World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 5.088

ORAL DOSAGES FORM: TABLET IN SUBLINGUAL FORMULATIONS

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Article Received on 22/07/2019 **Article Revised on 12/08/2019** **Article Accepted on 02/09/2019**

ABSTRACT

Among the various routes of drug delivery, the oral route is perhaps the one mostly preferred by patients and clinicians. The oral cavity is an alluring site for the delivery of drugs. But due to common problem of dysphasia number of population finds trouble in swallowing the conventional dosage form. Sublingual route is very useful when rapid onset of action is desired with great patient consistence than orally ingested tablets. Sublingual tablets can be formulated by different techniques. New sublingual advancements address patient needs and numerous pharmaceutical, going from upgraded life-cycle management to helpful dosing for paediatric, geriatric and mental patients with dysphagia.

KEYWORDS: Sublingual delivery, Improved bioavailability, Quick action.

1. INTRODUCTION

Oral administration is the most popular route for systemic effects for its ease of ingestion, pain, avoidance, versatility and most significantly, patient compliance. Solid oral delivery systems do not require sterile conditions hence they are less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Drugs have been connected to the mucosa for topical application for a long time. However, recently there has been interest in exploiting the oral cavity as a portal for delivering drugs to the systemiccirculation.[1]

The Drug delivery through sublingual route have desire to provide quick onset of pharmacological effect. Dysphasia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally retarted, un cooperative, 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 medication reaches directly in to the blood stream through the ventral surface of the tongue and base of the mouth.[2] The little volume of salivation is adequate to result in disintegration of the tablet in the oral cavity. Sublingual absorption is mostly rapid in action, but also short acting in duration.[3] 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 in the liver.[4]

1.1 Advantages

- To easy administration such as geriatric, pediatric and psychiatric patients.
- Liver is bypassed and also medication is protected from degradation due to pH and digestive enzymes of the center gastrointestinal tract.
- Easy, painless and convenient self-administration.
- Rapid onset of effect - particularly for pain, emesis, insomnia or allergy relief.
- Inexpensive to manufacture per dose.
- Flexible formulation options.
- Fast dissolution or disintegration in the buccal cavity, without requirement for water.
- A relatively fast onset of action can be achieved compared to the oral route, and the formulation can be evacuated if treatment is required to be discontinued.
- To get pharmacological effect with less drugs, less side effect.

1.2 Disadvantages

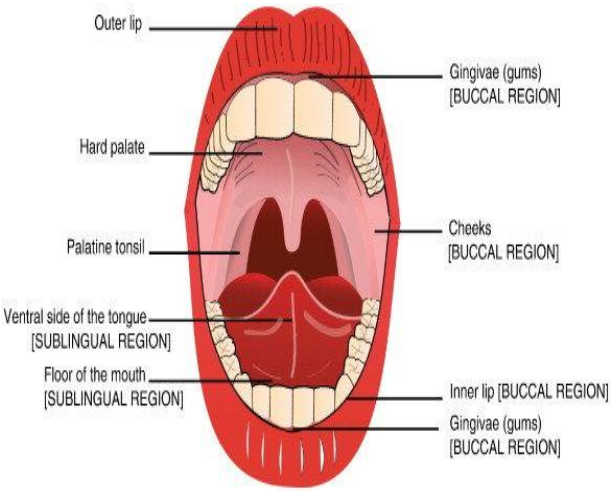
- To show Slow onset of action as compared to parenterals, liquid oral form and capsules.
- Administration of medications interferes with eating, talking and drinking.
- Unsuitable for bitter drugs.
- Area available for absorption is much less.
- Generally unsuitable for prolonged administration.

- Medication cannot be utilized when a patient is not uncooperative or conscious.

1.3 Anatomical structure of the oral mucosa

The oral cavity is separated into four regions from which absorption of drugs can take place the sublingual, buccal, gingival, and palatal regions.[5] These regions vary from each other in their histological formation and biochemical composition and the ability to retain dosage forms long enough to facilitate complete drug absorption. The sublingual membrane present on the floor of the mouth under the tongue is commonly used for both local and systemic drug delivery.[6]

The mucosal lining consists of three distinct layers. The outermost layer is the epithelial membrane composed of stratified squamous epithelial cells and acts as a protective barrier. The basement membrane is the innermost layer of the epithelial membrane. Below the epithelium lies the lamina propria followed by the submucosa. The lamina propria is a hydrated and less dense layer of connective tissue composed of collagen and elastic fibers. The oral submucosa has a rich supply of blood vessels.[7] Following absorption through the mucous membrane in the sublingual area, the drug directly diffuses into the venous blood which drains by means of the internal jugular vein, the subclavian vein, and the brachiocephalic vein directly into the superior vena cava through a general trunk. The venous return from these regions enters the systemic circulation, bypassing the hepatic metabolism, unlike oral administration. The direct flow of the drug into the systemic circulation results in better bioavailability of the drug and as wift commencement of therapeutic effect.[8]



Sublingual route of drug administration.

1.4 The mechanism of sublingual absorption

The cells of the oral epithelium and epidermis are also capable of absorbing by endocytosis (the uptake of particles by cells. These engulfed particles are generally too huge to diffuse through its wall. However, it is believed that acidic stimulation of the salivary glands, with the additional vasodilatation, facilitates absorption and uptake into the circulatory system. The salivary glands consist of lobules of cells which produce saliva through the salivary ducts into the mouth. The three pairs of salivary glands are present i.e. the parotid, the submandibular and the sublingual which lies on the floor of the mouth. The more acidic the taste, the more prominent the incitement of salivary yield; serving to maintain potential harm to acid-sensitive tooth polish by washing the mouth in bountiful killing liquid. The mouth is lined with a mucous membrane which is covered with squamous epithelium and contains mucous glands. The sublingual mucosal tissue is similar to that of buckle mucosa. In order for a medication to be effectively consumed sublingually, it needs to be able to travel across the buckle mucous membranes; by a process of diffusion known as osmosis overseeing both intestinal and sublingual retention.

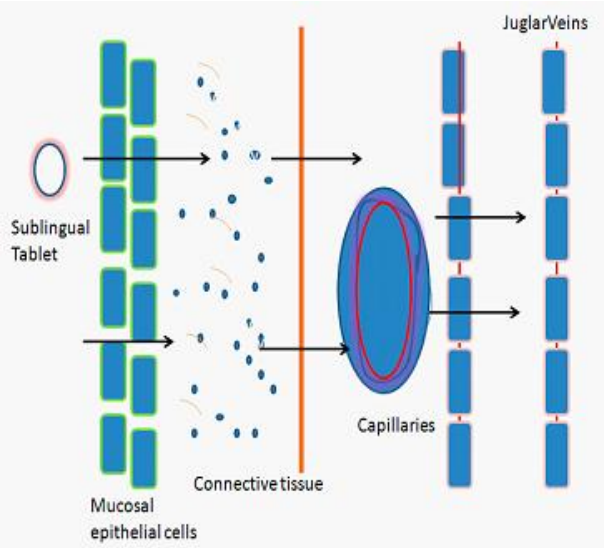


Figure: Mechanism showing sublingual absorption.

1.5 Factors affecting the sublingual absorption

1. Solubility in salivary secretion: Due to the high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of drug is necessary for absorption.[9]
2. Lipophilicity: For the medication to be retained totally through sublingual course should have somewhat higher lipid dissolvability than that required for GI ingestion which is vital for uninvolved permeation.[10]
3. Binding to oral mucosa: Systemic availability of drugs that bind to oral mucosa is poor.[9] Thickness of oral epithelium 100-200 μm is the thickness of sublingual epithelium which is not exactly buccal thickness. That's why the absorption of drugs is faster through thinner epithelium and also the immersion of drug in smaller volume of saliva is possible.[9]
4. pH and pKa of the saliva: The saliva's PH is 6.0; this pH favors the absorption of drugs which remain unionized. Also, if the pKa is greater than 2 for an

acid and less than 10 for a base, the absorption of the drugs through the oral mucosa occurs.[10]

1.6 Sublingual formulations: Sublingual formulations can be classified as:

Sublingual Tablets: Sublingual tablets are intended to be placed beneath the tongue and held until Absorption has taken place. They must dissolve or disintegrate quickly, allowing the medicament to be rapidly absorbed.

Sublingual Sprays: Sublingual sprays are the dosage forms in 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.

Sublingual Capsules: These are the solid dosage forms in which the powder was filled into capsule, it should be cut open and the contents are poured below the tongue. e. g. Nifedipine sublingual capsule.

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.

Table 1: Some popular sublingual drug with dosage form.[11]

Drug	Dosage form
Physostigmine salicylate	Sublingual Tablet
Scopolamine	Sublingual spray
Captopril	Sublingual Tablet
Furosemide	Sublingual Tablet
Nifedipine	Sublingual Tablet
Nitroglycerine	Sublingual Tablet
Vinpocetine	Sublingual Tablet
Terbutaline sulphate	Sublingual Tablet
AmlodepineBesylate	Fast dissolving sublingual tablet
Salbutamole Sulphate	Sublingual Film
Oxycodone	Sublingual spray
Fentanyl Citrate	Fast dissolving sublingual tablet
Zolmitripatn	Bioadhesive sublingual tablet
Ephedrine	Fast disintegrating sublingual tablet
Buprenorphine	Bioadhesive sublingual tablet

2. Evaluation tests

2.1 General appearance

The general appearance of a tablet is its visual identity and over all "elegance" which is essential for consumer acceptance. Include tablet's shape, taste, size, presence or absence of an colour, odour, surface texture, physical flaws and legibility of any identifying marking and consistency.[9]

2.2 Size and shape

The size and shape of the tablet can be dimensionally explained, monitored and controlled.[10]

2.3 Weight Variation

It was performed as per the method given in the USP. 20 tablets were selected randomly from each formulation, weighed separately and the average weight and % variation of weight was determined.

2.4 Hardness test

Using a Monsanto hardness tester the rigidity (hardness) of the tablet was determined.[12]

2.5 Friability

The friability of a sample of 20 tablets was estimated utilizing a Roche friabilator. 20 tablets which were previously weighed rotated at 25 rpm for 4 min. The weight loss of the tablets before and after.[13]

Measurement was calculated using the following formula----

$$\%\text{age friability} = \frac{\text{Initial wt.} - \text{Final wt.}}{\text{Initial wt.}} \times 100$$

2.6 Tablet thickness

The thickness of 3 randomly selected tablets from each formulation is determined in mm using a vernier caliper. The average values are calculated.[3,14]

2.7 Water absorption ratio

For measuring water absorption ratio, the weight of the tablet before keeping in the petri dish is noted (W_b). The wetted form of tablet was taken from petridish and reweighed (W_a). The water absorption ratio (R) can be the determined by equation.

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

2.8 Swelling property

Swelling property of the oral film is check by utilizing spit arrangement. Keep the film on the pre weighed steel mesh one part is place in the 50 ml saliva solution.

Weigh the film after specific time up to constant weight of film is come.[15]

2.9 In vitro Dissolution studies

The dissolution rate of the medication from the essential particles of the tablets is the significant factor in drug absorption. Therefore, a dissolution time is more indicative of the bioavailability of a drug from a tablet than the disintegration test.[16] Dissolution tests for sublingual tablet are done by the given monograph. The test was completed on 6 tablets using the apparatus specified in I.P. distilled water at 37ºC ± 2ºC was utilized as a breaking down 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.[9]

Table 2: Summary of general dissolution conditions.

SL. NO.	PARAMETER	SPECIFICATIONS
1	Dissolution medium	pH 6.8 phosphate buffer +0.5%
2.	Temperature	37 ±0.5 c
3.	Rotation speed	50 rpm
4	USP Type II	Paddle
5	Volume withdrawn	5 ml every 2 minutes
6	Lemda max	250 nm

The USP 1 (basket) apparatus may have certain applications for sublingual but is used less frequently due to specific physical properties of tablets.[17]

2.10 Drug Content Uniformity

Selected twenty tablets randomly and powdered. A quantity of this powder corresponding to 200mg of model drug was dissolved in 100 ml of 6.8 pH phosphate buffer, stirred for 15 min and filtered. The 1ml of filtrate was diluted with 100 ml with 6.8 pH phosphate buffer. Absorbance of this solution was measured at 250nm using**.** 6.8 pH phosphate buffer as blank and content of drug was estimated.[18]

2.11 In- vitro Disintegration Time

The disintegration time could be estimated with the help of Disintegration test apparatus. One tablet has to be placed in tube of the basket; the basket with the bottom surface made of a stainless steel screen (#10) and then it has to be immersed in 900 ml water-bath at 37 ± 1^{0}C. The time required for complete breaking down could be resolved with the assistance of a stopwatch. According to the pharmacopoeial standards, dispersible tablets must disintegrate within 3 mins.[19,20]

2. 12 Wetting Time

A piece of tissue paper folded twice was placed in a small Petri dish (ID = 6.5 cm) containing 6 mL of simulated saliva pH, a tablet was put on the amaranth powder containing paper the time required for upper surface of the tablet for formation of pink color was measured.

3. CONCLUSIONS

Compared to commonly used tablets, capsules and other oral dosage forms, sublingual absorption is generally much faster and more effective. Sublingual dosages are helpful for geriatric, pediatric and patients with swallowing difficulties, and in situations where potable fluids are not accessible. They also provide opportunity for the product line extension in the market place and extension of patent term of innovator. Sublingual absorption is efficient. Peak blood levels of most products administered sublingually are come to inside 10-15 minutes, which is much quicker than when those equivalent drugs are ingested orally.

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