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# SUBLINGUAL DRUG DELIVERY SYSTEM: A REVIEW

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## ABSTRACT

Sublingual route is the most popular route for systemic effects for its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. For drug absorption in oral cavity, sublingual area is most permeable to drugs. The drug delivered by the sublingual route bypasses the hepatic first-pass metabolism and providing acceptable bioavailability. Dysphagia (difficulty in swallowing) is common problem for all age or on reduce liquid intake have difficulties in swallowing the solid dosage forms. This review highlights the mechanism of sublingual absorption, factors affecting sublingual absorption, advantages, disadvantages and evaluation parameters.

**Keywords: Sublingual route, dysphagia, bioavailability, patient compliance**

## INTRODUCTION

Sublingual route is a convenient when rapid onset of action is desired with better patient compliance than orally ingested tablets. In terms of permeability, the sublingual area of the mouth (i.e. the floor of the mouth) is more permeable than the buccal area, which in turn is more permeable than the palatal (roof of the mouth) area. Systemic drug delivery through the sublingual route had emerged from the will to supply immediate onset of pharmacological effect **[1]**.

Sublingual verbal meaning is "under the tongue", administrating substance via mouth in such a way that the substance is rapidly absorbed via blood vessels under tongue. The proportion of drug absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolism and providing acceptable bioavailability.

Dysphagia (Difficulty in swallowing) is common problem of all age groups or on reduced liquid intake have difficulties in swallowing the solid dosage forms. Sublingual administration of the drug means placement of dosage form under the tongue & drug reaches directly into the systemic circulation **[2]**.

The drug is rapidly absorbed into the reticulated vein that's present underneath the oral mucosa, and transported it through the facial veins, internal vena jugularis, and braciocephalic vein then unloads in to systemic circulation **[3]**.

The small volume of salivation is adequate to result in disintegration of the tablet in the oral cavity. Sublingual absorption is usually rapid in action, but also short acting in duration. Oral mucosal drug delivery is an elective technique that offers several advantages because the oral mucosa is highly vascularised that drugs are absorbed through the oral mucosa directly enter the systemic circulation, by passing the GIT and first-pass metabolism within the liver **[4]**.

**SUBLINGUAL GLANDS**

Sublingual gland is the smallest vital salivary gland. Sublingual glands are present within the floor of mouth i.e. underneath the tongue. These glands produce mucin and help production of saliva, for necessary breakdown of drug. A secretion from the glands mix with food and help in chewing and making the food slippery in order that it can be easily swallowed **[5]**. Low production of saliva can make the process of swallowing far more difficult and lodge the food content within the throat. The absorption of the drug in the oral cavity is Sublingual > Buccal > Gingival >Palatal. Due to high permeability and vascularity, the sublingual route produce rapid onset of action. The drug gets diluted within the saliva and from there the drug is adsorbed across the mouth **[3]**.

**SUBLINGUAL ABSORPTION**

Sublingual, meaning actually 'under the tongue' refers to a way of administering substances via the mouth. The substances are rapidly absorbed via the blood Vessels under the tongue instead of via the digestive tract. The absorption through the mucous membrane in the sublingual region, the drug instantly diffuses into venous blood. The blood from the sublingual region of the oral cavity drains into a common trunk, which then drains via the internal jugular vein, the subclavian vein, and the brachiocephalic vein directly into the superior vena cava. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is simply surpassed by hypodermic injection **[1]**. For these formulations, the little volume of saliva is usually sufficient to result in tablet disintegration in the oral

cavity. Sublingual absorption is usually rapid in action, but also short acting in duration. Thus, venous return from these regions enters the systemic circulation, bypassing the presystemic drug elimination, unlike in oral administration **[5]**.

**FACTORS AFFECTING THE SUBLINGUAL ABSORPTION**

- **Thickness of oral epithelium:** The thickness of sublingual epithelium is 100-200 μm which is smaller amount as compared to buccal thickness. Therefore the absorption of drugs is quicker to the thinner epithelium and also the immersion of drug in smaller volume of saliva **[1]**.
- **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 vital for passive permeation **[2]**.
- **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 bigger than 2 for an acid and fewer than 10 for a base **[3]**.
- **Oil to water partition coefficient:** Oil to water partition coefficients of favorable compound are readily absorbed through the oral mucosa. An oil-water partition coefficient range of 40-2000 is taken into account optimal for the drugs to be absorbed sublingually **[6]**.
- **Solubility in salivary secretion:** Additionally to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of the drug is important for absorption.
- **Binding to oral mucosa:** Systemic availability of drugs that bind to oral mucosa is poor **[7]**.

**ADVANTAGES**

- Liver is bypassed and also drug is shielded from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
- 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.

- Due to rapidity in action, these sublingual dosage forms are widely utilized in emergency conditions e. g. asthma.
- The large contact surface of the mouth contributes to rapid and extensive drug absorption **[8]**.
- Ease to administer to those patients who are unable to swallow a tablet, e.g. paediatric, psychiatric patients and geriatric patients.
- Better suitability in administration of drug and accurate dosing.
- Water isn't necessary for swallowing the dosage form **[3]**.

**DISADVANTAGES**

- Not suitable for sustain release formulations.
- Sublingual medication can't be used when a patient is uncooperative.
- Sublingual administration of drugs interferes with eating, drinking, and talking.
- The patient shouldn't smoke while taking sublingual medication because smoking causes vasoconstriction of the vessels. This might decrease the absorption of the medication.
- Not suitable for bitter drug delivery **[3, 4]**.

**SUBLINGUAL FORMULATIONS**

Various Sublingual formulations can be classified as Sublingual Tablets, Sublingual films, Sublingual sprays and Sublingual capsules.

- **Sublingual Tablet:** The sublingual tablets are usually small, flat tablet intended to be inserted beneath the tongue, where the active ingredient is absorbed directly through the sublingual mucosa and dissolve very promptly in small volume of saliva. The various sorts of sublingual tablets commonly used are Fast disintegrating sublingual tablets, Bio adhesive sublingual tablets and Lipid matrix sublingual tablets **[7]**.
- **Sublingual Films:** These are the thin, transparent films, which are kept under the tongue form which drug will reach and absorbed into blood stream. e.g. diazepam.
- **Sublingual Sprays:** Sublingual sprays are the dosage forms during which the drug is dissolved or dispersed in a vehicle and filled in vial with metered value. On actuation a desired dose of the drug will deliver through the valve **[7]**.
- **Sublingual Capsules:** These are the solid dosage forms during which the powder was filled into capsule, it should be cut open and therefore

the contents are poured below the tongue. e.g. Nifedipine sublingual capsule **[4]**.

**SUBLINGUAL TABLETS**

Sublingual tablets are solid unit dosage form meant for placement under the tongue to produce immediate action by avoiding the first pass effect of drug by liver. The tablets are usually small and flat, compressed lightly to keep them soft. The tablet must dissolve quickly allowing the API to be absorbed quickly. It's designed to dissolve in small quantity of saliva. After the tablet is placed within the mouth below the tongue, the patient should avoid eating, drinking, smoking and possibly talking in order to keep the tablet in situ. Swallowing of saliva should even be avoided since the saliva may contain dissolved drug. Bland excipients are used to avoid salivary stimulation.

Examples of drugs administered by this sublingual route include antianginal like nitrites and nitrates, antihypertensive like nifedipine, analgesics like morphine and bronchodilators like fenoterol. Certain steroids like estradiol and peptides like oxytocin can also be administered e. g. fentanyl citrate, apomorphine, Prochlorperazine di maleate and hydrazine HCl **[7]**.

**MANUFACTURING TECHNIQUES USED IN SUBLINGUAL TABLET FORMULATION**

- **Direct Compression:** It is a commercial method which is used in the manufacture of sublingual tablets is the direct compression method. It is a simple, cost-effective and efficient process, as it employs ingredients that can be blended well and do not require further granulation steps prior to lubrication and compression. Sublingual tablets manufactured using direct compression possesses good mechanical strength and fast disintegration. This method is mostly suitable for the heat labile drugs. The mixture to be compressed must have adequate flow properties and cohere struggling thus making pretreatment as wet granulation unnecessary. The size of the tablet and its hardness must be generally maintained according to the specification for its disintegration and solubilization. This technique can now be applied to fast dissolving tablets because of the availability of improved tablet excipients, especially superdisintegrants like cross carmellose sodium, microcrystalline cellulose, crosspovidone, sodium starch glycolate and partially substituted hydroxypropyl cellulose,

effervescent agents (citric acid, sodium bicarbonate) and sugar based excipients (dextrose, fructose, isomalt, maltitok, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose, and xylitol) Sugar based agents are now being widely used as bulking agents as they possess high aqueous solubility, sweetness, good taste masking and pleasant mouth feel **[11]**.

- **Tablet Moulding:** Water soluble ingredients are used in this technology such as the tablet disintegrates and dissolves rapidly. In this method the powder blend is generally moistened with a hydro alcoholic solvent and is molded into tablets by the process of compression method. Air drying is used to remove the solvent. Binding agents such as sucrose, acacia or poly vinyl pyrrolidine gradually increases the mechanical strength of the tablet.
- **Spray Drying:** Spray dryers are widely used in the pharmaceuticals and biochemical process. They produce highly porous and fine powders and the solvent is evaporated during the process. Rapidly disintegrating tablets with the help of support matrix are produced with the help of other components such as bulking agents, sodium starch glycolate, acidic material like citric acid and alkali like sodium bicarbonate which increases its disintegration and dissolution.
- **Freeze Drying:** As compared to the direct compression method, freeze drying consumes more time and is much costlier producing tablets of poor mechanical strength. Tablets manufactured by this method generally have high porosity and dissolve instantly. Drugs which are heat sensitive can be produced by this method. Here an aqueous solution of a carrier is made where the drug is dispersed or dissolved. The mixture of the drug with the aqueous solution is finally poured into the wells of the blister packs. The trays are then passed through liquid nitrogen where the drug solution gradually freezes up. Blister packs are then kept in refrigerated chambers to continue the freeze drying process. Finally they are packed and shipped out.
- **Mass Extrusion:** Using the mixture of water soluble polyethylene glycol and methanol the active blend is softened, and expulsion of a

softened mass through a syringe to get a cylinder of the product into even segments using heated blades to make tablets. Here the bitter tasting drugs and their granules can be coated to mask the bitter taste **[11]**.

**EVALUATION PARAMETERS**

- **General Appearance:** The general appearance of a tablet, its visual identity and over all "elegance" is important for consumer acceptance. It include tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking **[9]**.
- **Size and Shape:** The size and shape of the tablet can be dimensionally verbalized, monitored and controlled **[2, 10]**.
- **Tablet Thickness:** Tablet thickness may be a crucial characteristic in reproducing appearance and also in enumerates by using filling equipment. Some filling equipment exerts the uniform thickness of the tablets as accounting mechanism.
- **Wetting Time:** A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish containing 6 ml of Sorenson's buffer pH 6.8. A tablet was placed on the paper, and therefore the time for complete wetting was measured **[2, 12]**.
- **Uniformity of Weight:** I.P. procedure was followed for uniformity of weight, 20 tablets were taken and their weight was determined individually and collectively on a digital weighing balance. From the collective weight the average weight of 1 tablet was determined. The limit for weight variation **[13]**.
- **Tablet Hardness:** Hardness of tablet is defined because the force applied across the diameter of the tablet within the order to break the tablet. The resistance of the tablet to chipping, snick or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet was determined using Monsanto Hardness tester **[14]**.
- ***In-Vitro*** **Dispersion Time:** In-vitro dispersion time was decided by dropping a tablet during a beaker containing 50 ml of Sorenson's buffer (pH 6.8). 3 tablets from each formulation were randomly selected and in vitro dispersion time was performed **[15]**.

- ***In-Vitro* Disintegration Test:** The In-Vitro disintegration test was carried out on 6 tablets using the apparatus laid out in I.P. 1996 distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds **[14]**.
- **Surface pH of the tablet:** pH of tablet is determine by allowing the tablet in keep with the contact with 1ml water for 2hr at room temperature and the pH is measured by bringing the pH meter electrode, in contact with the surface of the tablet and allowing it to equilibrate for 1min **[15]**.
- **Content uniformity:** The content uniformity is determined by following the assay method for active ingredient.
- **Friability:** The friability was determined by using Roche friabilator. A preweighed tablet was placed in the friabilator. Fraibilator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated within the friabilator for a minimum of 4 minutes. At the end of test tablets were dusted and reweighed, the loss within the weight of tablet is that the measure of friability and is expressed in percentage as **[14]**.

**%Friability = loss in weight of tablet / Initial weight of tablet x 100.**

## CONCLUSION

The study revealed that the sublingual tablet have proved to be better patient compliances. Drug delivery via. the sublingual route is better for pediatric and geriatric patient who have swallowing difficulty. Due to easy of administration and avoidance of the hepatic first pass metabolism, sublingual route provide a promising alternative to overcome the limitations of conventional drug delivery and parentral administration. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route. They provide a quick onset of action and improved bioavailability.

## REFERENCES

**[1]** Narang N and Sharma J, Sublingual mucosa as a route for systemic drug delivery, International Journal of Pharmacy and Pharmaceutical Sciences, 3, 2011, 18-22.

**[2]** Saheb R, Dhangar R, Patil ST, Pawar SP, Sublingual: A Route for Systemic Drug Delivery System, International Journal of Pharma and Chemical Research, 3(2), 2017, 301-306.

**[3]** Mathur P, Rana A, Saroha K, Mathur K, Sublingual Route: An Approach to Administered Drugs in Systemic Circulation, International Journal of Pharmaceutical Research Health Science, 7(1), 2019, 2869-73.

**[4]** Soni A, Kumar A, Jamwal S, Kumar A, and Dr. Chaudhary A, Oral dosages form: tablet in sublingual formulations, World Journal of Pharmaceutical and Life Sciences, 5(9), 2019, 133-137.

**[5]** Patel P, Patel J, Patel K, Nihar S, Shah S, A Review on Fast Dissolving Sublingual Film, JPSBR, 5(3), 2015, 279-285.

**[6]** Saha P, Verma S, Das Pratik S, Sublingual drug delivery: an indication of potential alternative route, International Journal of Current Pharmaceutical Research, 9(6), 2017, 5-7.

**[7]** Pawar P, Ghorpade H, Kokane B, Sublingual route for systemic drug delivery. Journal of Drug Delivery & Therapeutics, 8(6), 2018, 340-343.

**[8]** Sah S, Badola A, Kothiyal P, Sublingual tablets: an overview. Indian J. Pharm. Biol. Res, 4(2), 2016, 20-26.

**[9]** Singh M, Chitranshi N, Singh AP, Arora V, Siddiqi AW, An Overview on fast Disintegrating Sublingual Tablets, International Journal of Drug Delivery, 4(4), 2012, 407-417.

**[10]** Rathaur H and Gnanarajan G, Review on: Sublingual route for systemic drug delivery, Indo American Journal of Pharmaceutical Sciences, 5(1), 2018, 453-462.

**[11]** Rai TP, Pramanik A, Purakayastha D, Ghadge M, Garg S, Sublingual Route for the Systemic Delivery of Drugs, World Journal of Pharmaceutical Sciences, 7(1), 2019, 38-45.

**[12]** Aghera JN, Shah D, Suresh and Vadalia Kantilal R, Formulation and evaluation of sublingual tablets of losartan potassium, Asian Pacific Journal of Tropical Disease, 2012, 130-135.

**[13]** Godbole AM, Somnache SN, Thakker SP, Iliger SR, Joshi AS, Patel BV, Formulation and In-vitro Evaluation of Sublingual Tablets of Ondansetron Hydrochloride using Coprocessed

Excipients, Indian Journal of Pharmaceutical Education and Research, 48, 2014, 7-17.

**[14]** Sem S, Gupta A, Sharma A, Darwhekar GN, Formulation and Evaluation of Sublingual Tablet Containing Anti Emetic Drug, Journal of Drug Delivery and Therapeutic, 8(2), 2018, 107-111.

**[15]** Prathusha P and Kamarapu P, A Review on Sublingual Tablets. Journal of Formulation Science & Bioavailability, 1(1), 2017, 1-2.