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Review Article

**REVIEW ON: SUBLINGUAL ROUTE FOR SYSTEMIC DRUG
DELIVERY****Himanshi Rathaur*¹ and G.Gnanarajan²**

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Abstract:

Delivery of drug in the oral cavity through the oral mucosa is examined to be a promising alternative to the oral route. Sublingual means "under the tongue" which rapidly absorb the drug through the oral mucosa and enter into the systemic circulation. This route provides various advantages such as quick onset of action, patient compliance, hepatic first pass metabolism and increase bioavailability. Dysphagia is a common problem in pediatric, geriatric and psychiatric patients. In terms of permeability sublingual area of oral cavity is more permeable than buccal area which is in turn is more permeable than palatal area. Now a days most of the population need effective, faster and better relief within a short period of time. So, this route is the most appropriate route of administration and it rapidly dissolves in saliva. Many drugs like cardiovascular drugs, steroids, vitamin and barbiturates are applied in the sublingual drug delivery. This review highlights the difference between sublingual route and oral route in which sublingual route is more effective than oral route, advantages, disadvantages, factor affecting of sublingual route, various techniques are used to formulate the sublingual dosage form, taste masking, evaluation such as Hardness, Disintegration, Friability, In-vitro release study, Physicochemical properties of drugs, Consideration during sublingual formulation and market formulation.

Keyword: - Oral cavity, Sublingual, Dysphagia, Salivary glands, bioavailability, Hepatic metabolism

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INTRODUCTION:

Many non-identical routes are there in which drugs can be administered and create its pharmacological effects [1]. There are many ways to deliver drugs into the body like oral (through swallowing), sub mucosal (through sublingual mucosa), parenteral (through injection), transdermal (through the skin) [2]. The oral route of administration is considered as the accepted route because of its convenience. When put in the mouth, these dosage forms disintegrate rapidly to release the drug, which dissolves in the saliva. The drug gets absorbed from the pharynx, esophagus or from other sections of G.I.T as the saliva travels down and then enters into liver by the portal vein, it means hepatic metabolism occurs, then enters into systemic circulation and have low bioavailability [3]. Sublingual route of drug administration has various advantages over oral administration for systemic drug delivery like improving the patient compliance, increase bioavailability and avoids the first pass metabolism. Sublingual route is convenient for drug administration in the oral cavity through the oral mucosa and have a quick onset of action with better patient compliance than the oral route [4].

Dysphagia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children and psychotic patients. Most of the population finds difficulties in swallowing these solid dosage forms and it don't improves the patient compliance. These difficulties mainly in pediatric, geriatric and psychotic patients [5]. Drug delivery in the oral cavity through the mucus membrane called sublingual route. It is a most popular route of administration of drug due to the rich blood supply, high permeability and improves the patient compliance. The drug is diluted in saliva and the drug is absorbed through the oral mucosa across the oral cavity. Oral route is preferable route by the manufacturer due to highest patient acceptability. About 60% of all dosage forms are available as an oral solid dosage form. The Hepatic first pass metabolism, low bioavailability, and patient non-compliance and dysphagia patients who have difficulties in swallowing the solid dosage form turned the manufacturer to the parenterals and liquid orals. But the liquids like syrup, suspension have the problem of accurate dosing and parenterals are painful, time consuming for doctors and patient, so most patients non-compliance [6]. Many drugs are designed for sublingual administration, including cardiovascular drugs, steroids, barbiturates, enzymes, vitamins and minerals [7].

Aims of systemic oral mucosal drug delivery-

- Increase patient compliance
- Improve the drug bioavailability
- Reduce the side effect
- Avoids the hepatic first pass metabolism

- Aims of pharmaceutical scientist are to manufacturer effective, economical, efficient drug delivery through the oral mucosa membrane [8].

Salivary glands

Sublingual glands are present in the mouth under the tongue. They are also known as sublingual glands. They produce saliva and have many functions in the oral cavity. pH of the saliva is 6.8 to 7.2. The interior areas of the mouth are lubricated due to production of the saliva by the glands, which is compulsory for chewing and swallowing the food. The fluid is produced by the glands and mix with the food, so the food is easily chewed or swallows. The secretion of the saliva is less then, it can make a problem in swallowing the food. The drug is transferred from its site of administration into systemic circulation, so its absorption is directly proportional to layer thickness. The absorption of the drug follows in this way Sublingual > Buccal > Gingival > Palatal [6].

Drug delivery by the mucus membranes of the oral cavity can be subdivided as follows:

Sublingual Drug delivery- The administration of a drug is placed under the tongue through the sublingual mucosa which is directly entered into the blood stream. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transfer through the facial veins, internal jugular vein, and braciocephalic vein and then transfer into the systemic circulation.

Buccal Drug Delivery- The administration of drugs through buccal mucosa directly enters into the systemic circulation [9].

Onset of action

Determine the onset of action of different types of routes of administrations is as follows:

- Intravenous- 30-60 seconds
- Inhalation- 2-3 minutes
- **Sublingual- 3-5 minutes**
- Intramuscular- 10-20 minutes
- Subcutaneous- 15-30 minutes
- Rectal- 5-30 minutes
- Oral- 30-90 minutes
- Topical/transdermal- minutes to hours [10].

Advantages of sublingual drug delivery

- Avoids first pass effect, it directly enters into the systemic circulation and improve its bioavailability [7].
- Sublingual route is widely used in emergency conditions .Eg heart attack.
- Those patients who have difficulties to swallow tablet especially pediatric, geriatric

and psychiatric patients that sublingual route are Easy to administrate.

- There is no need of water for swallowing the solid dosage form, it is suitable for those patients who are travelling and do not have immediate access of water [11].
- Rapid onset of action can be reached compared to the oral route.
- Improved patient compliance due to ease of administration.
- It produces the advantages of liquid formulations in the form of solid dosage form.
- Low dosage gives high efficacy as hepatic first pass metabolism is avoided and reduces the side effects.
- The large contact surface of the oral cavity has a rapid transfer of the drug to the bloodstream, it's better and faster and extensive drug absorption.
- Fast dissolution or disintegration in the oral cavity through mucous membrane, without the need of water [4].

Disadvantages of sublingual drug delivery

- In Sublingual administration of drugs, no eating, drinking, and talking are permitted and this route is unsuitable for prolonged administration.
- Not suitable for sustained-delivery systems [4].
- Sublingual medication cannot be used when a patient is uncooperative or unconscious [6].

Anatomical structure of sublingual mucosa

The oral cavity comprises the lips, tongue, hard palate, soft palate and floor of the mouth. The lining of the oral cavity is also called as oral mucosa which includes buccal, sublingual, gingival mucosa. The buccal, sublingual and the mucosal tissues on the ventral surface of the tongue is account for about 60% of the oral mucosal surface area. Beneath the epithelium are the Basement membranes, lamina propria and sub mucosa [12].

The epithelium ends with the basement membrane known as basal lamina which connect the epithelium to the connective tissue. The connective tissue consists of lamina propria and submucosa region. The lower layer of lamina propria is connected to sub mucosa [13].

Oral mucosa is divided into 3 types which is present in the oral cavity-

- Lining mucosa-60%
- Masticatory mucosa-25%
- Specialized mucosa-15%

Oral mucosa consist of 2 layers-

- Stratified squamous epithelium
- Lamina propria [12].

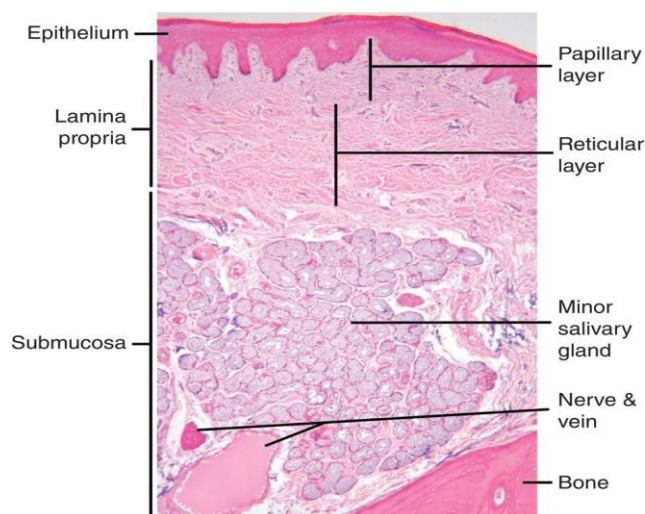


Fig1: Anatomy of Sublingual Mucosa

It is a mucus membrane inside the lining of the mouth and composed of an outermost layer of stratified squamous epithelium. Beneath the epithelium are basement membrane, lamina propria and sub mucosa as the innermost layer [14].

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 endocytosis. 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 [4].

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 [5].

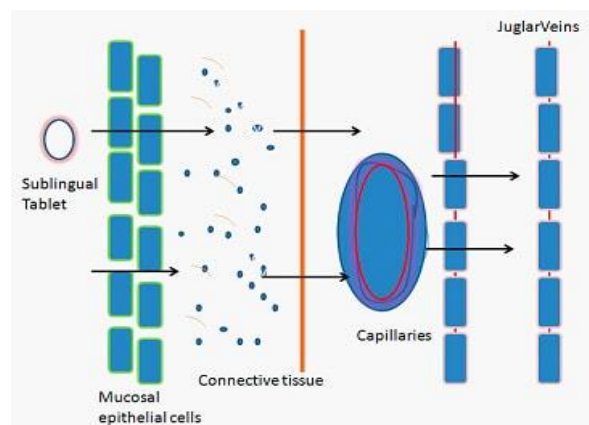


Fig. 2: Mechanism of Sublingual Absorption

It is absorbed by simple diffusion and permeable to the oral mucosa, sublingual tablet placed under the tongue through the oral mucosa and then the drug is absorbed into the reticulated vein and transported through the facial veins, brachiocephalic vein and internal jugular vein and directly enters into the systemic circulation [5].

Factor affecting the sublingual absorption

- **Lipophilicity of drug:** Those drugs which are absorbed through the oral mucosa, they must have slightly higher lipid solubility than that required for GI absorption.
- **Oil to water partition coefficient:** They absorbed in the oral cavity through the oral mucosa. oil-water partition coefficient range of 40-2000, it is important for those drugs which absorbed sublingually.
- **Solubility in salivary secretion:** In addition to high lipid solubility, the drug should be soluble in aqueous fluids [4].
- **pH and pKa of the saliva:** pH of the saliva is 6.0, and this pH favors the absorption of drugs which is unionized. The drugs are absorbed through the sublingual mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.
- **Oral mucosa binding:** Systemic availability of drugs that bind to oral mucosa is poor.
- **Thickness of oral epithelium:** 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 the thinner epithelium [5].

Sublingual formulation

Many sublingual Formulation are prepared which is classified as-

Sublingual Tablets

They are to be placed under the tongue and the drug absorbed directly in the oral cavity through the oral mucosa and directly enters into the blood stream which is better and faster. Thus absorption through the oral cavity avoids first pass metabolism and increase the bioavailability. After the tablet is placed under the tongue, the patient should avoid eating, drinking, and smoking. Swallowing of saliva should also be circumvented because the saliva contains dissolved drug [6].

Fast disintegrating sublingual tablets

These tablets disintegrate rapidly in the mouth. The small volume of saliva is usually sufficient to result in rapid tablet disintegration in the oral cavity. This drug incorporated in the oral cavity through mucous membrane and directly enters into the systemic circulation. The sublingual tablets have a faster onset of action than orally tablets and bypasses the hepatic first-pass metabolic [5].

Sublingual spray

They are the dosage forms in which the drug is dissolved in a medium and filled in container with a metered valve. Then a dose of the drug will be produced through the valve [5].

Bioadhesive sublingual tablets

It is defined as a formation of a bond between two biological surfaces. There are some problems related with sublingual tablet formulation that there is a possibility for a patient, that the swallow part of the dose before the active substance has been liberated and incorporated into systemic circulation. The addition of a bioadhesive component is a well-known method of increasing the risk of a more site-specific release [6].

Suitability of drugs for the preparation of sublingual tablets

- Drug should not bitter in taste.
- Dose lowers than 25mg.
- Small to moderate molecular weight.
- Good stability in saliva and water.
- Some drugs which receive extensive first pass metabolism and poor bioavailability.
- Many drug properties affect the formulation of sublingual tablets like solubility, crystal morphology, hygroscopicity, compressibility of drug [5].

Consideration before Developing Sublingual Tablets

Oral mucosal drug absorption is administered by- (a) the permeability of the oral mucous membrane and the anatomy of the elemental tissues (b) the physicochemical properties of the drugs (c) Characteristics of sublingual tablets. The focus of this review is on the latter two points, as an understanding of these elements enables the selection of drug candidates suitable for oral mucosal delivery and optimizes drug delivery [7]

Permeability of the oral mucosa and drug absorption

The salivary glands present in the oral cavity secrete saliva that has a pH of 5.5-7.0. Saliva comprises of proteins and carbohydrate complexes called mucus and enzymes such as amylase and carboxylesterase. Mucus is negatively charged at the physiological pH, forming a cohesive gelatinous film on all oral cavity surfaces. This cohesiveness on oral cavity surface permits the mucoadhesion of the drug to the epithelial tissue leading to drug absorption [8]. The epithelial membrane thickness in sublingual region is 100–200 μm . In Sublingual region, the epithelial membrane is non-keratinized. The permeability of the mucosa varies from region to region in the oral cavity depending on thickness and degree of keratinization of the epithelial membrane. Rapidly dissolving sublingual tablets are highly impressive for the emergency treatment of angina, breakthrough cancer pain, or migraine [7].

Physiochemical properties of drugs

For efficient absorption through the oral mucosa, the drug must be hydrophobic enough to partition into the lipid bilayer, but not so hydrophobic, such that once it is in the bilayer, it will not partition out again. Adequate oral absorption of drugs has been observed over a wide range of log P (octanol/water partition coefficient) values of 1 to 5. As the log P value increases beyond 5, the solubility in saliva is usually not enough to provide adequate concentration for diffusion through the lipid bilayer. According to the diffusive model of absorption, the flux across the lipid bilayer is directly proportional to the concentration gradient. Therefore, lower solubility in saliva results into lower absorption rates and vice versa. In general, a drug formulated for sublingual administration should have a molecular weight of less than 500 to facilitate its diffusion. Because drugs diffuse through the lipid bilayer in the unionized form, based on the pH-partition theory, the pKa of drugs also plays a big role in drug transport across the oral mucous membrane [7].

Characteristics of Sublingual Tablets

- Disintegration and dissolution play an important role in drug absorption when administered 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 [13].

Commonly used Superdisintegrants

Modified Starches- Sodium Carboxymethyl Starch (Sodium Starch Glycolate)

It is possible to synthesize sodium starch glycolate from a wide range of native starches, but potato starch is used as it gives the product with the best disintegrating properties. After selection of the appropriate starch source the second step is the cross linking of the potato starch. The effect of the introduction of the large hydrophilic carboxyl methyl groups is to distort the hydrogen bonding within the polymer structure. This allows water to penetrate the molecule and the polymer becomes cold water soluble. The effect of the cross linking is to reduce both the water soluble fraction of the polymer and the viscosity of dispersion in water.

Modified Cellulose- (Croscarmellose sodium)

Croscarmellose sodium is described as a cross-linked polymer of carboxymethyl cellulose. Apart from the differences between the starch and cellulose polymer backbones, there are the Differences between the synthetic processes used to modify the polymer. Most importantly, the DS of Croscarmellose sodium is higher than that of sodium starch glycolate, and the mechanism of cross linking is different.

Cross-linked polyvinylpyrrolidone- (Crosopvidone)

Crosopvidone quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth. Unlike other superdisintegrants, which rely principally on swelling for disintegration, Crosopvidone superdisintegrants use a combination of swelling and wicking. When examined under a scanning electron microscope, Crosopvidone particles appear granular and highly porous. This unique, porous particle morphology facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. Due to its high Crosslink density, Crosopvidone swells rapidly in water without gelling. Unlike other superdisintegrants which are either poorly compressible or non-compressible, Crosopvidone disintegrants are highly compressible materials as a result of their unique particle morphology. In contrast to sodium starch glycolate and Croscarmellose sodium, Crosopvidone superdisintegrants exhibit virtually no tendency toward gel formation, even at high use levels [15].

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 [18]

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 [7].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 [4].

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 [18].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 [7].

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 [19].

Advantage

- Provide rapid dissolution.
- Increase absorption and bioavailability of drugs.
- Low disintegration time when the tablet is prepared by this method [20].

Disadvantage

- It is a slow process and forms a hygroscopic product [18].
- Expensive and time consuming method.
- Cost of production is high.
- Water soluble drugs with low dose [20].

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 [19] and helps in reaching the rapid disintegration when tablet dissolves in saliva. Camphor, urea, ammonium bicarbonate, ammonium carbonate is used in evaporated substance [18].

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 [19].

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 [21]

Taste masking of sublingual tablets

Taste

It is a very important parameter to improve the patient compliance [22]. 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 [23].

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 [24].

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 [25].

Table1: Agents for masking the basic taste [25]

Basic taste	Masking agents
Sweet	Vanilla, Grape
Sour	lemon, cherry, orange
Metallic	Mint, Grape, Berries
Bitter	Liquorices, Coffee, Chocolate

These are 4 basic tastes- sweet, sour, metallic, and bitter and have various agents which mask the basic taste [25].

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 [23]

Evaluation of tablets

General appearance

To evaluate the tablet shape, size, taste, odor, color, texture [7]

Shape and size

The shape and size of the tablet can be similar, observed, and managed [7].

Thickness

Tablet thickness is an important characteristic in replicating occurrence and compute by using filling equipment. Some equipment is filled exerts the uniform thickness of the tablets [7]. 10 tablets were taken and then thickness was evaluated by vernier caliper [6].

Hardness

In this, firstly a tablet was kept between the 2 plungers of the hardness tester and creates a pressure which required breaking a tablet in a diametric way [6].

Hardness was measured by various testers-

- Monsanto
- Pfizer
- Scheuniger
- Strong-Cob [7]

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 [6]

Friability

6 tablets are selected from each formulation and placed in a friabilator. It was determined by Roche friabilator. Firstly weighs a compressed tablet then preweighed tablet were placed in the friabilator.

It consist of a plastic-chamber that revolves at 25 RPM (100 revolution), falling those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabalator for at least 4 minutes. Then reweighed the tablets and is expressed in percentage as [11]-

$$\% \text{Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{final weight}} \times 100$$

Uniformity of weight

According to IP randomly 20 tablets are weighed individually for single dose preparation and calculate the average weight [11].

Table2: Pharmaceutical limits for uniformity of weight (IP) [11]

Average weight(mg)	Percentage deviation (%)
80mg or less	10
More than 80mg or less than 250mg	7.5
250mg or more	5

Disintegration time

It is a simple method and evaluates the disintegration time of sublingual tablets [20]. Time could be measured by disintegration apparatus (Tablet disintegration machine I.P). One tablet has to be placed in the tube of the basket. The time required for complete disintegration could be determined with the help of stopwatch. According to the IP Sublingual tablets must disintegrate within 2 mins [18].

Dissolution test

According to I.P this test is planned to determine the acceptance with the dissolution requirement for solid dosage form. This test is important for tablets or capsules [26].

In-vitro release study of sublingual tablets was carried out by using USP dissolution testing apparatus(Electro-lab tablet Dissolution tester USP) type II (Paddle method).Using 900 ml of 6.8 pH phosphate buffer or simulated salivary fluid at 37 ± 2 C and 50 RPM. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 2, 4, 6, 8, 10, 12 and 14min. The samples were replaced with fresh dissolution medium of the same quantity and then absorbance was analyzed by a UV spectrophotometer (Agilent Technologies, carry 60 UV-Vis) [27].

Drug Content

Select 10 tablets from each formulation, then triturate in mortar pestal and form a powder. The powder equivalent mg of drug is accurately weighed and move to 100 ml volumetric flasks involving solution of desired pH. Then the flask is shaken and to mix the contents. The volume is made up to the mark with a solution and filtered. 1ml of the filtrate is diluted and drug content is estimated by double beam UV-visible spectrophotometer [6].

Wetting time

It is useful for quality control and produces the evaluation of this sublingual tablet. In disintegration test, the wetting test uses minimum water to evaluate the sublingual tablets, which were more characteristics of the amount of vapors present, sublingually [6]. The round tissue paper is placed in a

Petri dish and the tablet is placed on the paper and volume of distilled water is added and the time required to cover the entire tablet surface and recorded as the wetting time [18].

Water Absorption Ratio(R)

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

$$R = 100 \times \frac{W_a - W_b}{W_a}$$

Where, W_a = Weight of tablet after water absorption

W_b = Weight of tablet before water absorption

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 [28].

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 [20]-

$$\tan\theta = \frac{2h}{D}$$

$$D = 2r$$

$$\tan\theta = \frac{h}{r}$$

H=height of pile

r=radius of pile

Table3: Angle of repose [28]

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 [28].

Carr's compressibility index

In this the powder has the ability to decrease the volume under pressure and it is determined by the density [28].

The Carr's compressibility Index was calculated from Bulk density and tapped density of the blend [20]

%compressibility index = $\frac{\text{Tapped density} - \text{Bulk density}}{\text{tapped density}} \times 100$

Table4: Carr's index [28]

Compressibility	Flow properties
5-15	Excellent free flowing
12-16	Good free flowing
18-21	Fair
23-35	Poor
35-38	Very poor
≥40	Extremely poor

Compressibility gives an idea about flow properties of the granules as per Carr's index [28].

Hausner ratio

It is an important parameter which influences the mass of uniformity of the dose [28].

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{bulk density}}$$

Table 5: Marketed formulation of sublingual tablets [6]

Brand	Drug	Category	Strength
Temigesic	Buprenorphine	Opioid analgesic	200µg
Abstral	Fentanyl citrate	Opioid analgesic	5, 100, 200µg
Isordil,	Isosorbide dinitrate	Vasodilators	2.5,5,10mg
Edular	Zolpidem tartrate	Sedative	5,10mg
Saphris	Asenapine	Anti-psychotic agents	5,10mg
Aviten	Lorazepam	Anti-anxiety	1,2mg

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 recommended 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:

Recently, this review indicates that there are number of commercially available sublingual formulations invented by various techniques. Owing to ease of administration, avoids hepatic metabolism and increase bioavailability, Sublingual route provides a favorable alternative to overcome the limitation of oral and parenteral drug delivery. Many drugs have been formulated for sublingual drug delivery with an aim of rapid drug release, quick onset of action and improve the patient compliance. Compared to commonly used tablets, capsules and oral dosage forms, this delivery absorb in the oral cavity through oral mucosa and directly enter in to blood stream is generally much better, faster and more effective. The information available on this dosage form has good capacity to increase this delivery in handling a number of indications and this dosage form not only

improves the patient's compliance, but also reduces the onset of drug action and increases the bioavailability as compared to conventional dosage form.

Sublingual tablets were produced to beat the difficulty in swallowing ordinary tablet mainly in pediatric, geriatric, psychiatric patients with dysphagia. Therefore, the sublingual tablets are an accepted technology for systemic delivery of drugs

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