ABSTRACT
Drug delivery via the oral mucous membrane is considered to be a promising alternative to the oral route. Sublingual route is a useful when rapid onset of action is desired with better patient compliance than orally ingested tablets. In terms of 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. The portion of drug absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes giving acceptable bioavailability. Various techniques can be used to formulate sublingual tablets. New sublingual technologies address many pharmaceutical and patient needs, ranging from enhanced life-cycle management to convenient dosing for pediatric, geriatric, and psychiatric patients with dysphagia. This review highlights the different sublingual dosage forms, factors affecting the sublingual absorption, advantages, various in vitro and in vivo evaluation parameters and commercially available sublingual dosage forms.

KEYWORDS: Sublingual delivery, Oral cavity, Dysphagia, Improved bioavailability.

INTRODUCTION

The term sublingual, meaning literally ‘under the tongue’ 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 oral mucosa under the tongue 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.

Through the ventral surface of the tongue and floor of the mouth. 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. 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).

Sublingual glands\cite{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.

Sublingual absorption\cite{7,8}

- Sublingual, meaning literally 'under the tongue' refers to a method of administering Substances via the mouth.
- The substances are rapidly absorbed via the blood Vessels under the tongue rather than via the digestive tract.
Impressive absorption has been attained with sublingual administration of desoxycortisone acetate, morphine, captopril, nifedipine and 17-B Oestradiol interestingly, it has also been shown that the sublingual administration of 17-B Oestradiol requires only $\frac{1}{4}$ of the oral administration.

**Mechanism of sublingual route**[^9]

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).

**Physicochemical Criteria for Sublingual Drug Delivery**[^10-16]

**Drugs Used for Sublingual Formulation**

**Advantages**

- 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 travelling and do not have immediate access to water.
- 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.
- Pre-gastric absorption can result in improved bioavailability and as a result of reduced Dosage, improved clinical performance through a reduction of unwanted effects.
Sublingual formulation

Various Sublingual formulations can be classified as Sublingual Tablet, Sublingual film, Sublingual spray and Sublingual capsules.

Sublingual Tablets\(^{[22]}\)

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.

Fast Disintegrating Sublingual Tablets\(^{[23]}\)

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\(^{[24-25]}\)

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\(^{[26]}\)

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\(^{[27]}\)

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 nutraceuticals 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.

**Evaluation**

**Hardness and thickness**[^28]

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 (Pico India). The average values are 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)**[^28]

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 was 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.

**Disintegration test**\(^{[31]}\)

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 450 angle, without agitation, to distribute any tablet particles that might mask any remaining no disintegrated 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 limit for tablet disintegration.

**Test for film**

**Tensile Strength**\(^{[30]}\)

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.

\[
\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Film thickness} \times \text{film width}}
\]

**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 content increases.

**Percent Elongation**

\[
-\frac{L}{L_0} \times 100
\]

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.

\[
\text{Young's Modulus} = \frac{\text{Slope} \times 100}{\text{Film thickness}}
\]

Folding Endurance\[^{31}\]
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\[^{32}\]
The thickness of the polymer films was measured by using screw gauge. The thickness of each strip at six different areas was determined and standard deviation was calculated.

In vitro disintegration time\[^{33}\]
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 was measured in triplicate.

Uniformity of drug content\[^{34}\]
The film of area 1x1 cm\(^2\) was cut and dissolved in 6.8 phosphate buffer solution and made up to 100 mL in a volumetric flask. Then 1 mL was withdrawn from the solution and diluted to 10 mL. The absorbance of the solution was taken at 276 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated. The test was performed in triplicate.

In-vitro dissolution studies\[^{34}\]
Dissolution study was 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 was maintained at 37±0.5°C. Samples of 5ml were withdrawn at every 4 minute Interval, filtered (through 0.45µ) and replaced with 5ml of fresh dissolution medium. The Samples were suitably diluted and estimated spectrophotometric ally at 276 nm by using ELICO-164 double beam UV-Visible Spectrophotometer. The dissolution experiments were conducted in triplicate. Dissolution rate was studied for all designed formulations and dissolution parameters were calculated acceptable time limit for tablet disintegration.
Physicochemical Criteria for Sublingual Drug Delivery\(^{11-17}\)

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

Drugs Used for Sublingual Formulation

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine</td>
<td>Sublingual spray</td>
</tr>
<tr>
<td>Captopril</td>
<td>Sublingual tablet</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Sublingual tablet</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Sublingual tablet</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Sublingual tablet</td>
</tr>
<tr>
<td>Venpocetine</td>
<td>Sublingual tablet</td>
</tr>
</tbody>
</table>

CONCLUSION

Recently many drugs have been formulated for sublingual drug delivery with an objective of rapid drug release and restricting the region of drug release to mouth. Compared to commonly used tablets, capsules and other oral dosage forms, sublingual absorption is generally much faster and more efficient. Sublingual dosages are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. 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.

REFERENCES


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