



AN OVERVIEW ON SUBLINGUAL TABLETS FOR SYSTEMIC DELIVERY OF DRUG

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ABSTRACT

Delivery of drug through the oral mucosa membrane is considered to be a promising alternative to the oral route. Sublingual route is a useful when rapid onset of action is required with good patient compliance than orally ingested tablets. The drug absorbed through sublingual mucosa bypasses the hepatic first-pass metabolic processes giving acceptable bioavailability. For permeability, the sublingual area of the oral cavity (i.e. the floor of the mouth) is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. To formulate sublingual tablets various techniques can be used. New sublingual technologies address many pharmaceutical and patient needs, ranging from enhanced life-cycle management to convenient dosing for geriatric, pediatric and psychiatric patients with dysphagia (difficulty in swallowing). This review highlights the different sublingual dosage forms, advantages, various *in vitro* and *in vivo* evaluation parameters and commercially available sublingual dosage forms.

KEYWORDS: Sublingual mucosa, permeability, improved bioavailability, oral cavity.

INTRODUCTION

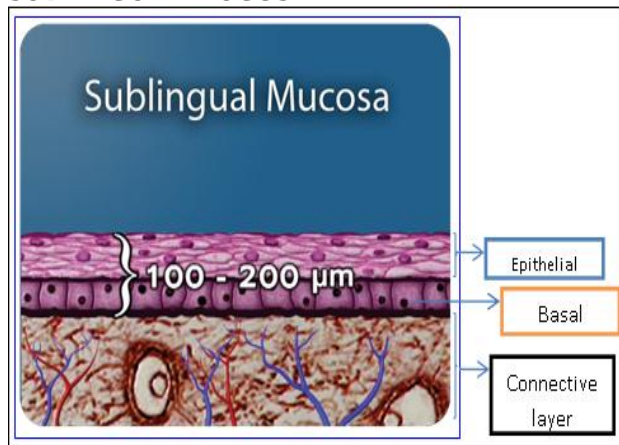
Delivery through sublingual route means placement of the drug under the tongue and drug directly reaches in the blood stream through the ventral surface. Systemic drug delivery through the sublingual mucosa had emerged from the desire to provide fast onset of effect. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially, children, elderly and patients who are mentally retarded, nauseated, uncooperative or on reduced liquid intake/diets have difficulties in swallowing these dosage forms.^[1,2]

The main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane.^[3] 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. Sublingual absorption is mostly rapid in action, but also short acting in duration. Nitroglycerine, for example, is an effective antianginal 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. Because of its short biological half-life (3-5 min.), however the blood concentration of nitroglycerine declines rapidly to a level below the therapeutic concentration within 10-15 min.^[4]

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In terms of permeability, the sublingual area of the oral cavity is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. The differences in permeability are generally based on the relative thickness, the blood supply, and degree of keratinization of these membranes. In addition to the differences in the permeability of the various mucous membranes, the extent of drug delivery is also affected by the physicochemical properties of the drug to be delivered.^[5]

Sublingual products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia).^[6]

SUBLINGUAL MUCOSA**Figure 0-1: Sublingual Mucosa.**

The sublingual mucosa is divided into two layers namely, Epithelium layer and Connective tissue layer. Epithelium is stratified non-keratinized type of squamous epithelium. It is relatively thin as compared to the buccal epithelium. Epithelium ends with basement membrane known as basal lamina, which connects the epithelium to the connective tissue and is 1 to 2 micrometer thick. Connective tissue layer which is about 150-500 micrometer thick, consists of the lamina propria and submucosa region. The lamina propria consists of, Collagen fibrils, Blood vessels and Nerve fibers. The submucosa is relatively dense connective tissue that contains a few salivary glands.

BLOOD SUPPLY TO SUBLINGUAL

The sublingual artery supplies blood to the salivary glands (sublingual gland) and branches into surrounding muscles as well as other mucus membranes of the mouth, tongue, and gums. Sublingual artery stems from the lingual artery, which constitutes the primary blood supply to the tongue and the floor of mouth region. Lingual artery branches from the external carotid artery. The blood vessels in this region branch off into smaller blood vessels that join with adjoining vessels to form an extensive network of blood supply. Because of this network – more perfusion than skin.

SUITABILITY OF DRUG

- No bitter taste.
- Should possess small molecular weight.
- Should have good stability in water and saliva.
- Remain partially non ionized at the oral pH.
- Drug having 1ST pass effect.

ADVANTAGES OF SUBLINGUAL DOSAGE FORM

- Due to high vascularization rapid absorption is there.
- Fast dissolution or disintegration in oral cavity without need of water or chewing.
- Oral mucosa is more permeable than skin.

- It's rapid onset of action compared to the oral route.
- If any irritation or discomfort occur, then it can be removed.
- Liver is bypassed- so advantage for highly liver metabolized drug.
- Drug is protected from degradation due to pH and digestive enzymes of the middle GIT.
- Improved patient compliance due to the elimination of associated pain with injections.
- Reduces dosage and side effects - as hepatic first pass metabolism is avoided.
- Due to rapid action these route sublingual dosage forms are widely used in emergency conditions.

Disadvantages of Sublingual Dosage Form

- Interfere with drinking, talking, eating.
- This site is not well suited for sustained release system.
- Limited surface area for the placement of dosage form.
- Requires taste masking of bitter drugs. Low dose of drug is required.

Types of Sublingual Dosage Form

1. **Fast disintegrating sublingual tablets:** Tablets that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly; (pediatric, geriatric) patients with swallowing difficulties and in situations where potable liquids are not available. FDT is defined as a solid dosage form that contains medicinal substance and disintegrates rapidly (within few seconds) without water when kept on tongue. The drug is released, dissolved, or dispersed in saliva and then swallowed and absorbed across the git. FDT in general offers improved convenience and are frequently preferred over conventional solid oral dosage forms. ODT may lead to significant improvements over current treatment options for specific patient group, for instance pediatric patients. The European medicines agency committee for medicinal products for human use (CHMP) described ODT as having-great promise for children. The potential benefits of ODT formulation could be fully realized by considering the additional requirements of this group. The size and disintegration time play a very important role in commercial potential of the formulation. A fast disintegration time reduces any choking hazard and will also make it harder to spit out the dose. Similarly, the taste and texture of pediatric formulation are critical to facilitate compliance in children, particularly in chronic conditions where repeated administration may be an issue. FDT sublingual tablets may show increased oral bioavailability. From the perspective of pharmaceutical industry, sublingual tablets may provide new business opportunities in the form of

product differentiation, line extension and life cycle management, exclusivity, uniqueness and patent life extension. ODT tablets are also called as orodispersible tablets, quick disintegrating tablets, and mouth dissolving tablets, fast disintegrating, fast dissolving, porous tablets, rapid dissolving tablets, and rapimelts. Water wicking and swelling are the 2 most important mechanisms of disintegrant action for most of the sublingual tablets. Water- wicking is the ability to draw water into the tablet matrix. Both the extent of water uptake and rate of water uptake are critically important. Exposure to water can cause ingredients to swell and exert pressure against surrounding tablet or capsule ingredients causing existing bonds between particles to break. In most of the sublingual tablets- sodium starch glycolate has been to promote rapid disintegration and dissolution of solid dosage form.^[7,8]

- 2 **Bioadhesive sublingual tablets:** The new sublingual tablet concept presented is based on interactive mixtures consisting of a water soluble carrier covered with fine drug particles and a bioadhesive component. With this approach it is possible to obtain a rapid dissolution in combination with bioadhesive retention of the drug in the oral cavity.^[9]
- 3 **Lipid matrix sublingual tablets:** Lipid matrix sublingual tablets are a bioavailable, quick, convenient and consistent dosage forms for many specially nutraceuticals that are often taken orally. Lipid matrix sublingual tablets is 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.
- 4 **Sublingual vitamin tablets:** The only sublingual vitamin that all doctors recommend is vitamin B12 (cyanocobalamin). Vitamin-B12 is very much helpful in our body metabolism. It is recommended to be taken orally.
- 5 **Sublingual immunotherapy:** Sublingual

immunotherapy, or SLIT, is a form of immunotherapy that involves putting drops of allergen extracts under the tongue. SLIT is usually delivered 1 of 2 ways-drops or tablets of allergen extracts are placed under the tongue, then either swallowed or spat out. Sublingual immunotherapy is very much helpful in the case of SAC (seasonal allergic conjunctivitis) and PAC (Perennial allergic conjunctivitis) which are spreading at a much faster rate among people who are working in industries and it needs longer sublingual immunotherapy, often one year around with mast cell stabilizers, antihistamines and sometimes local steroids. Conjunctivitis additionally needs corticosteroids and if needed cyclosporine drops are administered for longer time. WHO (WORLD HEALTH ORGANISATION) recommends SIT (allergen specific immunotherapy) for the patients with severe allergic conjunctivitis or asthma. SIT involves the monthly vaccination lasting for 3 years and this therapy may have side effects such as anaphylactic reactions. Therefore, other administration routes have been considered such as sublingual immunotherapy (SLIT) with daily administration for at least 3 years is a new promising and safe alternative for SIT. Sublingual immunotherapy has an advantage over subcutaneous immunotherapy and it is one of the most effective and safe treatment for allergic-rhinitis. SLIT has gained ample evidence of efficacy and safety and in some European countries is currently used more frequently than sublingual immunotherapy (SCIT). Apart from its better safety profile, the advantage of SLIT over SCIT are with regard to compliance, which is higher because SLIT does not need to be administered in a medical setting and is much more cost-effective, but the desired outcome exists only if SLIT meets its needs. In recent years' sublingual immunotherapy has emerged as an actual treatment option because of its clinical efficacy and safety.

Method of Preparation of Sublingual Tablets^[10]

Table 1 Preparation methods.

Sr.no.	Methods	Comment
1	Freeze drying	• Expensive, time consuming and produces tablets of poor mechanical strength. • But suitable for unstable or heat sensitive products.
2	Sublimation	• Prepared by addition of volatile salt substantial removal of volatile salt creates pores in tablets, which helps in achieving rapid disintegration.
3	Compression molding	• Tablets manufactured by this method pose special challenges during handling and shipping, because of the poor mechanical strength and may require special packaging.
4	Direct compression	• Does not require water or heat during formulation. • More economic. • Fewer manufacturing steps and equipment.
• No granulation step		

Evaluation of Sublingual Tablets^[11]

- 1. Hardness:** Tablets require a certain amount of strength, or hardness, to withstand the mechanical shocks of handling in manufacturing, packaging as well as in shipping. The hardness of the tablets here was measured using a simple Monsanto hardness tester. In this, a tablet is placed between the plungers, and was tightened from one end, and pressure required to break the tablet diametrically was measured.
- 2. Thickness:** Thickness is the only dimensional variable related to the process. The dimension of tablets was measured using the Vernier caliper or Micrometer. Tablet thickness should be controlled within a $\pm 5\%$ variation of the mean value.
- 3. Weight variation:** The weight of the tablet is routinely measured to ensure that the tablet contains proper amount of drug. 20 tablets were taken at random for the test and were weighed, individually and the average weight was calculated. The % deviation of each tablet from the average weight was calculated.
- 4. Friability:** In this test 50 tablets was weighed and placed in a Roche Friabilator test apparatus, and then the tablets was subjected to rolling and repeated shocks, resulting from free falls within the apparatus from the height of 6 inches. After 100 revolutions the tablets will be removed, de-dusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.
 $\% \text{Friability} = (\text{Initial weight of tablets} - \text{final weight of tablets}) / \text{Initial weight} \times 100$
- 5. Disintegration time:** By using USP tablet

disintegration apparatus with phosphate buffer of pH 6.8 as medium, the disintegration time for sublingual tablets could be determined. 900 ml of phosphate buffer is taken as the dissolution medium at 100 rpm and at temperature $37 \pm 2^\circ \text{C}$. The time in seconds taken for complete disintegration of the measured.

- 6. Wetting time:** A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of phosphate buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured.
- 7. Water absorption ratio:** - A piece of tissue paper folded twice was kept in a Petri dish containing 6 ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and weighed. Water absorption ratio, R was determined according to the following equation.

$$R = 100 (W_a - W_b) / W_b$$

Where, W_a is the weight after water absorption W_b is the weight before water absorption.

- 8. In-vitro drug release study:** - The drug release rate of sublingual tablet is from determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 300 ml of Simulated saliva fluid (Phosphate buffer pH 6.8). Dissolution test was carried out at $37 \pm 0.5^\circ \text{C}$ and 50 rpm. A sample (5 ml) of the solution should be withdrawn from the dissolution apparatus for every 2 mins; the sample can be replaced with the fresh dissolution medium. Then one has to filter the sample with the help of whatman filter paper. Absorbance of these solutions is measured.

Available Sublingual Marketed Products

Table 2: Marketed sublingual tablets.

BRAND NAME	STRENGTH	ACTION
Nitrostate Nitroglycerine	0.6, 0.4, 0.3 mg	Antianginal
Subboxone Buprenorphine	0.5, 2, 8 mg	Narcotic + opioid antagonist
Subulex Buprenorphine	2, 8 mg	Opioid analgesic
Avitan lorazepam	2, 1 mg	Antianxiety
Edular Zolpidem Tartrate	5, 10 mg	Sedative/ Hypnotics

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