Sublingual tablets: an overview

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ABSTRACT
Oral administration is one of the most convenient forms for the intake of drug due to ease of administration, painless, versatility, and paramount patient compliance. The demand of fast disintegrating tablets has been growing, during the last decades especially for geriatric and pediatric patients due to dysphasia. So the new drug delivery known as orally disintegrating tablets came to existence. As nowadays most of the people need effective relief within a short period of time so sublingual is the most suitable form of administration. These tablets disintegrate and dissolve rapidly in saliva due to interaction with our salivary enzymes.

Introduction
Drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Dysphasia (difficulty in swallowing) is a common problem of all age groups, especially geriatrics, pediatric, and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid intake/diets have difficulties in swallowing these dosage forms [1,2]. Sublingual means under the tongue. Drugs that are given sublingually reach directly into the systemic circulation through the ventral surface of the tongue and floor of the mouth. The drug is rapidly absorbed into the reticulated vein that lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and brachiocephalic vein and then drained into the systemic circulation. Considering the oral cavity sublingual area is the most permeable part of the buccal cavity. The decreasing order of permeability in the buccal cavity is the sublingual, the buccal area (cheek), then the palatal area. The order is generally based upon the relative thickness and the extent of blood supply to the specific part [3].

Sublingual glands
The sublingual glands also known as sublingual glands are present in the floor of oral cavity i.e. underneath the tongue. These glands produce mucin and help production of saliva, necessary for breakdown. It also provides lubrication that helps in the chewing and swallowing of the 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. Low levels of saliva production can make the process of swallowing much more difficult and will increase the potential for food to lodge in the throat. Along with providing lubrication, these glands also aid in the promotion of good oral hygiene [4].
The absorption is effected by the lipid solubility and hence the permeability of the solution commonly known as osmosis, the ionization, and the molecular weight of the drug. The cells of oral epithelium adsorb the drug by the process of endocytosis. It is unlikely that the same mechanism is observed throughout the stratified epithelium. However, it is believed that acidic stimulation of the salivary glands, with the accompanying vasodilatation, facilitates absorption 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 sublingual mucosal tissue is similar to that of buccal mucosa [5,7]. 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 acidic the taste is, greater the stimulation of salivary output; serving to avoid potential harm to acid-sensitive tooth enamel by bathing the mouth in copious neutralizing fluid. The sublingual artery travels forward to the sublingual gland, it supplies the gland and branches to the neighboring muscles and to the mucous membranes of the mouth, tongue and gums. Two symmetrical branches travel behind the jawbone under the tongue to meet and join at its tip. Another branch meets and anastomoses with the submental branches of the facial artery. The sublingual artery 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 [8,9].

Factors affecting the sublingual absorption[10]

- 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.

Advantages

- Rapid onset of action is achieved as compared to the oral route.
- Liver is bypassed and also drug is protected from metabolism due to 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.
- Low dosage gives high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects.
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
- Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions e.g. asthma.
- Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of anti-anginal drugs.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

Disadvantages

- Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
- Although this site is not well suited to sustained-delivery systems.
- Sublingual medication cannot be used when a patient is uncooperative.
- The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the vessels. This will decrease the absorption of the medication.
- Various types of sublingual dosage forms are available but tablets, films and sprays are in trends these days. For the preparation of these dosage forms different methods are described depends upon the feasibility and advantages over the others.

Techniques for Preparation of ODTs [11, 14]

The techniques used to manufacture ODTs can be classified as:-
1) Conventional techniques
2) Patented techniques
- Conventional Techniques
The various conventional technologies are developed for the preparation of Orally Disintegrating drug delivery system that are Freeze drying, Spray drying, Molding, Phase transition process, Melt granulation, Sublimation, Mass Extrusion,
Cotton Candy Process, Direct compression (Meyers et al, 1995 & Makino et al, 1993). Detail of all these conventional techniques is given in Table 1.

- **Patented Techniques**
  Rapid-dissolving characteristic of ODTs is generally attributed to fast penetration of water into tablet matrix resulting in its fast disintegration. Several technologies have been developed on the basis of formulation aspects and different processes and resulting dosage forms vary on several parameters like mechanical strength, porosity, dose, stability, taste, mouth feel, dissolution rate and overall bioavailability. Table 2 represents the list of unique patented technologies, their advantages, disadvantages.

### Table 1: Conventional techniques

<table>
<thead>
<tr>
<th>S.No</th>
<th>Technique</th>
<th>Method and Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Disintegrant addition</td>
<td>Involves the addition of superdisintegrants in optimum concentration to the formulation to achieve rapid disintegration/dissolution. For e.g. MCC and sodium starch glycolate are used in formulation of Efavirenz, Crystalline cellulose (AvicelPH-102) and low substituted HPEC used in oxybutinin and pirenzepine formulation. Crospovidone used in galanthamine HBr. Crospovidone (3%w/w) and crosscarmellose Na (5%w/w) used in prochlorperazine maleate formulation. <strong>Characteristics:</strong> similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friability.</td>
</tr>
</tbody>
</table>
| 2.   | Freeze drying or lyophilization | The drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze drying. Finally the blisters are packaged and shipped. **Characteristics:** The preparations are highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability. Dose incorporated: insoluble 400mg Water soluble drug loading: 60mg **Advantages of Freeze drying**  
  - Tablets produced by this technique possess very low disintegration time.  
  - Render tablets with great mouth feel due to fast melting effect.  
  - Provides immediate dissolution (5 sec).  
  - Increases absorption and bioavailability of drug.  
  - Lyophilization is useful for heat a sensitive drug that is thermo labile substances.  
  - Tablets prepared by lyophilization disintegration rapidly in less than 5 sec due to quick penetration of saliva in pores when placed in oral cavity.  
  **Disadvantages of freeze drying**  
  - Relatively expensive and time consuming process.  
  - The product obtained is poorly stable and fragile, sensitive to humidity rendering conventional packaging unsuitable.  
  - Very poor physical resistance,  
  - High cost of production,  
  - Low dose of water-soluble drugs |
| 3.   | Moulding                   | Water-soluble ingredients with a hydro alcoholic solvent is used and is molded into tablets under pressure lower than that used in conventional tablet compression. **Characteristics:** Molded tablets are very less compact than compressed tablet porous structure that enhances disintegration/ dissolution and finally absorption increased. **Advantages:** Very rapid dissolution (5–15 s) **Disadvantages:** High cost of production, Weak mechanical strength Possible limitations in stability |
| 4.   | Sublimation                | Inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate, and hexamethyl-enetramine were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structure. **Characteristics:** Porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc. **Advantages:** Good physical resistance & highly porous structure **Disadvantages:** Harmful residual adjuvant  
  - Extra equipments for heating  
  - Not applicable to volatile and heat sensitive drugs |
| 5.   | Spray drying               | By hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating agent and an acidic material (e.g. citric acid) and / or alkali material (e.g. Sodium bicarbonate) to enhance disintegration /dissolution. **Characteristics:** Prepared tablet disintegrates within 20 seconds when immersed in an aqueous medium |
| 6.   | Mass extrusion             | Involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shape of the product into even segments using heated blade to form tablets. |
Characteristics: The dried product can be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

7 Direct compression

Characteristics: Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression.

Advantages
- Requires fewer unit operations compared with wet granulation (shorter processing time and lower energy consumption)
- Fewer stability issues for actives that are sensitive to heat or moisture
- For certain compounds, faster dissolution rates may be generated from tablets prepared by direct compression compared with wet granulation; for example, Norfloxacin.
- Fewer excipients may be needed in a direct compression formula.

Disadvantages
- Issues with segregation – these can be reduced by matching the particle size and density of the active drug substance with excipients
- In general, the drug content is limited to approximately 30% or approximately 50 mg
- Not suited for poorly flowing drug compounds
- Static charges may develop on the drug particles or excipients during mixing, which may lead to agglomeration of particles producing poor mixing

8 Compaction

(a) Melt granulation

Characteristics: Prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate not only acts as binder and increase physical resistance of tablet but also helps the disintegration of tablet.

(b) Phase transition process

Characteristics: Prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after heating process due to increase of inter particle bond induced by phase transition of lower melting point sugar alcohol.

Characteristics: The compatibility increased and so sufficient hardness gained by the formulation.

12 Tableting

(standard)

Advantages:
- Low cost of production
- Use of standard equipment/materials
- High dose
- Good physical resistance

Disadvantages:
- Significant effects of the size and hardness of the tablets on disintegration property.

Tableting (effervescent)

Advantages:
- Use of standard equipment
- High dose Good physical resistance
- Pleasant effervescent mouth feel

Disadvantages:
- Operating in controlled low humidity
- Need of totally impermeable blister

Tableting (humidity treatment)

Advantages:
- Good physical resistance.
- Pleasant mouth feel

Disadvantages:
- Extra equipments for humidification and drying
- Possible limitations in stability
- High cost of production
- Not suitable for moisture sensitive compounds
- Fragile before humidity treatment

Table 2: Patented technology [15]

<table>
<thead>
<tr>
<th>S.No</th>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zydis</td>
<td>Quick dissolution, Self preserving and increased bioavailability.</td>
<td>Expensive process, poor stability at higher Temperature &amp; humidity.</td>
</tr>
<tr>
<td>2</td>
<td>Orasolv</td>
<td>Taste-masking is twofold, quick Dissolution</td>
<td>Low mechanical strength</td>
</tr>
<tr>
<td>3</td>
<td>Durasolv</td>
<td>Higher mechanical strength than Orasolv, Good rigidity.</td>
<td>Inappropriate with larger dose.</td>
</tr>
</tbody>
</table>
Evaluation parameters [16,20]

Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests. The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blend.

- **Disintegration time (DT):** A relatively simple method with rigorous conditions was developing to evaluate the DT of sublingual tablets. Each individual tablet was dropped into 10-mL glass test tube (1.5-cm diameter) containing 2 mL distilled water, and the time required for complete tablet disintegration was observed visually and recorded using a stopwatch. The visual inspection was enhanced by gently rotating the test tube at a 45° angle, without agitation, to distribute any tablet particles that might mask any remaining undisintegrated 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, 22 and 2 minutes is specified as the acceptable time limit for tablet disintegration.

- **Wetting time (WT):** Although a wetting test is not a USP standard test, 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 at the center of 2 layers of absorbent paper fitted into a rectangular plastic dish (11 cm × 7.5 cm). After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch.

- **Angle of repose:** For the angle of repose of the material was poured through a funnel to form a cone. The tip of the funnel should be held closed to the growing cone and slowly raised as the pile grows, to minimize the impact of falling particles. Stop pouring the material when the pile reached a predetermined height or the base a predetermined width. Rather than attempt to measure the angle of the resulting cone directly, divide the height by half the width of the base of the cone. The inverse tangent of this ratio is the angle of repose. Formula for angle of repose:

\[
tan \theta = \frac{h}{r}
\]

\( h = \) height of pile, \( r = \) radius of pile

<table>
<thead>
<tr>
<th>Angle of repose</th>
<th>Flow properties</th>
</tr>
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<tbody>
<tr>
<td>&lt;25</td>
<td>Excellent</td>
</tr>
<tr>
<td>25-30</td>
<td>Good</td>
</tr>
<tr>
<td>30-40</td>
<td>Passable</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Very poor</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Table 3: Angle of repose</th>
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</thead>
<tbody>
<tr>
<td><strong>Angle of repose</strong></td>
</tr>
<tr>
<td>&lt;25</td>
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<tr>
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<tr>
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<tr>
<td>Passable</td>
</tr>
<tr>
<td>Very poor</td>
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</table>

- **Bulk density:** – Bulk density of was determined by taking a known mass of powder in a 50 ml graduated measuring cylinder which is attached to the bulk density apparatus. The bulk density was calculated by following eq.

\[
\text{Bulk density} = \frac{\text{weight of powder in gm}}{\text{bulk vol. of powder}}
\]

- **Tapped density:** Tapped density was determined by tapping method using measuring cylinder containing weighed amount of powder. The cylinder was dropped 3 times from a height of 1 inch at an interval of 2 sec. tapped density was calculated by following eq.

\[
\text{Tapped density} = \frac{\text{mass of powder}}{\text{vol. of powder after tapping}}
\]

- **Carrs compressibility index:** This is an important property in maintaining uniform weight. It is calculated by using following formula.

\[
\% \text{compressibility index} = \left( \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \right) \times 100
\]
Table 4: Carr’s index

<table>
<thead>
<tr>
<th>Compressibility (carr’s index)</th>
<th>Flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-12</td>
<td>Free flowing</td>
</tr>
<tr>
<td>12-16</td>
<td>Good flow</td>
</tr>
<tr>
<td>18-21</td>
<td>Fair</td>
</tr>
<tr>
<td>23-35</td>
<td>Poor</td>
</tr>
<tr>
<td>33-38</td>
<td>Very poor</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Extremely poor</td>
</tr>
</tbody>
</table>

- **Hausner’s ratio:** A similar index to indicate the flow properties can be defined by Hausner’s ratio. Hausner’s ratio can be calculated by using following formula:

\[
\text{Hausner’s ratio} = \frac{(\text{Tapped density} \times 100)}{\text{bulk density}}
\]

Table 5: Hausner’s ratio

<table>
<thead>
<tr>
<th>Hausner’s ratio</th>
<th>Flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.25</td>
<td>Good flow</td>
</tr>
<tr>
<td>&gt;1.25</td>
<td>Poor flow</td>
</tr>
</tbody>
</table>

- **Weight variation:** 20 tablets were selected at random, individually weighed and the average weight was calculated. None of the tablets deviated from the average weight by more than ±7.5%.

- **Hardness test:** Tablets require a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks. The hardness of tablet was measured by Monsanto hardness tester. The hardness of sublingual tablet is important factor, because if the sublingual tablet is too hard, the solvent borne drug attenuation may not be absorbed into an interior portion of the tablet and therefore remains on a surface portion of the tablet, where the drug attenuation may not adhere to the sublingual tablet. If the sublingual tablet is too soft, the sublingual tablet may be disintegrated by the solvent of the drug attenuation.

- **Friability:** Twenty tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dusted, and reweighed. The percentage friability of the tablets was calculated by:

\[
\% \text{ friability} = \frac{\text{initial weight} - \text{final weight}}{\text{final weight}} \times 100
\]

Conclusion

The study revealed that the sublingual tablets have proved to be better patient compliance and better way of drug delivery for pediatric and geriatric patients. Sublingual drug deliveries have been used for formulation of many drugs especially for the drugs that require the rapid onset of action. These tablets overcome the difficulty in swallowing convenient tablet. The target population has expanded to those who want convenient tablets without water. The drug content of the tablets enters the systemic circulation through various glands present in sub lingual cavity. And thus rapid onset of action is achieved.

Reference

12. Meyers GL., Battist GE., Fuisz RC., Process and apparatus for making rapidly dissolving dosage units and


17. USP/NF. Official Monographs: Nitroglycerin Tablets.

