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REVIEW ARTICLE

A REVIEW: ON SUBLINGUAL TABLETS

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ABSTRACT:
Sublingual administration is usually preferred when a more rapid onset of action is required than orally taken tablets. Sublingual tablets provide rapid release of drug from the formulation, bypassing drug metabolism in the liver and entering the systemic circulation directly. Demand for rapidly disintegrating sublingual tablets has increased over the past decade, especially for elderly and paediatric patients with swallowing difficulties. Drug delivery systems are becoming increasingly complex as pharmaceutical scientists better understand the physicochemical and biochemical parameters associated with their performance. Various techniques can be used to formulate sublingual tablets. i.e., Direct compression, freeze-drying, etc. Sublingual tablets require faster disintegration. Therefore, explosives should be prescribed. i.e., It is a super disintegrant that is effective at low concentrations and has high disintegration efficiency. Tablets were evaluated for weight change, hardness, friability, wetting time, water absorption, disintegration time, and dissolution studies. This review focuses on different sublingual dosage forms, factors affecting sublingual absorption, benefits, various in vitro and in vivo evaluation parameters, and commercially available sublingual dosage forms.

Keywords: Sublingual tablet, Absorption,

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INTRODUCTION:

Oral administration is a route of administration in which a substance is taken by mouth. Many drugs are taken orally because they are intended to act systemically and reach different parts of the body through the bloodstream. A tablet is defined as a compressed solid dosage form containing a drug with or without excipients. According to the Indian Pharmacopoeia, a pharmaceutical tablet is a solid flat or biconvex shell unit dosage form prepared by compressing a drug or mixture of drugs with or without a diluent. They vary in shape and vary greatly in size and weight, depending on the amount of drug and the intended route of administration. This is the most common dosage form, with 70% of all drugs in tablet form. Solid drugs can be administered orally as powders, pills, sachets, capsules, or tablets. These dosage forms contain an amount of drug to be administered as a single unit and are technically known collectively as solid unit dosage forms, even if they are long-acting formulations representing several common drug doses increase. Tablets that rapidly disintegrate or dissolve in the patient's mouth are useful for patients who previously likely suffered from aphasia or hand tremors, such as infants, elderly patients, the mentally ill, and bedridden patients. Rapidly dissolving sublingual tablets disperse, or dissolve as soon as placed in the mouth and are

swallowed in liquid form. A sublingual tablet placed under the tongue provides an immediate systemic effect due to rapid or direct absorption of the drug through the mucous membranes of the mouth under the tongue. Drugs absorbed from the stomach enter the mesenteric circulation, which is connected by the portal vein. Absorption through the buccal cavity thus bypasses first-pass metabolism. Sublingual tablets are usually small and flat and should be pressed gently to keep them soft. The tablet should dissolve quickly so that the drug can be absorbed. Designed to dissolve in small amounts of saliva. Once the tablet is placed in the mouth under the tongue, the patient should not eat, drink, smoke, and possibly talk to keep the tablet in place. Systemic drug delivery via the sublingual route arose from the desire to provide immediate onset of pharmacological action. Sublingual products have a wide range of indications, from migraine (where rapid onset of action is important) to mental health (where patient compliance is important to treat chronic conditions such as depression and schizophrenia). The sublingual route leads to greater drug absorption over time than the oral route, second only to subcutaneous injection3-10. Sublingual administration is well suited for short-acting drugs. Most sublingually administered drugs are absorbed by simple diffusion. Here, the sublingual area acts like litmus paper and easily absorbs substances. However, not all substances are permeable and accessible to the oral mucosa. Most of the drugs that are administered are classified as anti - angiopathy categories. General body administration of drugs from the subordinate route came from the desire to provide an immediate start of pharmacological action. Subscribe is usually more effective than oral tablets, and the part absorbed from the hypogonal blood vessels to bypass the first passing liver metabolism process. Because the muscles and nervous system are not developed, children often experience dysphagia, but can easily overcome with the help of fast disintegrating sublingual tablets.

Physicochemical Criteria of drug for Sublingual Drug Delivery: The essential physicochemical characteristics of a drug for suitable candidate. The formulation of SLTs is summarized in Table 1.

Table 1: Physicochemical Criteria of drug for Sublingual Drug Delivery.

Physiochemical properties of drug	Accepted range
Dose	<20mg
Taste	Not intensely bitter
Stability	Good stable in saliva and water
Molecular weight	Small to moderate (163.3-342.3)
pKa	>2 for acidic drug <10 for basic drug
Log p	1.6-3.3
Lipophilicity	Lipophilic
No. of hydrogen bond accepter site	1-5 (2.93)
No. of hydrogen bond donor site	0-2.5 (1.26)
Polar surface area	13.0-16.0 (38.1)
No. of rateable bonds	0.5-6 (3.30)

Advantages:

1. Rapid onset of action is achieved as compared to the oral route.
2. Liver is bypassed and drug is protected from metabolism due to digestive enzymes of the middle gastrointestinal tract
3. Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications
4. Low dosage gives high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects.
5. The large contact surface of the oral cavity contributes to rapid and extensive drug absorption. Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions e.g., asthma.
6. Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of antianginal drugs.
7. They also present the advantage of providing fast dissolution or disintegration

in the oral cavity, without the need for water or chewing.

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.
4. The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the vessels. This will decrease the absorption of the medication.
5. Various types of sublingual dosage forms are available, but tablets, films and sprays are in trends these days. For the preparation of these dosage forms different methods are described depends upon the feasibility and advantages over the others.
6. One disadvantage, in any case, is tooth staining and brought about by long term utilization of this technique with acidic or generally burning medications and fillers.

Sublingual drugs absorption mechanism:

The drugs are absorbed across the mucous membrane by one of the following mechanisms:

1. Passive diffusion
2. Active or carrier-mediated transport
3. Endocytosis.

The process of passive diffusion is spontaneous, but the rate of diffusion depends on the molecular weight and solubility of the drug, concentration gradient, temperature, surface area of the membrane, and distance between the molecule and the membrane. When drugs are present in saliva in unionized form, they are absorbed by passive diffusion. A physical model has been proposed to describe drug absorption from saliva through the mucosal lipid bilayer into the systemic circulation. The rate of drug absorption through mucosa is directly related to its partition coefficient. Some compounds, such as glutamate, L-ascorbic acid, nicotinic acid, and thiamine, are transported via carrier-mediated processes. Absorption is affected by lipid solubility and hence solution permeability, commonly known as osmosis, ionization, and drug molecular weight. Cells of the oral epithelium adsorb drugs by endocytosis. The same mechanism is unlikely to be observed across stratified epithelia. However, acid stimulation of the salivary glands along with vasodilation is thought to enhance absorption and uptake into the circulatory system. The mouth is lined with mucous membranes covered with squamous epithelium and contains mucous glands. The sublingual tissue resembles that of the buccal mucosa. Salivary glands are made up of lobules of cells that secrete saliva into the mouth through salivary ducts. Her three pairs of salivary glands are the parotid, submandibular, and sublingual glands, located at the bottom of the mouth. The sourer it tastes, the more it stimulates salivation. Soak your mouth in a neutralizing solution to avoid damage to acid-sensitive tooth enamel. The sublingual artery leads to the sublingual gland, supplying the gland and branches to the adjacent muscles and mucous membranes of the mouth, tongue, and gums. Two symmetrical branches run behind the jawbone under the tongue and meet and join at their tips. Another branch meets and anastomoses with the inferior mental branch of the facial artery. The sublingual artery arises from the lingual artery, the body's main blood supply to the tongue and floor of the mouth. The lingual artery arises from the external carotid artery. Its proximity to the internal carotid artery allows quick access to that route, which supplies most of the cerebral hemispheres. Lipids present in the oral mucosa provide a major barrier to the permeability of hydrophilic drugs. On the other hand, well-hydrated connective tissue provides resistance to lipophilic drugs. Therefore, the possible transport pathways through the oral mucosa are either polar or non-polar. Nonpolar molecules pass through the lipid regions of the epithelium, whereas polar molecules migrate through ion channels present in the intercellular spaces of the epithelium or aqueous pores present in epithelial cells. Therefore, understanding the lipophilicity or hydrophilicity of a drug at the drug development stage is the most useful index

for evaluating its suitability for absorption through the oral mucosa. Because it repeats penetration and diffusion, it can move freely between body tissues. Active transport into cells leads to rapid metabolism of substances. Molecules such as glucose (fructose) and amino acids are essential for cell metabolism and special mechanisms have been developed to facilitate their rapid diffusion and penetration across cell membranes.

Factors affecting the sublingual absorption:

Drug Lipophilicity: For a drug to be fully absorbed under the tongue, the drug must have a lipid solubility slightly higher than that required for gastrointestinal absorption required for passive permeation.

Salivary Solubility: In addition to high lipid solubility, the drug should be soluble in aqueous oral fluids. i.e., Absorption requires biphasic solubility of the drug.

Salivary pH and pKa: The average pH of saliva is 6.0, so this pH favours the absorption of non-ionized drugs. Furthermore, drug absorption through the oral mucosa occurs at pKa values greater than 2 for acids and less than 10 for bases.

Binding to Oral Mucosa: Drugs that bind to the oral mucosa have low systemic availability.

Thickness Of Oral Epithelium: The thickness of the sublingual epithelium is 100-200 μm, so it is thinner than the cheek thickness. As a result, the epithelium becomes thinner and the drug is soaked in a small amount of saliva, resulting in faster absorption of the drug.

Oil-to-water partition coefficient: Compounds with good oil-water partition coefficient are easily absorbed through the oral mucosa. An oil-water partition coefficient range of 40-200 is considered optimal for drug absorption under the tongue.

Different types of sublingual tablets:

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

1. Fast-disintegrating sublingual tablets
2. Bio adhesive sublingual tablet
3. Lipid matrix sublingual tablet
4. Sublingual immunotherapy
5. Sublingual vitamin tablet

Methods of preparation of sublingual tablets:

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

Direct compression: It is simplest way to make tablets. Direct compression involves conventional equipment, commonly available excipients, and a limited number of processing steps. The mixture to be compacted must be sufficiently fluid and maintained under pressure, and no pre-treatment such as wet granulation is required. Additionally, it can accommodate higher drug doses and the final tablet weight can be slightly higher than other manufacturing processes. Disintegration and solubilization of direct compression are greatly affected by tablet size and hardness. Improved tablet excipients, especially super-disintegrants such as croscarmellose sodium, microcrystalline cellulose, crospovidone, sodium starch gluconate, partially substituted hydroxypropyl cellulose, effervescent agents (citric acid, sodium bicarbonate, etc.) The availability has made this technology applicable to rapidly dissolving tablets. and sugar-based excipients (e.g., dextrose, fructose, isomalt, maltose, mannitol, sorbitol, starch hydrolysates, polydextrose, and xylitol).

Freeze drying/ lyophilisation: Freeze-drying is used to produce tablets with a porous open matrix network that saliva readily disperses when placed in the mouth. The drug is encapsulated in a lyophilized water-soluble matrix to create an entity that dissolves quickly in the mouth. Apart from the matrix and active ingredient, the final formulation may contain other excipients that improve processing properties or enhance the quality of the final product. These include suspending agents, wetting agents, preservatives, antioxidants, colorants and fragrances. The preferred drug properties of lyophilized formulations are water

insolubility, low dosage, chemical stability, and small particle size. Freeze-drying technology has shown improved absorption and increased bioavailability, but freeze-drying is a relatively expensive and time-consuming manufacturing process. Other drawbacks include brittleness, making traditional packaging difficult to use, and reduced stability during storage and under stress conditions.

Molding: This technology uses water-soluble ingredients to allow tablets to break apart and dissolve quickly. The powder mixture is moistened with a hydroalcoholic solvent and formed into tablets using compression pressures lower than those used in conventional tablet compression. The solvent is then removed by air drying. Two problems commonly encountered in this process are reduced mechanical strength and reduced taste-masking properties. Binders such as sucrose, acacia and polyvinylpyrrolidone can be used to increase the mechanical strength of tablets. The heat-molding process uses an agar solution as a binder and as a mold to make tablets.

Sublimation: The basic principle in the production of fast-dissolving tablets by sublimation technology is to add a volatile substance to the tableting ingredients, mix the ingredients to obtain a substantially homogeneous mixture, and volatile salts are heated at 80 °C for 30 minutes. exposed to vacuum. It is exposed to remove volatile components, which creates pores in the tablet. Removal of volatile agents creates pores in the tablet that help achieve rapid disintegration when the tablet meets saliva. Examples of active ingredients include camphor, ammonium bicarbonate, naphthalene, and urea.

Spray drying: Spray drying produces highly porous, spherical particles as the processing solvent evaporates during the process. Using this process, carrier matrices such as hydrolysed and non-hydrolysed gelatine and other ingredients such as mannitol as a bulking agent, sodium starch glycolate, sodium carmellose as a disintegrant and acidic substances such as citric acid can be used to create fast-disintegrating tablets., and an alkali such as sodium bicarbonate to improve attenuation and resolution.

Mass-Extrusion: This technique uses a solvent mixture of water-soluble polyethylene glycol to soften the active mixture, methanol is used, the softened mass is expelled from an extruder or syringe, and a heated blade is used to exfoliate a cylinder of the product. formed into uniform segments to form tablets. Dried cylinders can also be used to coat bitter-tasting drug granules, thereby masking the bitter taste.

Melt granulation: Melt granulation is the process of efficiently agglomerating pharmaceutical powders using a binder that is a molten liquid, solid, or solid that melts during the process. A high shear mixer is used to carry out this process. In this process, frictional heat generated by heating jackets or impeller blades raises the product temperature above the melting point of the binder. The main advantage of this technology compared to conventional granulation is that it does not require water or organic solvents. This process does not require a drying step and uses less energy than wet granulation, so it is less time consuming.

EVALUATION:

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 determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of powder (M) is determined. Calculate the bulk density using formula: $\rho b = M/Vb$

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 determined by Carr's compressibility index (I), which is calculated by using the following formula:

$$I = (V0 – Vt) x 100/ Vo$$

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

$$Hausner's\ ratio = \rho t/ \rho d$$

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

Post compression parameters:

General Appearance: A tablet's overall look, visual identity and above all "elegance" are important for consumer acceptance. These include size, shape, colour, odour, taste, surface finish, physical imperfections and consistency of tablets, and readability of markings.

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 = (initial weight- final weight) x 100 (initial weight)

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 millilitres of solutions of water-soluble dye (eosin) are 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 too 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 were 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 sublingual's tablets is carried out using the Paddle Apparatus (USP) method. The dissolution test was carried out using 900 ml of suitable buffer at 37 + 0.50 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 determined 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.

Table 2: Marketed sublingual preparations:

Brand Name	Active constituents	Category	Strength available	Indication	Mfg. by
Sorbitrate	Isosorbide dinitrate	Vasodilators	2.5,5,10mg	Angina pectoris	Abbot India Ltd.
Ugesic	Piroxicam	Analgesic	20mg	Rheumatoid arthritis, inflammatory condition	Meyer organics Pvt Ltd.
Nurodil SL	Methycobalamine	As a vitamin	500,1500mcg	Anaemia	Opsiscare life science Pvt Ltd.
Avitan	Lorazepam	Antianxiety	1,2mg	Anxiety disorder	Pfizer Ltd.
Edular	Zolpidem tartrate	Sedative	5,10mg	Insomnia	Meda pharmaceutical
Nitrostat	Nitrogycerine	Antianginal	0.3,0.4,0.6mg	Coronary artery disease	Pfizer pharmaceuticals
Isordil	Isosorbide dinitrate	Vasodilator	2.5,5,10mg	Angina pectoris	IPCA pharmaceuticals
Ultracam	Piroxicam	Analgesic	20mg	Rheumatoid arthritis, inflammatory condition	Morfik laboratory Pvt Ltd.
Apotab 2	Apomorphine	Analgesic	2mg	Parkinson's disease	Alteus biogenics Pvt Ltd.
Kalox D3	Vitamin D3	As a vitamin	60000Iu,30000Iu	Muscle weakness, muscle aches	Oxford pharmaceuticals Pvt Ltd
Asenapt	Asenapine	Atypical antipsychotics	5,10mg	Schizophrenia, mania	Sun pharma
Subutex	Buprenorphine	Analgesic	2,8,16mg	Opioid addiction, moderate to severe pain	Reckitt Benckiser pharmaceuticals
Abstral	Fentanyl citrate	Narcotic analgesic	200,400,600,800mcg	Chronic pain breakthrough pain	Galen biopharmaceuticals
Ergomar	Ergotamine tatrate	Non-narcotic analgesic	1,2mg	Migraine	Rosedale pharmaceutical
Saphris	Asenapine	Atypical antipsychotics	5,10mg	Schizophrenia, mania	Merck
Mecobal-OD	Mecobalamin	As a vitamin	500,1500mcg	Nerve pain	Rapross pharmaceuticals

CONCLUSION:

This study found that sublingual tablets demonstrated better patient compliance and better modes of drug delivery in paediatric and geriatric patients. Sublingual drug delivery has been used in the formulation of many drugs. Especially for drugs that require rapid action. These tablets overcome swallowing difficulties. The target group has expanded to those who want to use tablets easily without water. The drug content of the tablets enters the systemic circulation through the capillaries located in the sublingual space. A rapid onset of action is thus achieved.

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