



Review Article

Sublingual Route: An Approach to Administered Drugs in Systemic Circulation

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Due to ease of administration, versatility, painless and paramount patient compliance oral administration is considered as most satisfactory route for the administration of drug. For drug absorption in oral cavity, sublingual area is most permeable to drugs. The sublingual route bypasses the hepatic first-pass metabolism, which assist greater bioavailability with better patient compliance. Sublingual route is the most suitable now a days because people need effective relief within a short period. These tablets have the advantage of rapid disintegration and dissolution in saliva. For the instant drug delivery to paediatric and geriatric patients fast disintegrating sublingual tablets have shown significant improvements for specific patient group. This review enlightens the mechanism of sublingual absorption, physicochemical properties of a few sublingually administered drugs, factors affecting sublingual absorption, advantages, and evaluation parameters.

Keywords: sublingual tablets, patient compliance, bioavailability, saliva etc.

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1. INTRODUCTION

Sublingual route of systemic drug delivery offers instant onset of therapeutic action. Dysphagia (difficulty in swallowing) is associated with all age groups, especially elderly, children, and mentally retarded patients, and nauseated patient.^{1,2} Sublingual Drug delivery is an alternative method for systemic drug delivery that possess some advantages over other methods of administration. Because of high vascularity of oral mucosa, drugs that are

absorbed through the oral mucosa directly enter the systemic circulation, by passing the gastrointestinal tract and first-pass metabolism.³The drug is rapidly absorbed into the reticulated vein that is present underneath the oral mucosa, and transported it through the facial veins, internal jugular vein, brachiocephalic vein and then unload in to systemic circulation.⁴ Passive diffusion is the primary mechanism for the absorption of the drug in to oral Mucosa is via lipoidal membrane. The absorption of the drug via sublingual route is 3 to 10 times greater than oral route. For these formulations, the small volume of saliva is required for atablet disintegration in the oral cavity.⁵ Nothing can change the patient's acceptability towards oral drug delivery in usage and have advantages of free from sterilizationProblems.⁶

1. SUBLINGUAL GLANDS

Sublingual gland is the smallest vital salivary gland.⁷Sublingual glands⁸are present in the floor of oral cavity 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 so that it can be easily swallowed.⁴ Low production of saliva can make the process of swallowing much more difficult and lodge the food content in the throat.⁵ 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 in the saliva and from there the drug is adsorbed across the oral cavity.⁹

2. MECHANISM INVOLVED IN SUBLINGUAL ABSORPTION

The absorption potential of buccal mucosa is affected by the lipid solubility and therefore the permeability of the solution (osmosis), the ionization (pH), and the molecular weight of the substances.^{5,9} In sublingual glands, the pattern of different branches are compact.⁸The venous blood from the sublingual region of the oral cavity drains into a common trunk, which then drains through the internal jugular vein, the subclavian vein, and the brachiocephalic vein directly into the superior vena cavaun like in oral administration.^{8,1}

2.2 CHARACTERISTICS OF DRUGS FOR SUBLINGUAL ADMINISTRATION:⁵

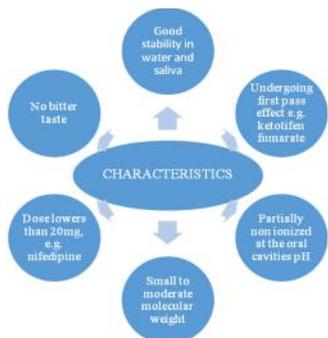


Fig 1. Characteristics of drugs for sublingual administration

Examples of drugs administered through sublingual route include antianginal like nitrites and nitrates, antihypertensive

like nifedipine, analgesics like morphine and bronchodilators like fenoterol. Certain steroids as estradiol and peptides like oxytocin can also be administered through sublingual route e.g. apomorphine, fentanyl citrate, hydrazine HCl, prochlorperazine dimaleate.¹⁰

Table 1: Fundamental propertiesof somesublingually administered drugs.¹¹

Drug	Molecular weight	largest dose	Water solubility	pKa	Log p
Nicotine	162.234	4mg	Slightly soluble	8.21	0.99
Buprenorphine	467.6	2-8 mg	Insoluble in water	8.24- 10.0	4.9
Nitroglycerin	227	0.6mg	1.8 mg/ml	-5.6	0.94
Ergotamine tartrate	583.68	2mg	Insoluble in water	6.3	2.4
Fentanyl citrate	336	0.8 mg	0.025 mg/ml (citrate)	8.4	2.9
Asenapine maleate	285.5	10 mg	3.7 mg/ml	8.6	4.9

2.3 ADVANTAGES^{10,12-13}

- Ease to administered 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 precise dosing.
- Water is not necessary for swallowing the dosage form.
- Good feeling inside the mouth helps to change the basic understanding of medication as "bitter pill", particularly for paediatric patients.
- Fast absorption of medicament which will successfully provide rapid onset of action.
- It provides advantages solid dosage form over liquid formulations.

2.4 DISADVANTAGES¹⁴⁻¹⁶

- Area available for absorption of drug is much less.
- Not suitable for bitter drugs delivery.
- Patient compliance is poor.
- Administration of highly ionic drug is not possible.
- Administration of high dose of drug is impossible.

2.5 FACTORS AFFECTING THE SUBLINGUAL ABSORPTION^{5, 10, 17}

a) Solubility in buccal secretion

Along with high lipid solubility, the drug must be soluble in aqueous buccal fluids i.e. biphasic solubility profile of drug is required for absorption.

b) Binding to the oral mucosa

Bioavailability of drugs that cohereto oral mucosa is poor.

c) 3.pH and pKa of the saliva

The mean pH of the saliva is 6.0, this pH favours the absorption of drugs which remain in unionized form. If the pKa is greater than 2 for an acid and less than 10 for a base then the absorption of the drugs through the oral mucosa occurs.

d) Lipophilicity of the drug

For the complete absorption through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption.

e) Thickness of the oral epithelium

Thickness of sublingual epithelium is 100-200 μm which is less as compared to buccal thickness. So the absorption of drugs is faster in sublingual region due to thinner epithelium.

3. In vitro and in vivo evaluation

3.1 In vitro evaluation:

a) General appearance¹⁹⁻²⁰

The general appearance of a tablet like its visual identity and over all "elegance" is necessary for consumer acceptance & compliance. General appearance characters include are tablet's size, colour, shape, presence or absence of an odour, surface texture, taste, physical flaws and legibility of any identifying marking.

b) Uniformity of weight²¹

According to I.P. procedure, weight of twenty tablets has to be determined individually and collectively on a digital weighing balance. The average weight of one tablet was calculated.

c) Hardness and thickness²¹⁻²²

Ten tablets were taken and their thickness was determine by using micrometer. Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. Hardness of the sublingual tablet was determined using Monsanto Hardness tester.

d) Friability²³⁻²⁵

Friability is the measurement of mechanical strength of tablets. For the determination of the friability Roche friabilator is used. A preweighed tablet was placed in the friability apparatus. This apparatus consist of a plastic-chamber that revolves at 25 rpm and dropping those tablets at a height of 6 inches in each revolution. The tablets were rotated in the friability apparatus for at least four minutes. At the end of tested tablets were dusted and reweighed again and percentage friability was calculated.

%Friability= Initial Weight –Final Weight/ Initial Weight x100

e) Disintegration time (DT)^{22,26}

A relatively easy method with rigorous conditions has been successfully developed to evaluate the DT of sublingual tablets. Each individual tablet is dropped into 10-mL glass test tube (1.5-cm diameter) containing 2 ml distilled water, and the time need for complete tablet disintegration is observed visually and recorded using as stopwatch. The visual inspection can be enhanced by gently rotating the test tube at a 45 degree, without agitation.

f) Wetting time (WT)^{25,27-28}

It is useful quality control tool for sublingual tablets. Using this test, the time required to penetrate the moisture in tablet completely is measured that correlated with the time required to release the drug in the presence of saliva.

g) Water absorption ratio²⁷⁻²⁸

A section of tissue paper folded twice is placed in a small Petri dish Containing 6 ml of water. One tablet is placed on the tissue paper and allowed to completely wet by water. The wetted tablet is then weighted. Water absorption ratio can be represented by R was determined using following equation.

$$R = 100 \times \frac{W_a - W_b}{W_a}$$

Where,

W_a = Weight of tablet following water absorption

W_b = Weight of tablet before water absorption

h) Drug Content²⁹⁻³⁴

Arbitrary ten tablets are selected from formulation, finely powdered and powder equivalent to certain mg of drug is weighed accurately. Different dilutions are made and drug content is precisely calculated.

i) In-vitro dissolution studies³⁵⁻³⁸

Dissolution study was carried out in paddle type apparatus using 300 mL of stimulated salivary fluid (pH 6.8) as dissolution medium at 50 revolution per minutes. Temperature of the dissolution medium was maintained at $37 \pm 0.5^\circ\text{C}$. Samples were diluted accordingly and estimated spectrophotometrically. The dissolution studies were conducted in triplicate.

3.2 In vivo evaluation:

a) Pharmacokinetic data analysis and bioavailability evaluation^{1, 34}

Rabbits are one of those laboratory animals, they do not have keratinized mucosa, thus they closely matched with human sublingual mucosal tissue. The maximal plasma concentration (C_{max}) and the time to reach maximum plasma concentration (T_{max}) can be directly obtained from the plasma data obtained from rabbits. The area under the plasma concentration curve can also be calculated by using the trapezoidal methods of determining the bioavailability.

b) Permeation studies^{5, 23}

Ex vivo permeation studies by using porcine oral mucosa is performed out using the modified Franz diffusion cell having internal diameter of 2.5cm. The buccal mucosa was excised and trimmed evenly from all the sides and then washed in isotonic phosphate buffer solution of pH 6.6 and immediately used. The membrane was stabilized before setting to separate the soluble components. The mucosa was set between the donor and receptor compartments. The receptor compartment was filled with 200 ml of isotonic phosphate buffer having pH 7.4 maintained at $37 \pm 0.2^\circ\text{C}$ and stirring with a magnetic stirrer at 50 rpm. One film having dimension 2 cm X 2 cm was previously moistened with simulated saliva. The compartment that acts as donor was filled with 1ml of simulated saliva of pH 6.8. Samples were taken at suitable interval by maintaining sink condition. The percentage of drug permeated was calculated by using UV-Visible spectrophotometer.

4. FUTURE PROSPECTS

Sublingual tablets are one of the most suitable candidates for the oral drug delivery especially for proteins and peptides that have limited bioavailability when administered by conventional tablet. Injections generally are not generally accepted by patients unless facilitated by sophisticated auto-injectors. The developments of enhanced oral protein delivery technologies by oral drug technologies which may release these drugs in the oral cavity are very promising approach for the delivery of high molecular weight peptides and proteins like hormones and insulin.

5. CONCLUSION

These tablets are formulated to release the medicaments with an increase rate of absorption. When compared to commonly used tablets, capsules and other types of oral dosage forms, sublingual absorption is generally much faster and more efficient. Sublingual dosages are appropriate for young children, patients with swallowing difficulties, elderly patients and in situations where potable water is not available. Due to the ease of administration and avoidance of the hepatic metabolism, sublingual route offers a promising alternative to overcome the limitations of conventional oral drug delivery and parenteral administration. Sublingual route offers quick absorption as well as fast onset of action. To fulfil the patient's needs, formulators and researchers have devoted considerable effort in developing a novel type of tablet dosage form for oral administration.

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