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Review Article

Sublingual drug delivery system: An overview

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ABSTRACT

Drug delivery via oral mucosa is considered to be the most promising route for administration of most of the drugs in pharmacy. Sublingual route is one of the non-invasive and excellent routes for administration of drug candidate. This route is very much familiar in pediatric, geriatric, psychiatric patients who face problem of dysphagia (difficulty in swallowing). Sublingual means 'beneath the tongue', i.e incorporating the substance via oral route in such a way that the drug would directly go into the systemic circulation after getting rapidly absorbed in vascular tissues below tongue. In the recent years, sublingual route has put inevitable place lots of advantages like bypassing hepatic first pass metabolism, self-medication, and acceptable bioavailability and improved patient compliance. In terms of permeability, sublingual area of oral cavity is more permeable than buccal area which in turn is more permeable than palatal area. This review emphasizes an updated review on sublingual dosage forms. It includes factors affecting sublingual absorption, merits and demerits, various *in-vitro* and *in-vivo* evaluation parameters and commercially available sublingual dosage forms.

Keywords: Sublingual route, Oral mucosa, Dysphagia, Acceptable bioavailability, patient compliance.

INTRODUCTION

The term sublingual plainly means 'under the tongue'. It refers to a method of administering drug substances via mouth in such a way that the drug substances are rapidly absorbed in systemic circulation via highly vascularized sublingual route in the oral mucosa rather than digestive tract. Dysphagia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid intake diets have difficulties in swallowing these dosage forms. Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream [1-6].

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.
For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity.[7]

Nitroglycerine, for example, is an effective anti-anginal drug but is extensively metabolized when taken orally (>90%). It is rapidly absorbed through the sublingual mucosa, and its peak plasma level is reached within 1-2 min. The blood concentration of nitroglycerine declines rapidly to a level below the therapeutic concentration within 10-15 min, because of its short biological half-life (3-5 min). This overview describes a complete representation of sublingual drug delivery system comprising merits and demerits, various dosage forms and their formulation parameters, commonly used superdisintegrants, evaluation and some commercially available sublingual dosage form.

ADVANTAGES OF SUBLINGUAL SYSTEM[5]:

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric patients and psychiatric patients.
- Convenience in administration of drug and accurate dosing as compared to liquid formulations.
- Water is not required for swallowing the dosage form, which is convenient feature for patients who are traveling and do not have immediate access to water.

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- Good mouth feels property helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
- Fast dissolution of medicament and absorption which will leads to rapid, onset of action.
- Some drugs are absorbed from the mouth pharynx and esophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
- It provides advantages of liquid formulations in the form of solid dosage form.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

DISADVANTAGES OF SUBLINGUAL SYSTEM:

- Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
- Although this site is not well suited to sustained-delivery systems.
- Sublingual medication cannot be used when a patient is uncooperative or unconscious.
- 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.

SUBLINGUAL GLANDS[6]:

- Sublingual glands are also known as the salivary glands which are present in the floor of Mouth underneath the tongue.
- These glands produce mucin and help to promote the production of saliva.
- The secretions of the glands, the interior area of the mouth is kept lubricated, which is necessary for chewing and swallowing food.
- The lubrication and binding functions of the sublingual glands cannot be underestimated.
- A secretion from the glands mix with food as it is chewed, making the material slippery and easily swallowed.
- Because of the saliva content of the masticated food, it can move without difficulty into the throat and on to the digestive tract.

MECHANISM OF SUBLINGUAL ROUTE[8]:

- 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).

FACTORS AFFECTING THE SUBLINGUAL ABSORPTION[9,10]:

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.

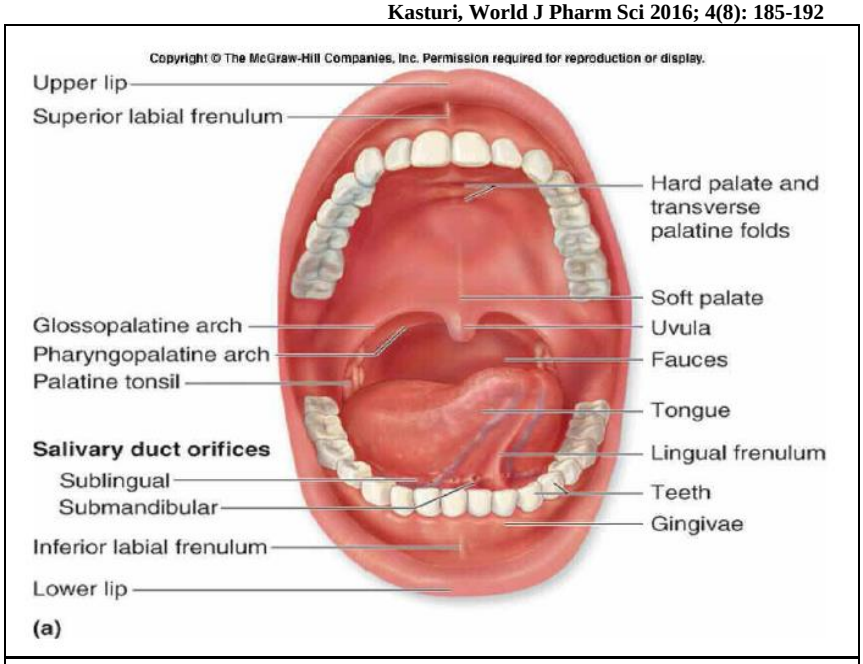
Solubility in salivary secretion: In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of drugs is necessary for absorption.

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 l ess 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 m ucosa. An oil-water partition coefficient range of 40-2000 is considered optimal for the drugs to be absorbed sublingually.



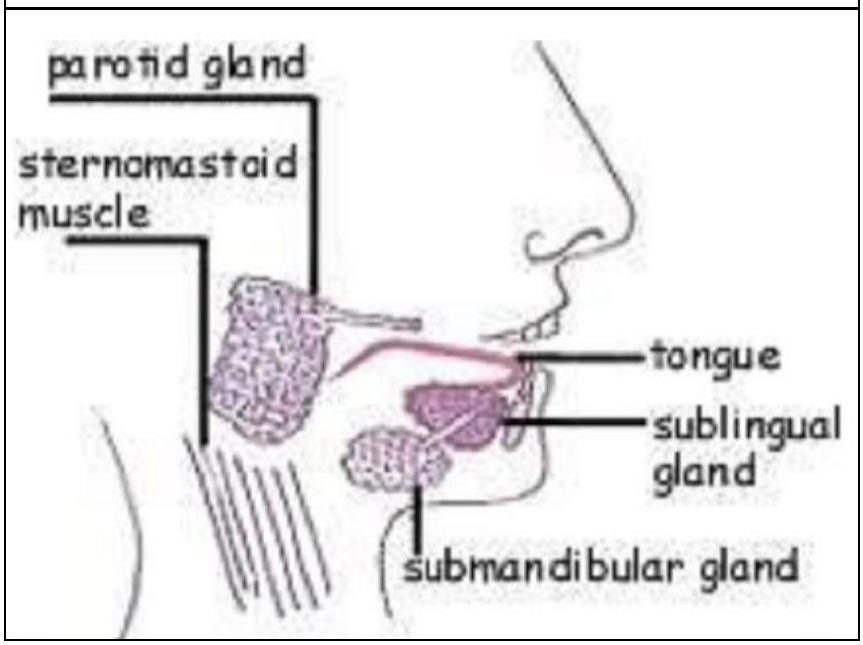


Figure 1: Sublingual Gland Figure 2: Oral Mucosa

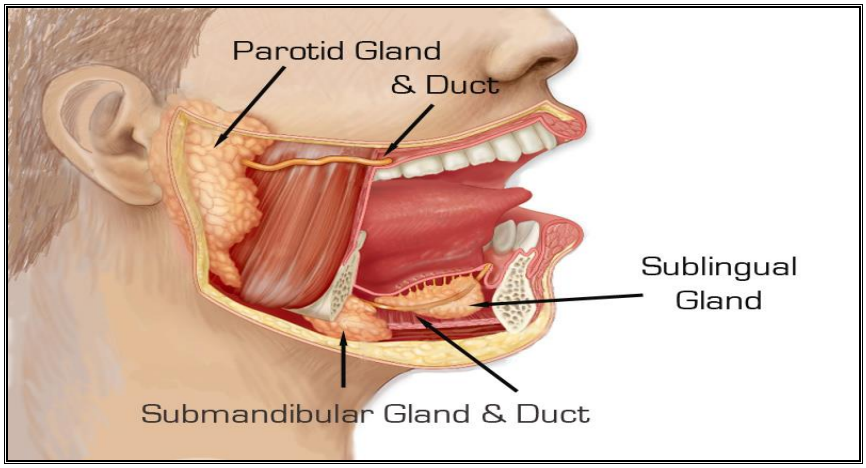


Figure 3: Sublingual gland and ducts in oral mucosa

VARIOUS SUBLINGUAL FORMULATIONS & METHOD OD PREPARATION:

Sublingual Tablets [11,12]: The sublingual tablets are usually small, flat and compressed lightly to keep them soft. These tablets are designed in such a way that they must dissolve quickly in small quantity of saliva and allow the drug to be absorbed through the sublingual mucosa. The various types of sublingual tablets commonly used are Fast disintegrating sublingual tablets, Bio adhesive sublingual tablets and Lipid matrix sublingual tablets. Direct compression is one of the techniques which require the incorporation of a super-disintegrant into the formulation, or the use of highly water-soluble excipients to achieve fast tablet disintegration.

Fast Disintegrating Sublingual Tablets [13]: These tablets disintegrate or dissolve rapidly in the mouth. The small volume of saliva is usually sufficient to result in rapid tablet disintegration in the oral cavity. The medication can then be absorbed into the systemic circulation from blood vessels in the sublingual mucosa. The sublingual route usually produces a faster onset of action than orally ingested conventional tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes.

Bio-adhesive Sublingual Tablets [14,15] : Bio adhesion is usually defined as the bond formation between two biological surfaces or between a biological surface and a synthetic surface. Problem associated with sublingual tablet formulations is the swallowing parts of the dose of the drug by patient before it has been released and absorbed into the systemic circulation through sublingual mucosa. Addition of a bio adhesive component to the formulation is a well-known approach of increasing the probability of a more site-specific drug release.

Sublingual Spray [16]: Sublingual sprays are the dosage forms in which the drug is dissolved or dispersed in a vehicle and filled in container with a metered valve. On actuation a desired dose of the drug will be delivered through the valve.

Lipid matrix sublingual tablets [17]: Such tablets are formulated using advances in sublingual and liposomal technology to create a dosage form that offers a faster and more complete absorption than traditional oral routes of Administration. The lipid matrix sublingual tablet is a bioavailable, quick, convenient and Consistent dosage form for many neutraceuticals that are often taken orally. For e.g., Glutathione MB12 (methylcobalamin) melatonin.

Sublingual vitamin tablet: Vitamin D i.e. cholecalciferol is a natural precursor of calcium regulating hormone calcitriol. Vitamin D is thus used in hypocalcaemia/ hyperparathyroidism. Because of its incomplete Absorption from GI tract, local intestinal degradation and hepatic metabolism, it is given Sublingually.

Sublingual films [18]: Orally fast-dissolving film is new drug delivery system for the oral delivery of the drugs. It is developed on the basis of technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal and intra-gastric absorption. It is prepared using hydrophilic polymers that rapidly dissolves or disintegrates in the mouth within few seconds and eliminates the fear of chocking as an alternative to fast dissolving tablets. Solvent casting method and Hot melt extrusion are commonly used methods for preparation of sublingual films.

EVALUATION:

Hardness and thickness [19]: The test is done as per the standard methods. The hardness of three randomly selected tablets from each formulation is determined by placing each tablet diagonally between the two plungers of tablet hardness tester (with the nozzle) and applying pressure until the tablet broke down into two parts completely and the reading on the scale is noted down. The thickness of three randomly selected tablets from each formulation is determined in mm using a vernier caliper. The average value is calculated.

Drug Content Randomly: Ten tablets are selected from formulation, finely powdered and powder equivalent mg of drug is accurately weighed and transferred to 100 ml volumetric flasks containing solution of desired pH. The flask is shaken to mix the contents thoroughly. The volume is made up to the mark with solution and filtered. One ml of the filtrate is suitably diluted and drug content is estimated using a double beam UV-visible spectrophotometer. This procedure is repeated thrice and the average value is calculated.

Wetting time (WT): It is useful for quality control and provides supportive evaluation of these sublingual tablets. Unlike the disintegration test, the wetting test uses minimal water, which may be more representative of the quantity of moisture available sublingually. Using this test, the time required for moisture to penetrate the tablet completely is measured and possibly represents the time required to release drug in the presence of minute volumes of saliva The tablet is placed above absorbent paper fitted into a petri dish. After the paper is thoroughly wetted with distilled water, excess water is completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet is then recorded using a stopwatch.

Water absorption ratio [19]: A piece of tissue paper folded twice is placed in a small Petri dish Containing 6 ml of water. A tablet is put on the tissue paper and allowed to completely wet. The wetted tablet is then weighted. Water absorption ratio, R is determined using following equation.

$$\text{Water absorption ratio (R)} = \frac{Wa - Wb}{Wa} * 100$$

R = 100 × Wa –Wb/Wa where,
Wa = Weight of tablet after water absorption
Wb = Weight of tablet before water absorption.

In-vitro **disintegrating test**[19]**:** Disintegration times for sublingual tablets is determined using USP tablet disintegration apparatus with desired medium. The volume of medium is 900 ml and temp is 37± 2 °C. The time in seconds taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus is measured.

Disintegration test [20,21]: A relatively simple method with rigorous conditions is developed. Each individual tablet is dropped into 10-ml glass test tube (1.5-cm diameter) containing 2ml distilled water, and the time required for complete tablet disintegration is observed visually and recorded using a stopwatch. The visual inspection is enhanced by gently rotating the test tube at a 45^0 angle, without agitation, to distribute any tablet particles that might mask any remaining undisintegrated portion of the tablets. In the USP disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without the covering plastic disks, and 2 minutes is specified as the acceptable time limit for tablet disintegration.

In-vitro **dissolution test** [22]**:** In-vitro release rate of sublingual tablets will be carried out using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus (Paddle method). A aliquot sample of the solution is withdrawn from the dissolution apparatus. The samples are replaced with fresh dissolution medium of same quantity. The samples are filtered through Whatman filter paper No 40 and analyzed in UV spectrophotometer. The percentage drug release is calculated using an equation obtained from the calibration curve.

TEST FOR FILM

Tensile Strength [23]**:** Tensile strength is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the film as given below:

$$\text{Young's Modulus} = Slope * \frac{Load\ at\ failure * 100}{Film\ thickness * Film\ width}$$

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

$$\text{Percent Elongation} = \frac{L}{Lo} * 100$$

Where,
L = Increase in length of film
Lo = Initial length of film.

Young's Modulus: Young's modulus or elastic modulus is the measure of stiffness of film. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

$$\text{Young's Modulus} = Slope * \frac{Slope * 100}{Film\ thickness * Cross\ head\ speed}$$

Folding Endurance [24]: Folding endurance is determined by drying process repeated folding of the film at the same place till the breaks. The number of times the film is folded without dry breaking is computed as the folding endurance value.

Thickness [25]: The thickness of the polymer films is measured by using screw gauge. The thickness of each strip at six different areas is determined and standard deviation is calculated.

***In-vitro* disintegration time[26]:** In vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates. The disintegration time of prepared films is measured in triplicate.

Uniformity of drug content [27]: The film of area 1x1 cm^2 is cut and dissolved in 6.8 phosphate buffer solution and made up to 100 mL in a volumetric flask. Then 1 mL is withdrawn from the solution and diluted to 10mL. The absorbance of the solution is taken at 276 nm and concentration is calculated. By correcting dilution factor, the drug content is calculated. The test is performed in triplicate.

***In-vitro* dissolution studies:** Dissolution study is carried out in USP paddle type apparatus using 300 mL of stimulated salivary fluid (pH 6.8) as a dissolution medium at 50 rpm. Temperature of the dissolution medium is maintained at 37±0.5ºC. Samples of 5ml are withdrawn at every 4 minute interval, filtered (through 0.45µ) and replaced with 5ml of fresh dissolution medium. The samples are suitably diluted and estimated spectrophotometrically at specific wavelength. The dissolution experiments are conducted in triplicate. Dissolution rate is studied for all designed formulations and dissolution parameters are calculated.

Table 1: Some commonly used superdisintegrants with their mechanism of action

Super-disintegrants	Commercially available	Mechanism of action	Special comment
Cross linked cellulose	Crosscarmellose® Ac-Di-Sol®, Nymce ZSX® Primellose®, Solutab®, Vivasol®, L-HPC	Swells 4-8 folds in < 10 seconds. Swelling and wicking both	Swells in two dimensions. Direct compression or Granulation Starch free
Cross linked PVP	Crosspovidone M® Kollidon® Polyplasdone®	Swells very little and returns to original size after compression but act by capillary action	Water insoluble and spongy in nature so get porous tablet
Cross linked starch	Explotab Primogel	Swells 7-12 folds in < 30 seconds.	Swells in three dimensions and high level serve as sustain release matrix
Crosslinked alginic Acid	Alginic acid NF	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation.

PHYSICOCHEMICAL CRITERIA FOR SUBLINGUAL DRUG DELIVERY [28,33]

Table 2: Some physicochemical properties for drug candidate

Physicochemical Properties of Drug	Accepted Range
Dose	< 20 mg
Taste	Not intensely bitter
Stability	Good stability in water & saliva
Molecular weight	Small to moderate (163.3-342.3)
pKa	>2 for acidic Drug < 10 for basic Drug
Log p	1.6 to 3.3
Lipophilicity	Lipophilic

Table 3: Some marketed product of sublingual tablet

Brand Name	Active Drug	Category	Strength
Subutex	Buprenorphine	Opioid Analgesic	2 and 8mg
Edular	Zolpidem tartrate	Sedatives/ Hypnotics	5, 10 mg
Suboxone	Buprenorphine hydrochloride	Narcotic + Opioid antagonist	2/0.5, 8/2 mg
Abstral	Fentanyl Citrate	Opioid Analgesic	50, 100, 200, 300, 400, 600, 800 μg
Avitan	Lorazepam	Antianxiety	1, 2 mg
Isordil	Isosorbide dinitrate	Vasodilators	2.5, 5 10mg
Nitrostat	Nitroglycerine	Antianginal	0.3 mg , 0.4 mg , or 0.6 mg

RECENT DEVELOPMENTS:

Nitroglycerine-delivering sublingual aerosol formulation (nitroglycerine in propellants) in a metered-dose spraying pump, Nitrolingual spray, is developed. It delivers nitroglycerine by spraying onto or under the tongue in the form of spray droplets, which ultimately increase the absorption and hence the bioavailability of nitroglycerine. The rapid onset of action is always required in case of hypertension.

CONCLUSION:

Sublingual drug delivery has been used for formulation of many drugs with the objective of rapid drug release, quick onset of action and restricting the region of drug release to mouth resulting to better compliance. Sublingual products are developed to overcome the trouble in swallowing conventional tablet, among pediatric, geriatric and psychiatric patients with dysphagia which is not generally seen in conventional tablets. The target population has expanded to those who want convenient dosing without water anywhere, anytime. Films have several advantages over the conventional dosage forms. So, they are of great importance during the emergency condition like allergy. Short term spasm and asthma a whenever immediate onset of action is desired. Therefore oral thin films are an accepted technology for systemic delivery of API's. The potential for such dosage forms is promising because strong market acceptance and patient demand. 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.

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