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Review Article

Sublingual Route for the Systemic Delivery of Drugs

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ABSTRACT

Sublingual delivery is one of the most effective alternate routes when compared with the oral drug delivery. A small amount of saliva is needed for complete disintegration of the sublingual tablets which shows more potent action and bioavailability. Sublingual route is more suitable for the geriatric and pediatric patients as they find it difficult for swallowing the oral dosage forms. The drug absorbed through the sublingual route bypasses the hepatic first–pass metabolism thus enhancing more bioavailability with lower doses and lower side effects. Relative thinness and rich blood supply of the sublingual mucous membrane provides a unique opportunity for systemic delivery of such drugs. Many pharmaceuticals are designed for sublingual administration, including cardiovascular drugs, steroids, barbiturates, enzymes, and increasingly, vitamins and minerals.

Keywords: Sublingual delivery, hepatic first–pass metabolism, pharmaceuticals

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INTRODUCTION

The sublingual route is a preferable route for the local and systemic administration of certain drugs. This process of delivery of drugs through the sublingual route has few distinct advantages over the oral drug delivery due to the presence of the rich supply of blood vessels beneath the mucosa, enhanced bioavailability, rapid onset of action, avoidance of hepatic fast pass metabolism and easy self medication.

Systemic delivery of drug through the sublingual route provides an immediate onset of pharmacological effect. Sublingual administration of the drug means placement of the drug beneath the tongue through which blood reaches directly into the blood stream through the ventral surface of the tongue and floor of the mouth. Through the reticulated veins the drug solutes are rapidly absorbed underneath the oral mucosa and transported through the facial veins, internal jugular veins, and braciocephalic vein and then drained into the systemic circulation.
The retention of the medication through the sublingual course is 3 to 10 times more prominent than oral course and is just surpassed by hypodermic infusion. For this a little volume of saliva is adequate for crumbling of the tablet in the oral cavity.

Drugs accessible as sublingual tablets are Isosorbide dinitrate, Nitroglycerin, Fentanyl citrate, Buprenorphine hydrochloride, Ergotamine tartrate, Ergoloid mesylates, Asenapine (Saphris), Buprenorphine hydrochloride and naloxone hydrochloride, Zolpidem tartrate (Intermezzo) and many more drugs.

Drug delivery can be classified into three categories:

1. Sublingual delivery, systemic delivery of drug beneath the tongue,
2. buccal delivery, drug administration through the linings of cheeks i.e. buccal mucosa, and
3. Local delivery, which is drug delivery into oral cavity for local action.

The main mechanism of absorption of drugs through the oral mucosa is via passive diffusion into the lipoidal membrane. The absorption of drugs through the sublingual route is 3-10 times greater than the oral route. Sublingual absorption is mostly rapid in action, but also short acting in duration. Nitroglycerin, for example, is an effective antianginal drug but is extensively metabolized when taken orally (>90%). It is generally absorbed through the sublingual mucosa and its peak plasma level is reached within 1-2 min. Many of the factors are considered during the sublingual absorption of drugs:-

1. Lipid solubility of drug
2. Saliva pH and pKa
3. Oral epithelium thickness
4. Partition coefficient

Many pharmaceuticals are designed for sublingual administration, including cardiovascular drugs, steroids, barbiturates, enzymes, and increasingly, vitamins and minerals.

Advantages of sublingual tablets over oral tablets

- 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 gastro intestinal 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 antianginal drugs.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

Formulations for sublingual drug delivery

1. **Fast disintegrating sublingual tablets:** These types of tablets generally disintegrate or dissolve rapidly in the mouth of patients, convenient for geriatric and pediatric patients who have difficulties in swallowing. These sublingual tablets are generally preferred over the conventional solid oral dosage forms.
2. **Bioadhesive sublingual tablets:** It is made up of mixture consisting of water soluble carrier, fine drug particles and a bioadhesive component. Bioadhesive sublingual tablets have a more retention time in the oral cavity thus providing a systemic drug delivery.
3. **Thin film drug delivery:** As compared to the fast disintegrating process, thin film

dissolves more rapidly. They are easy to carry dosage form and do not require any special packaging moreover they are less friable. The drug enters the systemic circulation with reduced hepatic fast pass effect. They are site specific as availability of large surface area promotes rapid disintegration and dissolution in the oral cavity.

4. **Lipid matrix sublingual tablet:** They are formulated using sublingual and liposomal technologies to promote a faster and more complete absorption of dosage forms. Lipid matrix sublingual tablets are often prepared for many specially nutraceuticals which are taken orally.
5. **Sublingual immunotherapy:** Drops of the dosage form are put under the tongue. Dosage forms of mast cell stabilizers, anti-histamines and local steroids are manufactured under this process. It has a greater advantage over subcutaneous immunotherapy for safe treatment of allergic rhinitis. It has a greater clinical efficacy and safety over the conventional dosage forms.
6. **Sublingual vitamin tablet:** Vitamin B12 is one of the most widely used sublingual tablets. It is recommended for taken orally which helps to maintain our body metabolism.

Table 1: Drugs used in sublingual tablets

Drug	Category	Dosage form
Ramipril	Antihypertensive agent	Tablet
Captopril	Antihypertensive agent	Tablet
Furosemide	Diuretic	Tablet
Ondansetron HCL	Antiemetic	Film
Salbutamol sulphate	Antiasthmatic agent	Film
Scopolamine	Opoid analgesic	Spray

Table 2: Excipients used in sublingual tablets

Excipients	Uses
Sodium Starch Glycolate	Superdisintegrant
Cross Carmellose Sodium	Superdisintegrant
Crospovidone	Superdisintegrant
HPMC	Tablet binder, Stablizing agent
Lactose Monohydrate	Diluent, Tablet binder

Absorption of drug through the sublingual region

The salivary pH is in the range of 5.5 to 7.0 and the saliva consists of mucus and enzymes such as amylase and carboxylesterase and forms a cohesive gelatinous film on all surfaces of the oral cavity. Mucoadhesion occurs due to the cohesiveness of the sublingual membrane leading to drug absorption. The epithelial membrane in the sublingual region is 100-200µm thick and is non-keratinised. As the supply of blood is maximum into the oral mucosa it allows fast absorption and increases the bioavailability of certain drugs after sublingual administration. Hence the sublingual region is one of the best sites for achieving maximum effect of a particular drug with rapid onset of action.

The absorption of the drug through the sublingual route is mainly affected by the lipid solubility and hence the permeability of the solution commonly known as osmosis, the molecular weight of the drug and ionization. Mucous membrane which is covered with squamous epithelium and contains mucous glands, sublingual mucosal tissue is similar to that of buccal mucosa.

The three pairs of salivary glands with the help of which absorption takes place are:-

1. The parotid
2. The submandibular
3. The sublingual

In addition to high lipid solubility of the drug the drug should also be soluble in aqueous buccal fluid i.e. biphasic solubility of drug is necessary for absorption. Moreover the two major routes in drug permeation through the oral mucosa are: the transcellular or intracellular route (where drugs permeate directly through the cells), and the paracellular or intercellular route (where drugs permeate by passive diffusion through space between the cells). From the above two routes of drug permeation, the paracellular route is mostly favoured for the hydrophilic drugs such as peptides/proteins which dissolve more readily in the aqueous fluids filling the intercellular space.

Cells of the oral epithelium and epidermis are also capable of performing endocytosis. The engulfed particles are usually too large to diffuse through the walls. This mechanism is used unlikely across the entire stratified epithelium. Again the acidic

stimulation of the salivary glands, accompanying vasodilation, facilates the absorption of drugs. Thus, the process of absorption of drugs through sublingual route provides an great ease and also the bioavailability of certain drugs gets increased. The saliva proves out to be a major factor in promoting the drugs to get absorbed through this region.

Manufacturing Techniques used in sublingual tablet Formulation

Direct Compression:- The commercial method which is used in the manufacture of sublingual tablets is the direct compression method. It is a simple, cost-effective and efficient process, as it employs ingredients that can be blended well and do not require further granulation steps prior to lubrication and compression. Sublingual tablets manufactured using direct compression possesses good mechanical strength and fast disintegration.

This method is mostly suitable for the heat labile drugs. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. The size of the tablet and its hardness must be generally maintained according to the specification for its disintegration and solubilization. This technique can now be applied to fast dissolving tablets because of the availability of improved tablet excipients, especially superdisintegrants like cross carmellose sodium, microcrystalline cellulose, crosspovidone, sodium starch glucolate and partially substituted hydroxypropyl cellulose, effervescent agents (citric acid, sodium bicarbonate) and sugar based excipients (dextrose, fructose, isomalt, maltitok, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose, and xylitol)

Sugar based agents are now being widely used as bulking agents as they posses high aqueous solubility, sweetness, good taste masking and pleasant mouth feel.

Tablet Moulding: - Water soluble ingredients are used in this technology such as the tablet disintegrates and dissolves rapidly. In this method the powder blend is generally moistened with a hydro alcoholic solvent and is molded into tablets by the process of compression method. Air drying is used to remove the solvent. Binding agents such as sucrose, acacia or poly vinyl pyrrolidine gradually increases the mechanical strength of the tablet.

Spray Drying: - Spray dryers are widely used in the pharmaceuticals and biochemical process. They produce highly porous and fine powders and the solvent is evaporated during the process. Rapidly disintegrating tablets with the help of support matrix are produced with the help of other components such as bulking agents, sodium starch glycolate, acidic material like citric acid and alkali like sodium bicarbonate which increases its disintegration and dissolution.

Freeze Drying: - As compared to the direct compression method, freeze drying consumes more time and is much costlier producing tablets of poor mechanical strength. Tablets manufactured by this method generally have high porosity and dissolve instantly. Drugs which are heat sensitive can be produced by this method. Here an aqueous solution of a carrier is made where the drug is dispersed or dissolved. The mixture of the drug with the aqueous solution is finally poured into the wells of the blister packs. The trays are then passed through liquid nitrogen where the drug solution gradually freezes up. Blister packs are then kept in refrigerated chambers to continue the freeze drying process. Finally they are packed and shipped out.

Mass Extrusion: - Using the mixture of water soluble polyethylene glycol and methanol the active blend is softened, and expulsion of a softened mass through a syringe to get a cylinder of the product into even segments using heated blades to form tablets. Here the bitter tasting drugs and their granules can be coated to mask the bitter taste.

Evaluation Parameters

Disintegration Time (DT):- It is a simple method which is used to evaluate the disintegration time of sublingual tablets. It contains a glass test tube of 10ml, where each tablets are dropped containing 2ml of distilled water. Again, the time required is gradually noted for the complete disintegration of the tablets using a stopwatch.

Wetting Time (WT):- A minimal quantity of water is taken in this test and the time required for penetration of the moisture into the tablets is measured. This test confirms the release of the drug in the presence of minute quantity of saliva. An absorbent paper which is fitted into a rectangular plastic dish is taken where the tablets are placed at the centre position. The time required to diffuse the water from the absorbent paper to the tablets are noted using a stopwatch.

Surface pH: - Due to change in pH (in vivo) the surface pH of the tablets must be determined for any possible side effects. Acidic or alkaline pH may cause irritation to the buccal mucosa. A glass rod is used for the purpose where the tablets are allowed to swell by keeping them in contact with 1.0 ml of saliva for 2 hrs and the pH is noted by bringing the electrode in contact with the surface of the formulation and is allowed to equilibrate for 1 minute. The surface pH is determined.

Angle of Repose: - Here, the powder material is poured through a funnel which forms a cone. When the pile of the powder reaches a predetermined height, stop pouring the material. Measure the angle of cone relative to its height and the base with the predetermined width. Divide the height by half the width of the base of the cone.

$$\tan\theta = h/r$$

Where, h= height of the pile, r = radius of the pile.

Table 3: Angle of repose as an indication of powder flow properties

Angle of repose	Flow properties
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk Density: - Bulk density is determined by taking a graduated cylinder of 50ml which is generally attached to a bulk density apparatus. Bulk density can be calculated by the following equation-

Bulk density = weight of powder in gm/ bulk volume of the powder.

Tapped Density: - It is determined by placing a graduated cylinder which is filled up by the drug and excipients blend. The cylinder is then tapped from the bottom which results in filling up of the empty voids between the particles. The tapping is continued until no further change in volume is noted. It is calculated by the following formula.

Tapped Density= Weight of the powder/Volume of the tapped packing.

Compressibility Index:- Compressibility index of a blend can be determined by the compressibility index measurement. It is calculated by the following formula-

Compressibility index (%)= [(TD-BD)x100]/TD]

Uniformity of Weight:- Uniformity of weight is followed according to the procedure given in IP. As such twenty tablets are taken and their weights are determined individually with the help of a digital weighing balance. The average weight of a single tablet is then determined by the collective weights of twenty tablets.

Table 4: Pharmaceutical limits for weight variation according to Indian pharmacopoeia

Average weight of tablets	% variation allowed
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

Hardness and Thickness: - Ten tablets are taken and their thickness is determined using a micrometer. The force which is applied across the diameter of the tablet in order to break the tablet is defined as the hardness of the tablet. Chipping, abrasion or breakage of a tablet during handling or transportation generally depends on the strength of the tablet i.e. hardness. Instrument which is used to determine the hardness of a tablet is the Monsanto hardness tester.

Friability:- Roche Friabilator is the instrument which is used to determine the friability of a tablet. It consists of a plastic chamber which revolves at a speed of about 25 rpm dropping down the tablets from a distance of 6 inches in each revolution. The tablets are rotated in the friabilator for about 4 minutes. Tablets are then dusted and reweighed, the loss in the original weight is the measure of friability and is expressed in percentage as –

% Friability= loss in weight/Initial weight x 100

Disintegration Test: - This test is carried out using the apparatus filled up with distilled water at 37^0C $\pm$ 2^0C, using 6 tablets. Time taken is recorded in seconds until no palable mass remains in the apparatus.

Drug Content: - Ten tablets are selected randomly from the formulation and are powdered finely. Drug is accurately weight and is transferred to a 100ml volumetric flask containing solution of a desired pH. The flask is shaken gradually to mix the contents. The volume is made up to the mark and the solution is filtered out. 1 ml of the filtrate is simply diluted and the drug content is estimated using a double beam UV Spectrophotometer. The procedure is repeated thrice to calculate the average value to determine the drug content.

In-Vitro dissolution studies: - Dissolution studies are carried out using USP paddle type apparatus containing salivary fluid of pH 6.8 as a dissolution medium at 50 rpm. Temperature is maintained at 37 ± 0.5^0C. 5 ml of the samples are withdrawn at every 4 minute interval of time and are gradually filtered and replaced with 5 ml of fresh dissolution medium. The samples are again diluted and are

estimated using a double beam UV-Visible Spectrophotometer at 276 nm. The above procedure is repeated for almost three times and the dissolution parameters are calculated.

Table 5: Patented Technologies for Sublingual Tablets

S.No	Technique	Advantages	Disadvantages
1.	Ziplet	Good mechanical strength	As soluble component dissolves, rate of water diffusion in the tablet is decreased.
2.	Zydis	Quick dissolution and increased bioavailability	At higher temperature and humidity it is poorly stable and is expensive process.
3.	Duraslov	Higher mechanical strength and good rigidity	Inappropriate with larger doses.
4.	Orasolv	Two fold taste masking, good dissolution	Low mechanical strength
5.	Wow tab	Hardness and dissolution rate is adequate	Moderate bioavailability
6.	Oraquick	Good for heat sensitive drugs	-
7.	Flashtab	Conventional tableting technology	-
8.	Flashdose	High dissolution	Limit to heat sensitive drugs

Table 6: Patents of sublingual medications

Patent No	Title	Inventor	Assignee	US Classification
US3428728	Timed release sublingual medications	Paul Meredith Terrill	Eli Lilly and company	514|509
US3873727	Stabilization of molded sublingual nitroglycerin tablets	Paul Meredith Terrill	Eli Lilly and company	514|509

Table 7: Marketed products of sublingual tablets

Brand Name	Drug	Category
Nitrostat	Nitro-glycerin	Antianginal
Avitan	Lorazepam	Antianxiety
Edular	Zolpidem Tartrate	Sedatives/Hypnotics
Abstral	Fentanyl Citrate	Opiod analgesic
Subulex	Buprenorphine	Opiod analgesic
Isordil	Isosorbide Dinitrate	Vasodilators
Suboxone	Buprenorphine	Narcotic +Opioid antagonists

Conclusion

With the help of sublingual drug delivery system rapid drug release can be achieved. Compared to the oral dosage forms, sublingual route of drug delivery is generally much faster and more efficient. It a convenient dose for young and elderly patients who have difficulty in swallowing. Peak blood levels are achieved within 10-15 minutes of administration as compared to the oral dosage forms. Various types of commercially available sublingual dosage forms have been discussed in the above table.

Future Prospects

Delivery of drugs such as proteins and peptides are one of the most suitable candidates which can be given through sublingual route of administration as they have limited bioavailability when administered through conventional tablet. Enhanced oral protein delivery technologies by ODTS which release the drug in the oral cavity has very high advantage for delivery of high molecular weight proteins and peptides.

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