



REVIEW ARTICLE

Sublingual Drug Delivery: An Extensive Review

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ABSTRACT

The demand of fast disintegrating tablets has been growing during the last decade, due to the characteristics of fast disintegrating sublingual tablets for the potential emergency treatment. 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. Drug delivery through the oral mucous membrane is considered to be a promising alternative to the oral route. Fast disintegrating sublingual tablets may lead to significant improvements over current treatment options for specific patient group, for instance pediatric and geriatric patients. This review highlights the mechanism of sublingual absorption, factors affecting sublingual absorption, formulation techniques, types of sublingual tablets, advantages, evaluation parameters and commercially available sublingual dosage forms.

KEYWORDS

Angina, Dysphagia, Improved Bioavailability, Sublingual Delivery, Technique

INTRODUCTION

Tablet that disintegrate or dissolve rapidly in the patient mouth are convenient for young children, elderly patients, mentally retarded and bedridden patients who used to suffer most probably with the problem of dysphagia and hand tremors. Sublingual tablet when placed in the mouth, rapidly get dispersed or dissolved and swallowed in the form of liquid. When sublingual tablets placed under the tongue, it produces immediate systemic effect by enabling the drug absorbed quickly or directly through mucosal lining of the mouth beneath the tongue. The drug absorbed from stomach goes to mesenteric circulation which connects through portal vein. Thus absorption through oral cavity avoid first pass metabolism.

The sublingual tablets are usually small and flat, compressed lightly to keep them soft. The tablets must dissolve quickly allowing the API to be absorbed quickly. It is designed to dissolve in small quantity of saliva; after the tablet is placed in the mouth below the tongue, the patient should avoid eating, drinking, smoking and possibly talking in order to keep the tablet in place. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological action¹⁻³. Sublingual products have been designed for numerous indications ranging from migraine (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). Sublingual route provides 3-10 times greater absorption of the drug than oral route and is only surpassed by hypodermic injection. Sublingual route is very much appropriate for short acting drugs. Most of

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the drugs which are administered through the sublingual route are absorbed by simple diffusion; here the sublingual area acts like a litmus paper readily soaking up the substances; however not all the substances are permeable and accessible to oral mucosa. Majority of drugs which are administered through sublingual route falls in the category of antianginal drug. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolic processes⁴. Because of under developed muscular and nervous system swallowing problems is common in children, and this could be easily overcome with the help of fast disintegrating sublingual tablets. Oral route of drug administration has been considered as the most popular one because it holds an edge over other routes such as it is the most natural, uncomplicated, convenient, safe means to administer drugs, greater flexibility in dosage form design, ease of production and low cost. By selecting the appropriate pharmaceutical excipients in the correct proportion, in combination with optimal manufacturing techniques the sublingual tablets could be prepared effectively⁵. In past few days oral mucosa including buccal mucosa and sublingual mucosa has received much attention compared to conventional oral administration.

Asenapine sublingual tablets provide improved bioavailability which is used for the treatment of schizophrenia and manic/mixed episodes of bipolar disorder. Asenapine when administered sublingually its bioavailability comes out to be 35% but only, less than 2% if ingested orally. Asenapine sublingual tablets are available in 5mg and 10mg strengths which dissolve in saliva within approximately 10 seconds⁶. In the same way Manidipine sublingual tablets could be given to adult and elderly patients who are suffering from hypertension⁷. Patients with cystic fibrosis in order to improve their quality of life are going for lung transplantation and in this case

sublingual Tacrolimus for immunosuppression in lung transplantation proves to be a best alternative in cystic fibrosis. Sublingual Tacrolimus a new calcineurin inhibitor provides pharmacokinetic advantages such as good permeability, rapid absorption, acceptable bioavailability and easy accessibility. From an economic point of view sublingual route holds an edge over intravenous route^{8,9}.

Sublingual Glands

Another name of sublingual gland is salivary glands which are present in the floor of the mouth, underneath the tongue. Drugs having short delivery and infrequent dosing regimen could be delivered successfully through sublingual route because of high permeability and rich blood supply, the sublingual route produces a rapid onset of action. A good oral hygiene could be promoted with the help of sublingual glands. Sublingual glands are also known for their binding and lubricating functions, and sublingual gland secretion makes the food slippery and easily swallowable. High content of saliva in the masticated food helps the food to move without any difficulty.

Saliva secretion plays a major role in shaping the principle physiological environment of oral cavity in terms of pH, fluid volume and composition. Saliva secretion has been promoted by 3 major salivary glands which are parotid, submaxillary, sublingual glands. However minor salivary or buccal glands are also involved in saliva secretions which are situated in or immediately below the mucosa. Saliva regulates oral microbial flora by maintaining the oral pH and enzyme activity. Sublingual glands are known for their viscous saliva with limited enzymatic activity whereas parotid and submaxillary gland produces watery secretion. Saliva helps in lubricating the oral cavity; it facilitates swallowing and prevents demineralization of the teeth. Approximately 0.5-2.0L of saliva has been secreted by salivary gland. However the volume of saliva which is available constantly is around 1.1ml, thus providing a relatively low fluid volume available for drug release from delivery systems compared

to GIT. If we compare the GI fluid and saliva, saliva is relatively less viscous. The flow rate of saliva which depends on 3 factors like the time of day, the type of stimulus and the degree of stimulation.

Table 1: Thickness and Surface Area of oral cavity membranes

Oral Cavity Membrane	Thickness	Surface Area
Buccal mucosa	500-600	5.2
Sublingual mucosa	100-200	26.5
Gingival mucosa	200	-
Palatal	250	20.1

Figure 1: shows mechanism of transportation of drugs through sublingual route into the arterial circulation¹⁸

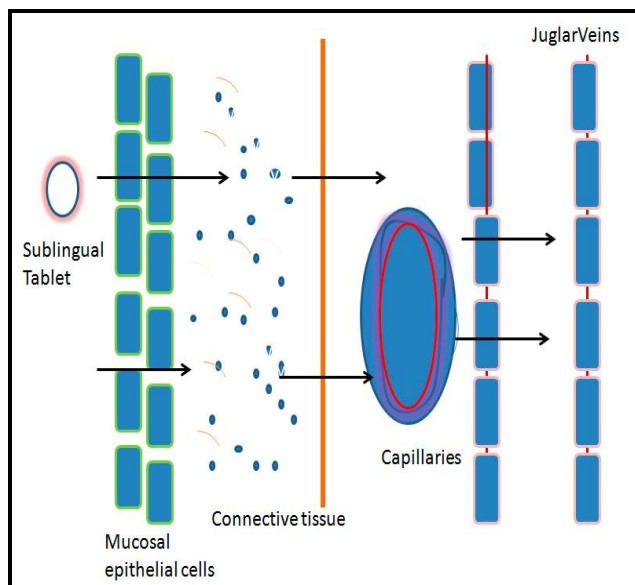


Figure 1: Mechanism showing sublingual absorption of drugs

Drugs for Sublingual Administration

Sublingual drug administration is applied in the field of cardiovascular drugs, steroids, some barbiturates and enzymes. It has been a

developing field in the administration of many vitamins and minerals which are found to be readily and thoroughly absorbed by this method. Nutrition which are absorbed sublingually avoids exposure to the gastric system and liver, means direct nutritional benefits particularly important for sufferers of gastrointestinal difficulties such as ulcers, hyperactive gut, coeliac disease, those with compromised digestion. Drugs like cardiovascular drugs such as nitrites and nitrates, analgesics such as morphine, antihypertensive such as nifedipine, bronchodilators such as fenoterol could be administered successfully through sublingual route to show their rapid onset of action. Treatment of angina pectoris, hypertension, and antiatherosclerotic activity could be done effectively with the sublingual dosage form because it offers the fast release of drug from the formulation and it reaches the systemic circulation directly which bypasses the first pass metabolism of drugs. Fast disintegrating sublingual tablets could be used for the potential emergency treatment. The demand of fast disintegrating sublingual tablets has been increasing day by day because of the swallowing difficulties of geriatric and pediatric patients. Because of easy administration and better patient compliance, fast disintegrating sublingual formulations has become popular as NDDS (NOVEL DRUG DELIVERY SYSTEM).

Drugs like lisinopril could be delivered through sublingual route for the treatment of hypertension which is caused by obesity, stress, decreased physical activity, increased salt intake, and decreased calcium and potassium intake. Treatment of cardiovascular disease could be done effectively because it offers faster disintegration of tablet, faster onset of action, and rapid absorption of drug by sublingual mucosa blood vessels. Moreover, drug candidates that undergo pregastric absorption when formulated as ODT may show increased oral bioavailability. Sublingual route is mostly useful for fastest onset of action as in the case of angina pectoris. The use of an ODT formulation of ondansetron has been found to be helpful in the treatment of children as young as 6 months of age suffering from gastroenteritis and dehydration¹⁹⁻²¹.

Advantages of Sublingual Tablets

- When sublingual tablets placed under the tongue, it produces immediate systemic effect by enabling the drug absorbed quickly or directly through mucosal lining of the mouth beneath the tongue.
- Dose gets reduce
- Onset of action is very fast
- Improved bioavailability
- Less side effects
- Effective in disease like nausea, vomiting, migraine, schizophrenia.
- No need of water for administering tablet
- Provides sustained drug delivery
- Ease of drug administration gets increased
- Sublingual area is much more permeable than buccal area
- Bypass GI tract and hepatic portal system, therefore it increases the bioavailability of orally administered drugs that otherwise undergo hepatic first pass metabolism^{22, 23}.

Disadvantages of Sublingual Tablets

- Area available for absorption is much less
- Unsuitable for bitter drugs
- Poor Patient compliance
- Eating, drinking, and smoking is not allowed
- Administration of highly ionic drug is not allowed
- Administration of high dose is not possible^{24, 25}.

Mechanism of Sublingual Absorption

The absorption potential of oral mucosa is influenced by the lipid solubility and therefore the permeability of the solution, ionization potential, pH, molecular weight of the substance. Absorption of some drugs through oral mucosa is shown to increase when carrier pH is increasing (more acidic) and decrease with a lowering pH (more alkaline). Cells of oral epithelium and

epidermis are also capable of absorbing by endocytosis (the uptake of particles by a cell as if by wrapping itself around it). These engulfed particles are usually too large to diffuse through its wall. The oral cavity is highly acceptable by the patients; the mucosa is relatively permeable with rich blood supply. It is robust and shows short recovery times after stress or damage and the virtual lack of langerhans cell makes the mucosa tolerant to potential allergens. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery. Besides the biochemical characteristics of the buccal and sublingual membrane which are responsible for the barrier functions and permeability. Various factors of the drug molecule influence the extent of permeation through the membrane lipid solubility, degree of ionization, pKa of the drug, pH of the drug solution, presence of saliva, membrane characteristics, molecular weight and size of the drug. Various physicochemical properties of the formulation and the presence or absence of permeation enhancers all affect the absorption and permeation of drugs through oral mucosa. However oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within gastrointestinal tract. So there has been a growing interest in the delivery of the therapeutic agents through various transmucosal routes to provide a therapeutic amount of the drug to the proper site in body to promptly achieve and then maintain the desired concentration. The sublingual route provides rapid absorption and acceptable bioavailability of many drugs and is one of the most convenient, accessible and well accepted route. The sublingual mucosa is considered to be more permeable than buccal area and it is not able to provide the rapid absorption and good bioavailability. The sublingual mucosa is difficult for device placement because it lacks an expanse of smooth muscles or immobile mucosa and is constantly washed by a considerable amount of saliva. Because of high permeability and rich blood supply sublingual route provides a rapid onset of action. Moreover the absorption of drugs through the highly vascular lining of mouth moves the

drug through the sublingual or buccal capillaries and veins to the jugular veins and superior vena cava directly to the heart and arterial circulation, without passing the liver, thus avoiding hepatic first pass metabolism. Moreover drugs showing poor and erratic absorption from the stomach; or intestine can be administered through the oral mucosa²⁶⁻²⁸.

Types of Sublingual Tablets

Fast Disintegrating Sublingual Tablets

Tablets that disintegrate or dissolve rapidly in the patients mouth are convenient for young children, the elderly; (pediatric, geriatric) patients with swallowing difficulties and in situations where potable liquids are not available. FDT is defined as a solid dosage form that contains medicinal substance and disintegrates rapidly (within few seconds) without water when kept on tongue. The drug is released, dissolved, or dispersed in saliva and then swallowed and absorbed across the GIT. FDT in general offers improved convenience and are frequently preferred over conventional solid oral dosage forms. ODT may lead to significant improvements over current treatment options for specific patient group, for instance pediatric patients. The European medicines agency committee for medicinal products for human use (CHMP) described ODT as having great promise for children. The potential benefits of ODT formulation could be fully realized by considering the additional requirements of this group. The size and disintegration time play a very important role in commercial potential of the formulation. A fast disintegration time reduces any choking hazard and will also make it harder to spit out the dose. Similarly the taste and texture of pediatric formulation are critical to facilitate compliance in children, particularly in chronic conditions where repeated administration may be an issue. FDT sublingual tablets may show increased oral bioavailability. From the perspective of pharmaceutical industry, sublingual tablets may provide new business opportunities in the form of product differentiation, line extension and life cycle management, exclusivity, uniqueness and patent

life extension. ODT tablets are also called as orodispersible tablets, quick disintegrating tablets, and mouth dissolving tablets, fast disintegrating, fast dissolving, porous tablets, rapid dissolving tablets, and rapimelts. Water- wicking and swelling are the 2 most important mechanisms of disintegrant action for most of the sublingual tablets. Table 2 depicts the excipients used in formulation of sublingual tablets. Water- wicking is the ability to draw water into the tablet matrix. Both the extent of water uptake and rate of water uptake are critically important. Exposure to water can cause ingredients to swell and exert pressure against surrounding tablet or capsule ingredients causing existing bonds between particles to break. In most of the sublingual tablets-sodium starch glycolate has been to promote rapid disintegration and dissolution of solid dosage form^{29, 30}.

Bioadhesive Sublingual Tablets

The new sublingual tablet concept presented is based on interactive mixtures consisting of a water soluble carrier covered with fine drug particles and a bioadhesive component. With this approach it is possible to obtain a rapid dissolution in combination with bioadhesive retention of the drug in the oral cavity³¹.

Lipid Matrix Sublingual Tablets

Lipid matrix sublingual tablets is a bioavailable, quick, convenient and consistent dosage forms for many specially nutraceuticals that are often taken orally. Lipid matrix sublingual tablets is 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

Sublingual Vitamin Tablets

The only sublingual vitamin that all doctors recommend is vitamin B12 (cyanocobalamin). Vitamin B12 is very much helpful in our body metabolism. It is recommended to be taken orally.

Sublingual Immunotherapy

Sublingual immunotherapy, or SLIT, is a form of immunotherapy that involves putting drops of

allergen extracts under the tongue. SLIT is usually delivered 1 of 2 ways-drops or tablets of allergen extracts are placed under the tongue, then either swallowed or spat out. Sublingual immunotherapy is very much helpful in the case of SAC (seasonal allergic conjunctivitis) and PAC (Perennial allergic conjunctivitis) which are spreading at a much faster rate among people who are working in industries and it needs longer sublingual immunotherapy, often one year around with mast cell stabilizers, antihistamines and sometimes local steroids. Conjunctivitis additionally needs corticosteroids and if needed cyclosporine drops are administered for longer time. WHO (WORLD HEALTH ORGANISATION) recommends SIT (allergen specific immunotherapy) for the patients with severe allergic conjunctivitis or asthma. SIT involves the monthly vaccination lasting for 3 years and this therapy may have side effects such as anaphylactic reactions. Therefore other administration routes have been considered such as sublingual immunotherapy (SLIT) with daily administration for at least 3 year is a new promising and safe alternative for SIT. Sublingual immunotherapy has an advantage over subcutaneous immunotherapy and it is one of the most effective and safe treatment for allergic-rhinitis. SLIT has gained ample evidence of efficacy and safety and in some European countries is currently used more frequently than sublingual immunotherapy (SCIT). Apart from its better safety profile, the advantage of SLIT over SCIT are with regard to compliance, which is higher because SLIT does not need to be administered in a medical setting and is much more cost-effective, but the desired outcome exist only if SLIT meets its needs. In recent years sublingual immunotherapy has emerged as an actual treatment option because of its clinical efficacy and safety.

Technology used in Preparation of Sublingual Tablets

Among different techniques which could be used for the formulation of sublingual tablets are as follows-freeze drying technology, spray drying technology, sublimation method, and direct compression technology. Direct compression

could be considered as an ideal method for formulating sublingual tablets because of following edges which it holds over other methods-

- Doesn't require water or heat during formulation
- More economic in comparison to other procedures
- Fewer manufacturing steps and pieces of equipment
- Reduces labor costs
- Less process validation
- Lower consumption of power
- Avoidance of high compaction pressure involves in producing tablets by slugging or roll compaction
- Greater stability of tablets on aging
- Prime particle dissociation. Each primary drug particle is liberated from the tablet mass and is available for dissolution. Disintegrate rapidly to the primary particle size.
- Elimination of granulation process.
- No pretreatment of the powder blend is required
- Elimination of variabilities in wet granulation process³².

Direct compression is one of these techniques which require incorporation of a superdisintegrant into the formulation or use of highly water soluble excipients to achieve fast tablet disintegration. Direct compression is appropriate for chemicals with flowing and cohesive properties. Direct compression is the ideal method for heat-labile medications; However the direct compression method is very sensitive to the changes in the type and proportional of excipients and in the compression forces, when used to achieve tablets of suitable hardness without compromising the rapid disintegration characteristics; unique packaging methods such as strip packaging, could be used to compensate for the problem of extreme

friability of rapidly disintegrating tablets. Bi et al were the first to evaluate the ideal excipients proportions and other related parameters using a superdisintegrant in order to formulate durable fast disintegrating sublingual tablets for oral administration^{33, 34}. A combination of superdisintegrants i.e, sodium starch glycolate; croscarmellose sodium, crospovidone were used along with directly compressible mannitol to enhance mouth feel. In the present date orodispersible tablets are designed with a view to enhance patient compliance. To improve the compression characteristics of the mixture-Some powder are difficult to compress even if adhesive is incorporated but granules of same formulation can be much more easily compressed. The granulation of toxic material will reduce the hazard of generation of toxic dust which may arise when handling powders. The materials which are slightly hygroscopic can lead to cohesion, hygroscopic. The term direct compression is used to define the process by which tablets are compressed directly from powder-blends of active ingredient and suitable excipients which will flow uniformly in the die cavity and forms a firm compact. Direct compression methods are very popular because it reduces the number of steps involved and the materials required. The choice of superdisintegrants for a tablet for a tablet formulation depends largely on the nature of drug being used. Water-soluble material tends to dissolve rather than disintegrate if an appropriate amount of disintegrant is included in the formulation. The correlation between tablet disintegration and dissolution is not always observable. Lubricants are the agents that act by reducing friction by interposing an intermediate layer between the tablet constituents and the die-wall during compression and ejection. Lubricants are classified according to their water-solubility. Lubricants are most effective when used at lower concentration than water-soluble lubricants. They tend to retard the drug dissolution rate as they decrease the effective drug-solvent interfacial area by changing the surface characteristics of the tablets. To formulate rapidly disintegrating or dissolving tablets direct compression is one of the cheapest and convenient techniques. Direct

compression is one of the best techniques to achieve tablets of suitable hardness without compromising the rapid disintegration characteristics, extremely fast tablet disintegration would be required to enhance the release of drug from tablets for rapid absorption by the sublingual mucosa blood vessels³⁵.

Challenges in Direct Compression Technology

Like any other process, direct compression has its own technical issues; among which the most important are-

- High weight and dose variation of the tablets
- Low mechanical strength of the tablets
- Capping and lamination of the tablets
- Adhesion or sticking of powder material on punch tips
- High friction during tablet ejection.

In direct compression properties of powder intended to be formed tablets and the design, condition of the press play an important role in this technology. It should be ensured that the powder possesses adequate physical properties and also that a suitable well conditioned tablet press is used in terms of the use of forced-feed devices; and polished, smooth dies and punches. Important technical properties of a powder which must be controlled to ensure the success of a tableting operation are-

- Homogeneity and segregation tendency
- Flowability
- Compressibility
- Compactability
- Friction and adhesion properties of the powder³⁶

Fast Melting Technology

It is known to be one of the most innovated methods in oral drug delivery system, is a rapidly growing area of drug delivery. The initial success of the FMT formulation led to the development of various technologies. These technologies, however still have some limitation also.

FROSTA-a new technology used for making FMT.

The frosta technology utilizes the conventional wet- granulation process and tablet press for cost-effective production in tablets, the frosta tablets are mechanically strong with friability of <1% and are stable in accelerated stability conditions, when packaged in bottle containers. They are robust enough to be packaged in multi-tablet vials. The initial success of the FMT formulation led to the development of different technologies; the FMT technologies can be classified as follows-

- Freeze drying
- Molding/Sublimation
- Compression

Whatever technology is used, the important properties of successful FMT are instant absorption of water into the core of the tablets and then fast disintegration of associated particles into separate components.

FMT technology has certain advantages-

- Easy handling
- Low cost of production
- Easy administration
- No suffocation risk³⁷⁻³⁹.

Sublimaton

The basic principle involved in preparing fast dissolving tablets by sublimation technique is addition of a volatile salt to the tableting component to obtain a substantially homogeneous mixture and volatilizing salt. The removal of volatilizing salt creates pores in the tablet, which helps in achieving rapid disintegration when the tablet comes in contact with saliva.

The tablets were subjected to vacuum at 80°C for 50 min to eliminate volatile components and thus create pores in the tablet; volatile salts such as camphor, ammonium bicarbonate, naphthalene, urea etc; were also used as sublimable components to prepare porous tablets^{40, 41}.

Lyophilization

It is one of the most common processing methods for removing moisture from biopharmaceuticals and it also increases the stability, tolerance and shelf-life of these products. It is one of the well-established processes within the industry.

Advantages

- It improves the stability of pharmaceutical products.
- Drying takes place at very low temperature therefore enzyme action gets inhibited.
- Final dry product occupies the same volume as the original solution.
- Yield highly soluble products
- Proteins don't get denatured as occur with other drying methods.

Disadvantages

- It yields a very hygroscopic product.
- Slow process
- It requires complicated plant which is very expensive. Uses
- The method is applied only to prepare biological products for example-
- Antibiotics (other than penicillin)
- Blood products and Vaccines (such as BCG, Yellow fever, Smallpox).

Evaluation of Sublingual Tablets

General Appearance

The general appearance of the tablet and overall elegance is very much important for consumer-acceptance. Therefore the organoleptic properties such as Colour, Taste, Shape and size should be evaluated properly.

Hardness

The hardness of the tablet could be determined using the Monsanto hardness tester (cadmach). The tablet is placed diagonally between the 2 plungers of the tablet hardness tester; and then pressure is applied until the tablet broke down

into two pieces; and the reading on the scale is noted down⁴².

Friability

The friability of the tablet could be determined with the help of a Roche Fibrillator. Friability is a measure of the mechanical strength of the tablet. 10 or 20 preweighed tablets are placed in the fibrillator and then it has to be rotated at a speed of 25 rpm for 4 mins. Finally % weight loss should be calculated. The weight loss should not be more than 1%⁴³.

$$\% \text{ FRIABILITY} = \frac{\text{Loss in weight}}{\text{Initial weight}} \times 100$$

Uniformity of Weight

It could be determined with the help of a digital weighing balance. The weight of one tablet could be determined from the collective weight of all tablets. The individual tablets are weighed on a digital weighing balance and then it has to be compared with the average weight. In table 3 IP limits for weight variation is shown⁴⁴.

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