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Sublingual Tablet – An Alternate Route to Systemic Drug Delivery – A Review

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Abstract:
Fast disintegrating sublingual tablets are those which delivers drug beneath the tongue then disintegrate rapidly within few minutes. In solid dosage form tablets are very widely used dosage form in oral drug delivery system due to its various advantages over other dosage form, but besides advantages there is few disadvantages like mental disability, motion sickness, sudden exposure of allergies. For such difficulties new drug delivery system like immediate dissolving tablets were developed. Drug absorbed through sublingual area and bypasses the hepatic first –pass metabolic processes giving acceptable and higher bioavailability. The one third of geriatric and paediatric populations has swallowing problems, resulting in poor patient compliance with tablet drug therapy which leads to minimized overall therapy effectiveness. It helps in improving efficacy of active API's and provide more drug utilization. Sublingual immediate dissolving dosage form which offers the advantages of easiness in dosing and better dosing in the absence of water or other fluid. these type of drug delivery formulations are very suitable for allergic rhinitis, cold, CNS disorders where rapid drug onset of action is required for faster relief. Sublingual area of oral drug delivery is more permeable then buccal route and gives higher bioavailability. Different methods or techniques are used to formulate the sublingual dosage form. Various evaluation parmameters of sublingual tablets are determined such as friability, weight variation, hardness, drug content, disintegration time and in vitro drug release.

Keywords: Sublingual; bioavailability; CNS Disorders; Buccal route

Introduction:

The sublingual dosage form offers fast release of drug from the formulation and it reaches the systemic circulation directly It also enhances the bioavailability. So, without need of swallowing, we can achieve fast release of drug [1]. The oral mucosal lining offers a preferable route for the local and systemic administration of certain drugs and for the treatment of some diseases. Tablets that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. Since the drug can be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa. Sublingual route provides 3-10 times greater absorption of the drug than oral route and is only surpassed by hypodermic injection. Sublingual route is very much appropriate for short-acting drugs. Most of the drugs which are administered through the sublingual route are absorbed by simple diffusion; here the sublingual area acts like a litmus paper readily soaking up the substances; however not all the substances are permeable and accessible to oral mucosa. Majority of drugs which are administered through sublingual route falls in the category of anti anginal drug. [2] Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and braciocephalic vein and then drained in to systemic circulation.

[3] Sublingual drug delivery (SL) of the medication implies arrangement of the medication under the tongue and drug comes to straightforwardly into the circulation system through the ventral surface of the tongue and floor of the mouth. The fundamental system for the retention of the medication into oral mucosa is by means of latent dissemination into the lipoidal film. The retention of the medication through the sublingual course is 3 to 10 times more prominent than oral course and is just surpassed by hypodermic infusion. [3]

Any type of substance might be managable to sublingual organization on the off chance that it breaks down effectively in spit. Powders and vaporizers may all exploit this technique. In any case, various components, for example, pH, molecular weight, and lipid solubility, may figure out if the course is down to earth. In view of these properties, an appropriately solvent medication may diffuse too gradually through the mucosa to be powerful. [4]

Systemic drug delivery provide immediate onset of pharmacological effect through the sublingual route. [5]

Sublingual Glands:

Salivary glands which are present in the floor of the mouth under neath the tongue. They are also known as sublingual glands. They produce mucin in turn produces saliva. The interior area of the mouth remains lubricated due to production of the saliva by the glands, which is necessary for chewing and food swallowing. The fluid which is produced by the glands gets mix with the food, so the food gets easily chewed. Due to low secretion of the saliva it can create problem in swallowing the food and potential for food lodge in the throat increases. The absorption is transfer of the drug from its site of administration into systemic circulation, so it can be said that absorption is directly proportional layer thickness. The absorption of the drug following this way Sublingual > Buccal > Gingival >Palatal. Due to high permeability and rich blood supply, the sublingual route can produce rapid onset of action so the drug with short delivery period can be delivered and dose regimen is frequent. The drug gets diluted in the saliva and from there the drug is adsorbed across the oral cavity. For example: Glyceryl nitrate-a potent coronary vasodilator which is used for rapid symptomatic relief of angina. After administration, its gets pharmacologically active after 1-2 minutes. Oral spray was found to provide rapid relief of symptom with first class metabolism. The extent of first class metabolism when compared to the sublingual spray decreased to 48% with sublingual tablets and 28% with the oral dose. Nitrate which appears in the plasma concentration can be maintained for 24 hours when administrated sublingually. [6]

Mechanism of sublingual absorption:

The absorption potential of oral mucosa is influenced by the lipid solubility and therefore the permeability of the solution (osmosis); the ionization (pH); and the molecular weight of the substances. For example, absorption of some drugs via oral mucosa is shown to increase when carrier pH is lowering (more acidic) and decrease with a lowering of pH (more alkaline).(3,4)The main mechanism involved in drug transfer across the oral mucosa is passive diffusion, although facilitated diffusion has also been shown to take place for some drug substances primarily with nutrients. Passive diffusion involves the movement of a drug from the region of higher concentration to the region of lower concentration across biological membrane.

Then the drug further diffuses into the venous capillary system and eventually reaches to the systemic circulation via the jugular vein. The physicochemical characteristics of a drug are very important for the diffusion process. Although passive diffusion is undoubtedly the major transport mechanism for drugs, the absorption of nutrients from the oral cavity has been shown to involve carrier systems (facilitated diffusion), which lead to a more rapid absorption than the concentration gradient (Passive diffusion).[7]

Factors affecting Drug Absorption:

Besides the biochemical characteristics of the buccal and sublingual membranes, which are responsible for the barrier function and permeability, various factors of the drug molecule influence the extent of permeation through the membranes. The lipid solubility, degree of ionization, pKa of the drug, pH of the drug solution, presence of saliva and the membrane characteristics, molecular weight and size of the drug, various physicochemical properties of the formulation, and the presence or absence of permeation enhancers, all affect the absorption and the permeation of drugs through the oral mucosa.[8]

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 all-important for absorption. [9]

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 absolutely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is all-important 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 aswell 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. 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. [10]

Drug	**Manufacturer**
Nitroglycerin (Nitrostat)	Pfizer
Isosorbide dinitrate	Multiple manufacturers
Fentanyl citrate (Abstral)	Galena Biopharma
Buprenorphine hydrochloride	Multiple manufacturers
Ergotamine tartrate (Ergomar)	Rosedale Therapeutic
Ergoloid mesylates	Watson
Asenapine (Saphris)	Merck Sharp & Dohme
Buprenorphinehydrochloride and sodiumloxone hydrochloride	Multiple manufacturers
Zolpidem tartrate (Intermezzo)	Purdue Pharma

Table.1: Marketed product available as sublingual tablets.

Significance:

1. A relatively rapid onset of action can be achieved compared to other routes such as oral route, and the formulation can be removed at any time if therapy is required to be discontinued.
2. Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
3. Low dosage gives more efficacy as hepatic first pass metabolism is bypassed and also reduces the risk of side effects.
4. Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions e.g. asthma.
5. Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of antianginal drugs.[12]

Advantages:

1. Ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric patients and psychiatric patients.
2. Convenience and easy in administration of drug and accurate dosing as compared to liquid formulations.
3. Water is not required for swallowing this type of dosage form, which is convenient feature for patients who are traveling and do not have immediate access to water.
4. Good mouth feels property helps to change the basic view of medication as "bitter pill".
5. Fast disintegration, dissolution of medicament and absorption which will leads to rapid, onset of action.
6. Some drugs are absorbed from the mouth pharynx and oesophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
7. It provides advantages of liquid formulations in the form of solid dosage form.[13]

Disadvantages:

1. Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
2. Although this site is not well suited to sustained-delivery systems.
3. Sublingual medication cannot be used when a patient is uncooperative or unconscious.
4. 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.
5. The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
6. Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract. [13]

Categories	**Examples**
Semi natural/natural	Agarose ,chitosan, gelatin,pectin ,guar,xanthan,gellan,hyaluronic acid,
Synthetic	Acrylic acid, PEG, CMC, thiolated CMC, sodium CMC, MC, HPMC ,HPC, methylhydroxyethylcellulose, polyacrylates, PVA ,PVP,thiolated polymers,

Table.2: Mucoadhesive Polymers used in Sublingual drug delivery

ACTIVE INGREDIENTS:	**THERAPEUTIC CATEGORY**	**DOSE**
Acyclovir	Anti viral	50mg
Nifedipine	Anti angina	10mg
Nicotine	Para sympathomimetic stimulant	6-10mg
	stimulate uterine contractions	
	antihypertensive	
Oxytocin	antimicrobial	2-5mg
	antacid	
Pindolol	antihypogonadism	5mg
Propolis	antidiabetic	500mg
Sodium fluoride	antibiotic	0.5-5mg
Testosterone	antiAcrodermatitis enteropathica	40-50mg
Insulin	antiarrhythmic	
Lectoferrin	anti endometriosis	2-4gm
Zinc sulphate	antihelmintic	20-40mg
	Antipsoriatic	
Lignocane		30-50mg
Danazol		50-250mg
Arecoline		50-200mg
acitretin		25-30mg

Table.3: Active ingredients delivered via Oral Buccal Route

Pre-Formulation Studies:

Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre sieved granules into a graduated cylinder via a large funnel and measure the volume and weight.

Bulk density = weight of granules/ Bulk volume of granules

Bulk density was expressed in g/cc.

Tapped density:

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

Tapped density = weight of granules/ Tapped volume of granules

Carr's Index (CI):

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$$CI = \frac{\text{(Tapped Density-Bulk Density)}}{\text{Tapped Density}} \times 100$$

Hausner's ratio:

It indicates the flow properties of the powder. It is expressed as ratio of tapped density to the bulk density of the powder or granules.

Hausner's ratio = Tapped density/Bulk density.

Angle of repose:

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in various angles of friction and response. The method used to find the angle of repose is to pour the powder over a conical funnel on a level, flat surface and measure the included angle with the horizontal.

$\theta = Tan^{-1}h/r$

Where, h= height of the heap

r= Radius of the heap

Moisture content:

The moisture content of the excipients was determined gravimetrically. Approximately 5 gm of sample was uniformly placed onto the sample pan, and then the heating cycle to be started. The percentage of moisture content was calculated from the weight loss of the sample by heating.[18]

Methods of formulation of Sublingual Tablets:

Direct compression method:

This is a commonly used method for preparation of sublingual dosage forms and it is a simple and most economical method. Direct compression Method is best suitable for heat labile drugs. In this method we are using direct compressible and soluble ingredients, lubricant and a superdisintegrant (for example Crospovidone, Microcrystalline cellulose etc.), dry binder, sweeteners and flavors.[19]

Direct compression:
It involves direct compressing the powdered material into tablets and containing 25% or less of drug substances can be formulated, with a suitable additives which acts as a carrier or vehicle for the drug. Tablets are subjected to compression in machine which may be single station or multiple station . [20]

For direct compression following characteristics should be in tablets. [20]
- Should be free from defects like cracks,
- Should able to with stand mechanical stress.
- Physically and chemically, mechanically stable.

During processing of tablets during compression, there several processing problems encountered such as: -picking, sticking, capping, lamination, mottling:

***Picking*:** The tablet surface material may be removed by a punch during compression.
***Sticking*:** adhesion of tablet to the die wall, which may occur due to excessive moisture in the tablet.
***Capping*:** it is partial or complete separation of tablet from the top or bottom crowns of the tablet from the main body.
***Lamination*:** Segregation of a tablet into two or more distinct layers. Capping and lamination may occur due to air entrapment during processing
***Mottling*:** Unequal distribution of color on tablet surface results in mottling.

Evaluation Tests :

Hardness test
The hardness of the tablets was determined by using Hardness testers like Electro lab hardness tester, Monsanto hardness tester. The tablets should be resistance to breakage under storage conditions.

Wetting time:
Place the tablet at the center of absorbent paper fitted into a petridish, After the paper was completely wetted with refined water, overabundance water was totally depleted out of the dish. The time required for the water to diffuse from the wetted retentive paper all through the entire tablet was then recorded utilizing a stopwatch.[20]

Friability:
Roche friabilator can be utilized to decide the friability. Check the weight of tablets and place them in friabilator, The tablets were pivoted in the friabilator for no less than 4 minutes. At the end of test tablets were cleaned and reweighed, the misfortune in the heaviness of tablet is the measure of friability.

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight} \times 100}{\text{Initial weight}}$$

In-vitro disintegration test:
This test can be performed by using USP disintegration apparatus, distilled water was used as medium. The time required to obtain complete disintegration of all tablets was noted.

In-vitro dissolution test:
This test can be performed by using USP dissolution test apparatus type II, 500 ml of distilled water was taken as a dissolution medium, samples were collected at predetermined time intervals and analyze the collected samples using HPLC.

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

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

Uniformity of Weight:
I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. [20]

Conclusion:
The study revealed that the sublingual tablets have proved to be better patient compliance and better way of drug delivery for pediatric and geriatric patients. Sublingual drug deliveries have been used for formulation of many drugs n especially for the drugs that require the rapid onset of action. These tablets overcome the difficulty in swallowing convenient tablet. The target population has expended to those who want convenient tablets without water. The drug content of the tablets enters the systemic circulation through various glands present in sub lingual cavity. And thus rapid onset of action is achieved.

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