SUBLINGUAL DELIVERY: A PROMISING APPROACH TO IMPROVE BIOAVAILABILITY

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ABSTRACT
Drug delivery via oral mucous membrane is considered to be a promising alternative to the oral route which offers several advantages. Drug is administration via the sublingual mucosa (the membrane of the ventral surface of the tongue and the floor of the mouth) to the systemic circulation. Sublingual route offers several advantages such as bypasses extensive hepatic first pass metabolic process which can help to improve bioavailability, rapid onset of action, patient compliance, self-medicating. Dysphagia (difficulty in swallowing) is common among in all ages of people and more in pediatric, geriatric, psychiatric patients, drug administration without water. Sublingual mucosa of oral cavity is more permeable than buccal mucosa which is in turn is more permeable than palatal mucosa. There are many different techniques used to formulate the sublingual dosage forms. This review contains advantages, disadvantages, sublingual gland, mechanism of sublingual absorption, factor affecting on sublingual absorption and evaluation parameter of sublingual dosage form.

Keywords: Oral mucosal delivery, Sublingual drug delivery.

INTRODUCTION
Oral mucosal drug delivery is one of the alternative methods of systemic drug delivery that offers several advantages. Because the oral mucosa (sublingual) is highly vascularised, drugs directly goes to systemic circulation via sublingual drug delivery and bypassing the gastrointestinal tract and hepatic first-pass metabolism in the liver. So we achieved rapid onset of action and improve the bioavailability via a more comfortable route (sublingual) than the oral conventional route. Not all drugs can be administered through the oral mucosa because its depend upon the characteristics of the oral mucosa and the physicochemical properties of the drug.
The mucosal lining of the oral cavity are readily accessible, robust, and heal rapidly after local stress or damage. Sublingual drug delivery systems can be easily localized and are well accepted by patients which having a problem of swallowing tablet via oral route. The total surface area of the oral cavity is about 100 cm$^2$. The mucosal membranes of the oral cavity can be divided into five regions: the floor of the mouth (sublingual), the buccal mucosa (cheeks), the gums (gingiva), the palatal mucosa, and the lining of the lips. These sublingual mucosal regions are different from each other in terms of anatomy, permeability to drug, and their ability to retain a system for a desired length of time. Although the buccal mucosa is less permeable than the sublingual mucosa $^{[1]}$.

Drug delivery via the membranes of the oral cavity can be subdivided as follows:

(1) **Sublingual delivery**

Which is the administration of the drug via the sublingual mucosa (the membrane of the ventral surface of the tongue and the floor of the mouth) to the systemic circulation.

(2) **Buccal delivery**

Which is the administration of the drug via the buccal mucosa (the lining of the cheek and area between the gums and upper and lower lips) to the systemic circulation.

(3) **Local delivery**

Which is drug delivery to periodontal, gingival, and odontal delivery, for the local treatment of conditions of the oral cavity, principally aphthous ulcers, bacterial and fungal infections, and periodontal disease.

These oral mucosal sites differ greatly from one another in terms of anatomy, permeability to an applied drug, and their ability to retain the delivery system for the desired length of time $^{[2]}$.

The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and brachiocephalic vein and then drained in to systemic circulation. Onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels.
bypasses the hepatic first-pass metabolic processes. The main mechanism for the absorption of the drug into oral mucosa is via passive diffusion into the lipoidal membrane\[^{3-6}\].

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. 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.\[^6\]

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)\[^7\].

**ADVANTAGES:**\[^8\]

- Rapid onset of effect - particularly good for pain, emesis, insomnia or allergy relief
- Easy, painless, discrete and convenient self-administration
- Virtually all of drug absorbed across mucosa, none swallowed

www.pharmasm.com       IC Value – 4.01  3872
Avoids first pass liver metabolism
Less variability in therapeutic effect, more predictable pharmacokinetics
Optimal effect achieved with less drugs, less side effects
No need for water, easy for patients who have difficulty swallowing
Inexpensive to manufacture per dose
Flexible formulation options
No irritation or damage to tissues
For drug which are unstable in gastric pH.
The blood supply is rich with a capillary network close to mucosa.

DISADVANTAGES: [8].
Saliva containing drug if swallowed, then the purpose is not achieved.
Not suitable for drug which degrade in oral cavity.
Large doses of drugs cannot be administered.
Sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
Holding the dose in mouth is inconvenient, if any is swallowed that portion must be treated as an oral dose and subjected to first pass metabolism.
Not suitable for sustain release formulations.
It can’t be used when patient is uncooperative or unconscious.
The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the blood vessels. This will decrease the absorption of the medication.

SUBLINGUAL GLANDS
Salivary glands which are present in the floor of the mouth underneath the tongue. They are also known as sublingual glands. They produce mucin in turn produces saliva. The interior area of the mouth remains lubricated due to production of the saliva by the glands, which is necessary for chewing and food swallowing. (Figure 1 and 2)
The fluid which is produced by the glands gets mix with the food, so the food gets easily chewed. Due to low secretion of the saliva it can create problem in swallowing the food and potential for food lodge in the throat increases. The absorption is transfer of the drug from its site of administration into systemic circulation, so it can be said that absorption is directly proportional layer thickness. The absorption of the drug follows in this way Sublingual > Buccal > Gingival > Palatal. Due to high permeability and rich blood supply, the sublingual route can produce rapid onset of action so the drug with short delivery period can be delivered and dose regimen is frequent. The drug gets diluted in the saliva and from there the drug is adsorbed across the oral cavity.  

THE MECHANISM OF SUBLINGUAL ABSORPTION

The absorption potential of the buccal mucosa is influenced by the lipid solubility and therefore the permeability of the solution (osmosis), the ionization (pH), and the
molecular weight of the substances. For example, absorption of some drugs via the buccal mucosa is shown to increase when carrier pH is lowering (more acidic) and decrease with a lowering of pH (more alkaline).

The cells of the oral epithelium and epidermis are also capable of absorbing by endocytosis (the uptake of particles by a cell as if by hollowly wrapping itself around it. These engulfed particles are usually too large to diffuse through its wall). It is unlikely that this mechanism is used across the entire stratified epithelium. It is also unlikely that active transport processes operate within the oral mucosa. However, it is believed that acidic stimulation and uptake into the circulatory system. The mouth is lined with a mucous membrane which is covered with squamous epithelium and contains mucous glands. The buccal mucosa is similar to the sublingual mucosal tissue. The salivary glands consist of lobules of cells which secrete saliva through the salivary ducts into the mouth. The three pairs of salivary glands are the Parotid, the Submandibular and the Sublingual which lies on the floor of the mouth. The more acid the taste the greater the stimulation of salivary output, serving also to avoid potential harm to acid sensitive tooth enamel by bathing the mouth in copious neutralizing fluid. With stimulation of salivary secretion oxygen is consumed and vasodilator substances are produced, and the glandular blood flow increases, due to increased glandular metabolism. The sublingual artery travels forward to the sublingual gland, it supplies the gland and branches to the neighbouring muscles and to the mucous membranes of the mouth, tongue and gums. Two symmetrical branches travel behind the jaw bone under the tongue to meet and join at its tip. Another branches meets and anastomoses with the sub mental branches of the facial artery. The sublingual artery system stems from the lingual artery – the body’s main blood supply to the tongue and the floor of the mouth – which arises from the external carotid artery. The proximity with the internal carotid artery allows fast access to its route supplying the greater part of the cerebral hemisphere\textsuperscript{[10]}.
OSMOSIS

In order for a nutrient to be effectively absorbed sublingually, it needs to be able to travel across the buccal mucosa membranes; by a process of diffusion known as osmosis which applies to all forms of absorption by the body; governing both intestinal and sublingual absorption. The distribution of water across the cell walls depends on the osmotic difference in the blood, between the intracellular and extracellular fluid. The distribution of water across the blood vessel walls is determined by the in-vivo osmotic pressure of plasma and the total outward hydrostatic pressure. Unlike the cell membrane, the capillary wall is freely and rapidly permeable to small molecules. The diffusion of the water across a membrane that is only permeable to water depends on the molecular weight of the particle. Small particles that readily dissolve in water, rarely present a problem in permeation and diffusion, and so are able to move freely between the tissues of the body. Active transportation into cells leads to rapid metabolisation of the substances. Molecules such as glucose (fructose) and amino acids are essential for cell metabolism and special mechanisms have evolved to facilitate their rapid diffusion and permeation across cell membranes.\[10]\.

Overview of the oral cavity

Structure

Figure: 2. Structure of oral cavity\[2]\n
Figure: 3. Schematics of Oral mucosa\[2]\n
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The oral mucosa is composed of an outermost layer of stratified squamous epithelium, below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the
rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized \[2\].

**SUITABILITY OF DRUG FOR PREPARATION OF SUBLINGUAL TABLET:**

- For the drug delivering through sublingual route should have following property.
  - No bitter taste
  - Dose lowers than 20mg, e.g. nifedipine
  - Small to moderate molecular weight
  - Good stability in water and saliva
  - Partially non ionized at the oral cavities pH
  - Undergoing first pass effect e.g. ketotifen fumarate

- Many drug properties could potentially affect the performance of sublingual tablets like solubility, crystal morphology, particle size, hygroscopicity, compressibility and bulk density of drug.

- Some drugs undergoes extensive first pass metabolism which results in poor bioavailability of its oral dosage forms, that kind of drugs are suitable for sublingual dosage form.

- Drugs that are unstable in parenteral preparation are suitable for sublingual dosage form.
Many pharmaceuticals are designed for sublingual administration, including cardiovascular drugs, steroids, barbiturates, enzymes, antiemetics, vitamins, minerals and vaccines.

**FACTORS AFFECTING ABSORPTION**

- **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 necessary for passive permeation.

- **Solubility in salivary secretion**: In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of drug is necessary for absorption.

- **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 greater than 2 for an acid and less than 10 for a base.

- **Binding to oral mucosa**: Systemic availability of drugs that bind to oral mucosa is poor.

- **Thickness of oral epithelium**: As the thickness of sublingual epithelium is 100-200 μm which is less as compared to buccal thickness. So the absorption of drugs is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva.

- **Oil to water partition coefficient**: Compounds with favorable oil-to-water partition coefficients are readily absorbed through the oral mucosa. An oil-water partition coefficient range of 40-2000 is considered optimal for the drugs to be absorbed sublingually.

Different formulations for sublingual drug delivery system-

- Fast-disintegrating sublingual tablets
- Bioadhesive sublingual tablet
Thin film drug delivery
Lipid matrix sublingual tablet
Sublingual immunotherapy
Sublingual vitamin tablet

<table>
<thead>
<tr>
<th>Superdisintegrant</th>
<th>Commercilly available</th>
<th>Mechanism of action</th>
<th>Special comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross linked Cellulose</td>
<td>Crosscarmellose®</td>
<td>Swells 4-8 folds in &lt; 10 seconds. Swelling and wicking both</td>
<td>Swells in two dimensions. Direct compression or Granulation Starch free.</td>
</tr>
<tr>
<td></td>
<td>Ac-Di-Sol®, Nymce ZSX®, Primellose®, Solutab®, Vivasol®, L-HPC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross linked PVP</td>
<td>Crosspovidone M®, Kollidon®, Polyplasdone®</td>
<td>Swells very little and returns to original size after compression but act by capillary action</td>
<td>Water insoluble and spongy in nature so get porous tablet</td>
</tr>
<tr>
<td>Crosslinked starch (Sodium Starch glycolate)</td>
<td>Explotab®, Primogel®</td>
<td>Swells 7-12 folds in &lt; 30 seconds.</td>
<td>Swells in three dimensions and high level serve as sustain release matrix</td>
</tr>
<tr>
<td>Crosslinked alginic Acid</td>
<td>Alginic acid NF</td>
<td>Rapid swelling in aqueous medium or wicking action</td>
<td>Promote disintegration in both dry or wet granulation.</td>
</tr>
</tbody>
</table>
TABLE 2: MARKETED PRODUCTS OF SUBLINGUAL TABLET

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Category</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstral Fentanyl Citrate</td>
<td>Opioid Analgesic</td>
<td>50, 100, 200, 400, 600, 800 μg</td>
</tr>
<tr>
<td>Subutex Buprenorphine</td>
<td>Opioid Analgesic</td>
<td>2 and 8mg</td>
</tr>
<tr>
<td>Avitan Lorazepam</td>
<td>Antianxiety</td>
<td>1, 2 mg</td>
</tr>
<tr>
<td>Edular Zolpidem tartrate</td>
<td>Sedatives/ Hypnotics</td>
<td>5, 10 mg</td>
</tr>
<tr>
<td>Isordil Isosorbide dinitrate</td>
<td>Vasodilators</td>
<td>2.5, 5 10 mg</td>
</tr>
<tr>
<td>Suboxone Buprenorphine</td>
<td>Narcotic + Opioid antagonist</td>
<td>2/0.5, 8/2 mg</td>
</tr>
<tr>
<td>Nitrostat Nitroglycerine</td>
<td>Antianginal</td>
<td>0.3 mg, 0.4 mg, or 0.6 mg</td>
</tr>
</tbody>
</table>

EVALUATION \[^{11-27}\]

Tablets from all the formulation can be subjected to following quality control test.

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

Size and Shape:
The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet thickness:
Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Thickness of tablet is determined by using micrometer.
Uniformity of weight:
I.P. procedure for uniformity of weight is follow, take and weigh twenty tablets individually and collectively on a digital weighing balance. Calculate the average weight of one tablet from the collective weight. The limit for weight variation is given in table-3.

**TABLE 3: IP LIMITS**

<table>
<thead>
<tr>
<th>Average Weight</th>
<th>% Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg or less</td>
<td>10</td>
</tr>
<tr>
<td>80-250</td>
<td>7.5</td>
</tr>
<tr>
<td>250 &gt;</td>
<td>5</td>
</tr>
</tbody>
</table>

Tablet hardness:
Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation determine by using Hardness tester.

**Friability:**
It is measured of mechanical strength of tablets. Roche friabilator can be used to determine the friability by following procedure. A preweighed tablet is place in the friablator. Friablator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotate in the friabalator for at least 4 minutes (25rpm). At the end of test tablets are reweigh and the loss in the weight of tablet is the measure and calculate % friability.

\[
\% \text{Friability} = \frac{\text{loss in weight}}{\text{Initial weight}} \times 100
\]

Wetting time:
A piece of tissue paper (12 cm X 10.75 cm) folded twice and which will place in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet put on the paper, and measure the time for complete wetting.
Surface pH:
The surface pH of the tablets is determined in order to investigate the possibility of any side effects due to change in pH in vivo, since an acidic or alkaline pH may cause irritation to the buccal mucosa. A combined glass electrode is used for the purpose. The tablets are allowed to swell by keeping them in contact with 1.0 ml of simulated saliva for 2 hours and pH which will be noted by bringing the electrode in contact with the surface of the formulations and allowing it to equilibrate for 1.0 min.

In-vitro dispersion time:
In-vitro dispersion time is measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation are randomly selected and in vitro dispersion time is performed.

In-vitro Disintegration test:
The test is carried out on 6 tablets using the apparatus specified in I.P. 1996 distilled water at 37°C ± 2°C is used as a disintegration media and the time in seconds will take for complete disintegration of the tablet with no palpable mass remaining in the apparatus is measured in seconds.

In vitro dissolution test:
In-vitro dissolution test of sublingual tablet is carried out as per monograph of tablet.

Stability testing of drug (temperature dependent stability studies):
The tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 40 ± 1 °C
(ii) 50 ± 1 °C
(iii) 37 ±1 °C and RH 75% ± 5%

The tablets are withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the
kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25 °C.

**Test for film**

**Tensile Strength:**

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 plasticizer content increases.

\[
\text{Percent Elongation} = \frac{L \times 100}{L_0}
\]

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:

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

**Folding Endurance:**

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:
The thickness of the polymer films is measured by using screw gauge. The thickness of each strip at six different areas is determined and standard deviation is calculating [30].

**In-vitro disintegration time:**
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 [31].

**CONCLUSION**
Sublingual drug delivery has been used for formulation of many drugs with view point of rapid drug release and quick onset of action. Peak blood levels administered sublingually are achieved within 10-15 minutes, which is generally much faster than when ingested orally. Sublingual dosages are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available and who want convenient dosing without water anywhere, any time. The potential for such dosage forms is promising because strong market acceptance and patient demand. Sublingual absorption is efficient. Various types of sublingual dosage forms are available in market like tablets, films and sprays.

**References**


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