets [23].

Tensile strength:

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the by the applied load at rupture divided by the cross-section area of the film as given below.

Tensile strength = Load at failure x 100/ film thickness x film width

Percent elongation:

A film sample stretches when stress is applied and it is referred to as strain. Strain is basically the formation of film divided by original dimension of the sample. Elongation of film increases as the content increases.

$$\text{Percent elongation} = [(L-L_o)/L_o] \times 100$$

Where L = increase in length of film

L_o = Initial length of film

Folding endurance:

Folding endurance is determined by drying process repeated folding of the film at the same place till the breaks. The number of times the film is folded without dry breaking is completed as the folding endurance value.

Wetting time:

A piece of tissue paper (12 x 10.75 cm) folded twice was placed in a small petri-dish (ID = 6.5 cm) containing 6ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. It is useful for quality control and provides a supportive evaluation of these sublingual tablets. Using this test, the time required for moisture to penetrate the tablet completely is measured and possibly represents the time required to release the drug in the presence of minute volume of saliva [24].

Friability:

It is the measure of mechanical strength of tablets. Roche friabilator can be used to determine the friability by following procedure. A pre-weighed tablet was placed in the friabilator and the equipment in a Roche friabilator. 20 tablets are to be weighed and placed in a Roche friabilator and the equipment has to be rotated at 25rpm, for 4 min. The tablets were taken out, deducted and reweighed. The percentage friability of the tablets can be calculated by:

% Friability = Initial weight – Final weight x 100 / Initial weight

In vivo evaluation

Pharmacokinetic data and bioavailability evaluation:

Rabbits have been described as one of the few laboratory animals that do not have keratinized mucosa, thus closely look like sublingual mucosal tissue. The maximal plasma concentration (Cmax) and the time to reach maximal plasma concentration (Tmax) can be directly obtained from the plasma data [25].

Permeation studies:

Ex vivo permeation studies through porcine oral mucosa can be carried out using the modified Franz diffusion cell of the internal diameter of 2.5 cm. The buccal mucosa has to be excised and trimmed evenly from the sides and then washed in isotonic phosphate buffer of pH 6.6 and used instantly. The membrane need to be balanced before organizing to remove the soluble components. The mucosa has to be mounted between the donor and receptor compartments. The receptor compartment has to be filled with 200 ml of isotonic phosphate buffer f pH 7.4 which is maintained at 37+-0.2^{0}C and hydrodynamics has to be maintained by stirring with a magnetic bead at 50 rpm. The donor compartment has to be filled with 1 ml of simulated saliva of pH 6.8. Samples are to be withdrawn at suitable intermission replacing the same amount with fresh medium. The

percentage of drug permeated can be determined by measuring the absorbance in a UV-Visible spectro-photometer [26-27].

Recent developments:

Nitro-glycerine-delivering sublingual aerosol formulation (nitro-glycerine in propellants) in a metered-dose spraying pump, Nitro-lingual spray, was developed. It delivers nitro-glycerine by spraying onto or under the tongue in the form of spray droplets, which eventually increase the absorption and therefore the bioavailability of nitro-glycerine. The rapid onset of action is always essential in case of hypertension.

Conclusion:

In this review, enlisted a number of commercially avail sublingual delivery systems manufactured using wide range of technologies. It has number of good potential to enhance drug delivery in treating a number of indications. In contrast to conventional dosage forms, sublingual drugs outweighs them in bioavailability and patient compliances therefore it is widely accepted technology for systemic delivery of drug.

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