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A REVIEW ON SUBLINGUAL TABLETS

Amit kumar*, Kamal Saroha, Ruchika Mohan, Chetna, Karambir

Affilfiation:

Department of Pharmaceutics, Kurukshetra University, Kurukshetra , Haryana, India

ABSTRACT

Sublingual route is usually preferred when rapid onset of action is required than orally ingested tablets. Sublingual tablets offer fast release of drug from the formulation and it reaches systemic circulation directly, which bypasses the metabolism of drug in liver. The demand of fast disintegrating sublingual tablets has been growing, during the last decade especially for geriatric and pediatric patients because of swallowing difficulties. Drug delivery system are becoming more complex as pharmaceutical scientist acquire better understanding of the physiochemical and biochemical parameters pertinent to their performance. Various techniques can be used to formulate sublingual tablets i.e. direct compression, freeze drying etc. The sublingual tablets require faster disintegration. So, we need to formulate disintegrates i.e. superdisintegrants which are effective at low concentration and have greater disintegrating efficiency. Tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution study. This review highlights the different sublingual dosage form, factors affecting sublingual absorption, advantages, various *in vitro* and *in vivo* evaluation parameters and commercially available sublingual dosages forms.

Key Words: Sublingual route, oral cavity, dysphagia, improved bioavailability

INTRODUCTION

The sublingual route usually produces a faster onset of action than the orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes. A fast dissolving tablet system can be defined as a dosage form for oral administration, which when placed in mouth, rapidly dispersed or dissolved and can be swallowed in form of liquid. Recently fast dissolving formulation is popular as NDDS because it is easy to administer and lead to better patient compliance. Pediatric and geriatric patient have difficulty in swallowing the conventional

dosage forms. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity so these dosage forms dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract[1-3].

In terms of permeability, the sublingual area of the oral cavity is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. The differences in permeability are generally based on the relative thickness, the blood supply, and degree of keratinization of these membranes. In addition to the differences in the permeability of the various mucous membranes, the extent of drug delivery is also affected by the physicochemical properties of the drug to be delivered[4].

Sublingual products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia) [5]

Mechanism of sublingual absorption

The cells of the oral epithelium and epidermis are also capable of absorbing by endocytosis (the uptake of particles by cells. 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 of the salivary glands, with the accompanying vasodilation, facilitates absorption and uptake into the circulatory system. The mouth is lined with a mucous membrane which is covered with squamous epithelium and contains mucous glands. The sublingual mucosal tissue is similar to that of buccal mucosa[6].

The salivary glands consist of lobules of cells which secrete saliva through the salivary ducts into the mouth. The three pairs of salivary glands are present i.e. the parotid, the submandibular and the sublingual which lies on the floor of the mouth. The more acidic the taste, the greater the stimulation of salivary output; serving to avoid potential harm to acid-sensitive tooth enamel by bathing the mouth in copious neutralizing fluid.

In order for a drug to be effectively absorbed sublingually, it needs to be able to travel across the buccal mucous membranes; by a process of diffusion known as osmosis; governing both intestinal and sublingual absorption. The distribution of water across cell walls depends on the osmotic difference

in the blood between the intracellular and extracellular fluid. Small particles that readily dissolve in water, rarely present a problem in permeation and diffusion, and so are able to move freely between the tissues of the body. Active transportation into cells leads to rapid metabolism of the substances. Molecules such as glucose (fructose) and amino acids are essential for cell metabolism and special mechanisms have evolved to facilitate their rapid diffusion and permeation across cell membranes[7].

The main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion

into the lipoidal membrane .The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is only surpassed by hypodermic injection.[8]

Factors affecting the sublingual absorption[9]

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.

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.

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.

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

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.

Oil-to-water partition coefficient: Compounds with favorable oil-to-water partition coefficients are readily absorbed through the oral mucosa. An oil-water partition coefficient range of 40-200 is considered optimal for the drugs to be absorbed sublingually.

Different formulations for sublingual drug delivery system-

Defination: Sublingual tablets are those dosages forms that are placed beneath the tongue, permitting direct absorption of the active ingredient by the oral mucosa.

_ Fast-disintegrating sublingual tablets

_ Bioadhesive sublingual tablet

_ Lipid matrix sublingual tablet

_ Sublingual immunotherapy

_ Sublingual vitamin tablet

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Formulation

Drug(Active ingredients)

Croscarmellose sodium(Synthetic superdisintegrant)

Camphor(Subliming agent)

Avicel PH102(Directly compressible excipient)

PVP K30 (Binder)

Mannitol (Diluent)

Saccharin sodium (Sweetening agent)

Magnesium stearate (Lubricant)

Talc (Glidant)

Technologies used for Sublingual tablets[19-23]

The various technologies for developing/formulating are:

1. Direct compression
2. Freeze drying/ lyophilisation
3. Molding
4. Sublimation
5. Cotton candy process
6. Spray drying
7. Mass extrusion
8. Melt granulation

1. **Direct compression**

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Also high doses of drug can be accommodated and final weight of tablet can easily exceed than other production methods. Directly compressed tablet's disintegration and solubilization are strongly affected by tablet size and hardness. This technique can now be applied to fast dissolving tablets because of the availability of improved tablet excipients, especially superdisintegrants like cross carmellose sodium, microcrystalline cellulose, crosspovidone, sodium starch glucolate and partially substituted hydroxypropyl cellulose, effervescent agents (e.g. citric acid, sodium bicarbonate) and sugarbased excipients (e.g dextrose, fructose, isomalt, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose, and xylitol).

Disintegrants

Disintegrants are substances or mixture of substances added to drug formulation that

facilitate the breakup or disintegration of tablet contents into smaller particle that dissolve more rapidly. In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants affects the rate of disintegration and hence dissolution. Microcrystalline cellulose, cross linked carboxymethyl cellulose sodium, cross linked polyvinyl pyrrolidine and partially substituted hydroxypropyl cellulose, though water insoluble, absorb water and swell due to capillary action and are considered as effective disintegrants in the preparation of fast dissolving tablets. The presence of other formulation ingredients such as water soluble excipients and effervescent agents further increase the process of disintegration.

2. **Freeze drying/ lyophilisation**

Lyophilization is used to prepare tablets that have porous open matrix network into which saliva rapidly disperses when placed in mouth. The drug is entrapped in a water soluble matrix which is freeze dried to produce a unit which rapidly disperses when placed in mouth. Apart from the matrix and active constituents, the final formulation may contain other excipients, which improve the process characteristics or enhance the quality of the final product. These include suspending agents, wetting agents, preservatives, antioxidants, colours and flavours. The preferred drug characteristics for freeze drying formulations are water insolublility, low dose, chemically stable, small particle size.

The freeze-drying technique has demonstrated improved absorption and increase in bioavailability but lyophilization is relatively expensive and time consuming manufacturing process. Other drawbacks include fragility, which make the use of conventional packing difficult and poor stability during storage and stressful condition.

3. Molding

In this technology, water soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air drying. Two problems commonly encountered in the process are poor mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidine can increase the mechanical strength of the tablet.

In heat-molding process agar solution is used as a binder and as well as a mold to manufacture a tablet.

4. Sublimation

The basic principle involved in preparing fast dissolving tablets by sublimation technique is addition of a volatile substance to the tabletting component, mixing the components to obtain a substantially homogenous mixture than volatizing salt are subjecting to vacuum at 80º C for 30 minutes to eliminate volatile components and thus create pores in the tablet. . The removal of volatizing agents creates pores in the tablet, which help in achieving rapid disintegration when the tablet comes in contact with saliva. Examples of agents are camphor, ammonium bicarbonate, naphthalene, urea, etc.

6.Spray drying

Spray drying produces highly porous and spherical particles as the processing solvent is evaporated during process. This process can be used to prepare rapidly disintegrating tablets by using support matrix such as hydrolysed and non hydrolysed gelatin and other components like mannitol as bulking agent, sodium starch glycolate, cross carmelose sodium as disintegrants, acidic material like citric acid and alkali like sodium bicarbonate to enhance disintegration and dissolution.

7.Mass-Extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble

polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking bitter taste.

8.Melt granulation

Melt granulation is a process in which pharmaceutical powders are efficiently agglomerated by the use of binder which can be a molten liquid, a solid or a solid that melts during the process. For accomplishing this process, high shear mixer are utilized, where the product temperature is raised above the melting point of binder by a heating jacket or by the heat of friction generated by impeller blades. The main advantage of this technique as compared to conventional granulation is that no water or organic solvent is needed. This process is less time consuming as there is no drying step and uses less energy than wet granulation.

Advantages

Sublingual administration has certain advantages over oral administration. Being more direct, it is often faster, and it ensures

that the substance will risk degradation only by salivary enzymes before entering the bloodstream, whereas orally administered drugs must survive passage through the hostile environment of the gastrointestinal tract, which risks degrading them, either by stomach acid or bile, or by the many enzymes therein, such as monoamine oxidase (MAO). Furthermore, after absorption from the gastrointestinal tract, such drugs must pass to the liver, where they may be extensively altered.

• Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions e.g. angina.

• Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.

• Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious patients; convenience of administration as compared to injections or oral medications.

• Low dosage gives high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects.

• The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.

• 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.

• Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of antianginal drugs.

• They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water i.e during travelling.

Disadvantages

• Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.

• Although this formulation is not well suited to sustained-delivery systems.

• Sublingual medication can not be used when a patient is uncooperative.

• 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.

Evaluation[10-18]

Pre Compression Parameters

Angle of Repose

Angle of repose is determine using funnel method. The blend is poured through funnel

fixed at height that can be raised vertically until a maximum cone height (h) is obtained. Radius of the heap (r) was measure and angle of repose was calculated using the formula

$\theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

Bulk Density

Apparent bulk density (ρb) is determine by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of powder (M) is determine. Calculate the bulk density using formula

ρb = M/ Vb

Tapped Density

The measuring cylinder containing known mass of blend is tap for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight (M) of the blend is measured. Calculate the tapped density (ρt) using the following formula

pt = M/ Vt

Carr's or Compressibility Index

The simplest way of measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility. The compressibility index of the granules is determine by Carr's compressibility index (I), which is calculated by using the following formula

$I = (V_0 – Vt) \times 100/ Vo$

Hausner's Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula

Hausner's ratio = ρt/ ρd

Where ρt is tapped density and ρd is bulk density. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression parameters

General Appearance

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

Size and Shape

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

Hardness

The crushing strength or hardness of the tablets is measure with help of a Monsanto hardness tester and expressed in kg/cm^2.

Uniformity of Weight

Weight variation test is done with 20 tablets. It is the individual variation of tablet weight from the average weight of 20 tablets.

Friability -

The friability of tablets using 10 tablets as a sample was measured using a Roche Friabilator. Tablets are rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets are then reweighed after removal of fines and brushing and the percentage of weight loss is calculated.

%Friability =

$$\frac{\text{(initial weight- final weight)}}{\text{(initial weight)}} \times 100$$

Wetting Time

The wetting time of the tablets is measure using a very simple process. Five circular tissue papers of 10 cm diameter are placed in a Petri dish of 10-cm diameter. Ten milliliters of solutions of water-soluble dye (eosin) is add to the Petri dish. A tablet is carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablet is noted as the wetting time.

Water absorption ratio

A piece of tissue paper folded twice is placed in a small Petri dish Containing 6 ml of water. A tablet is placed on the tissue paper and allowed to completely wet. The wetted tablet is then weighed. Water absorption ratio, R was determined using following equation.

$$R = 100 \times Wa - Wb/Wa$$

Where, Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption

***In vitro* Disintegration Time**

Disintegration time for sublingual tablets is determine using disintegration apparatus(USP) with suitable media. The volume of medium is 900 ml and temp was 37± 0.2 °C. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured. To comply the test all tablets should disintegrate within 3 minutes.

***In vivo* Disintegrating Time**

The time required for the tablets to disintegrate in the mouth cavity was determined by holding the tablets in mouth. The test is performed in five healthy human male volunteers in the age group of 23 to 28 years.

In vitro drug release study

In-vitro release rate study of sublinguals tablets is carried out using the Paddle Apparatus(USP) method. The dissolution test was carried out using 900 ml of suitable buffer at 37 + 0.5^{0}C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at fixed time interval and withdrawn volume was replaced with fresh dissolution media. The % release of drug is calculated.

Surface pH

The surface pH of the tablets is determine in order to investigate the possibility of any side effects due to change in pH in vivo, since an acidic or alkaline pH may cause irritation to the buccal mucosa. A combined glass electrode is used for the purpose. The tablets are allowed to swell by keeping them in contact with 1.0 ml of simulated saliva for 2 hours and pH is noted by bringing the electrode in contact with the surface of the formulations and allowing it to equilibrate for 1.0 min.

Accelerated stability study -

In order to determine the change in *in vitro* release profile on storage, stability studies are carried out at 40 ^{o}C in a Humidity chamber having 75% RH. Sample was withdrawn at various time intervals and the study was conducted for 60 days. The sample was evaluated for change in *in vitro* drug release pattern, hardness, Wetting time, percent drug content and disintegration time.

Marketed Sublingual Preparations:

Brand name	Active constituent	Category	Strenght available
Abstral	Fentanyl	Opioid Analgesic	50, 100, 200, 400mg
Subutax	Buprenorphine	Opioid Analgesic	2, 8mg
Avitan	Lorazepam	Antianxity	1, 2mg
Edular	Zolpidem Tartrate	Sedative	5, 10mg

Isordil	Isosorbide dinitate	Vasodilator	2.5, 5mg
Saphris	Asenapine	Antipsychotic agent	5, 10mg
Prohealth Melatonin	Melatotin	Hormone	2mg
Nitrostat	Nitroglycerine	Antiangial	0.3, 0.4, 0.6mg
Temgesic	Buprenorphine	Opioid Analgesic	200mg
Suboxone	Buprenorphine+ Naloxone	Narcotic+ Opioid Analgesic	2/0.5, 8/2mg

Conclusion

Recently many drugs have been formulated for sublingual drug delivery with an objective of rapid drug release and restricting the region of drug release to mouth. Compared to commonly used tablets, capsules and other oral dosage forms, sublingual absorption is generally much faster and more efficient. Sublingual dosages are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where portable liquids area not available. 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.

Future prospective

Future prospective in the development of Sublingual tablets is bright and the various technologies used are still relatively new. Tablets prepared by these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth without water. Various drugs which have limited bioavailability, low-molecular weight, high permeability or which degrade rapidly in the stomach can be successfully formulated in the form of mouth dissolving tablets as these tablets are absorbed through oral cavity and thus pregastric absorption of drugs avoid hepatic metabolism, which reduces the dose and increases the bioavailability. Thus sublingual tablets may be developed for most of the drugs like anti-diabetic anti-coagulants, anti-gout agents, anti-hypertensive agents, anti-neoplastic agents, immunosuppressants,

anti-thyroid agents, corticosteroids, lipid regulating agents, proteins, peptides and recombinant drugs, nutritional agents, neuro-muscular agents, in the near future.

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