



SUBLINGUAL MUCOSA AS A ROUTE FOR SYSTEMIC DRUG DELIVERY

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ABSTRACT

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

Keywords: Sublingual delivery, Oral cavity, Dysphagia, Improved bioavailability

INTRODUCTION

Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Dysphagia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/diets have difficulties in swallowing these dosage forms^{1,2}.

Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The 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 braciocephalic vein and then drained in to systemic circulation.

The main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane³. 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 delivered⁴.

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)⁵.

Sublingual glands

Sublingual glands are also known as the salivary glands which are present in the floor of mouth underneath the tongue. These glands produce mucin and help to promote the production of saliva. Because of the secretions of the glands, the interior area of the mouth is kept lubricated, which is necessary for chewing and swallowing food.

The lubrication and binding functions of the sublingual glands cannot be underestimated. A secretion from the glands mix with food as it is chewed, making the material slippery and easily swallowed. Because of the saliva content of the masticated food, it can move without difficulty into the throat and on to the digestive tract. 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.

Absorption means transfer of drug from its site of administration to the systemic circulation, so it is obvious that absorption is directly proportional to the membrane layer thickness. Sublingual > Buccal > Gingival > Palatal having mucosa thickness of 100-200, 200, 250, 500-600 micrometer respectively. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action which makes it an appropriate route for drugs with short delivery period and in frequent dosing regimen. The drug is released in to saliva and its subsequent spreading may cause the drug to be absorbed across the oral cavity⁶.

Sublingual absorption

Sublingual, meaning literally 'under the tongue' refers to a method of administering substances via the mouth in such a way that the substances are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract. There is considerable evidence that most sublingual substances are absorbed by simple diffusion; the sublingual area acting rather like litmus paper, readily soaking up the substances. However, not all substances are permeable and accessible to oral mucosa.

One of the best known drugs used regularly with great success is Glyceryl trinitrate - a potent coronary vasodilator which is used for the rapid symptomatic relief of angina. It has been found impressively effective when administered sublingually; pharmacologically active after only 1 - 2 minutes. The administration via an aerosol spray was found to provide rapid relief of symptoms, with first-class metabolism. The extent of first-

class metabolism when compared to the sublingual spray decreased to 48% with sublingual tablets and 28% with the oral dose. Following sublingual administration, nitrate appears in plasma concentrations can be maintained for 24 hours⁷.

Sublingual Verapamil (a calcium channel antagonist prescribed for the management of angina, hypertension and certain supraventricular arrhythmias) was effective in controlling the ventricular rate following sublingual administration⁸. Experiments with some analgesics showed many-times more rapid absorption from the mouth than the less lipid-soluble morphine. Impressive absorption has been attained with sublingual administration of desoxycortisone acetate, morphine, captopril, nifedipine and 17-B Oestradiol – interestingly, it has also been shown that the sublingual administration of 17-B Oestradiol requires only 1/4 of the oral dose.

Mechanics of sublingual absorption

The absorption potential of oral 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 oral mucosa is shown to increase when carrier pH is lowering (more acidic) and decrease with a lowering of pH (more alkaline)^{7,9}.

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 of the salivary glands, with the accompanying vasodilation, 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 mucosa¹².

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 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^{10,11}.

Osmosis

In order for a drug to be effectively absorbed sublingually, it needs to be able to travel across the buccal mucous 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 cell walls depends on the osmotic difference in the blood between the intracellular and extracellular fluid. 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 membranes¹¹.

Drugs for sublingual administration

Medically, 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. Sublingually absorbed nutrition, which avoids exposure to the gastric system and liver, means direct nutritional benefits, particularly important for sufferers of gastro-intestinal difficulties such as ulcers, hyperactive gut, coeliac disease, those with compromised digestion, the elderly and invalids – the nutritional benefit is independent of gastro-intestinal influences^{12,13}. Examples of drugs administered by this route include antianginal like nitrites and nitrates, anti hypertensive like nifedipine, analgesics like morphine and bronchodilators like fenoterol. Certain steroids like estradiol and peptides like oxytocin can also be administered e.g. fentanyl citrate, apomorphine, prochlorperazine dimaleate {PRO}, and hydrazine HCl {HYD},

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

Factors affecting the sublingual absorption¹⁴

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

- A relatively rapid onset of action can be achieved compared to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- Liver is bypassed and also drug is protected from degradation due to pH and 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 antianginal 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 can not be used when a 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.

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.

Method of preparation of sublingual formulations

Sublingual tablets

Various techniques can be used to formulate sublingual tablets. Direct compression is one of the techniques which require the incorporation of a superdisintegrant into the formulation, or the use of highly water-soluble excipients to achieve fast tablet disintegration. Direct compression does not require the use of water or heat during the formulation procedure and is the ideal method for moisture and heat-labile medications. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressible tablet's disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent. Disintegration efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness^{15, 16}.

Films

Solvent casting is a process which comprises of casting a dope from a casting die onto a casting support, drying the cast dope on the casting support form film, stripping off the film from the casting support, and further drying the film while conveying the film with carrying it at both side edges of the film by a pin tenter, wherein residual volatile component content of both side edges of the film being carried by the pin tenter is from 30 mass % to 320 mass % of solid matter at the beginning of being cared by the pin tenter¹⁷. Solvent Evaporation technique can also be used instead of solvent casting for the preparation of sublingual films.

Sublingual sprays are also in trend which improves the time to reach maximum plasma concentration as compared to other types of sublingual dosage forms. E.g. in case of oxycodone, maximum plasma concentrations is reached with in 20 minutes when compared with immediate release oral tablets (1.3 hours), intramuscular (1 hour), and intranasal oxycodone (0.42 hour) in healthy volunteers⁸.

In Vitro and In Vivo Evaluation

Physical evaluation

All batches of sublingual formulations like tablets and films were evaluated for weight variation and drug content. But hardness and friability were calculated for tablets. As 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. Preferably, the solvent borne drug attenuation should be absorbed into the interior of the sublingual tablet. Weight variation test was conducted by selecting 20 tablets at random as

per I.P. Sublingual films were also evaluated for thickness using micrometer screw gauge¹⁸, tensile strength¹⁹, folding endurance¹⁹, surface pH²⁰, and swelling index²¹.

Disintegration time (DT)

A relatively simple method with rigorous conditions was developed 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 disintegration²³.

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. Tablet WT was measured by a procedure modified from that reported by Bi et al.²⁴ 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.

In vivo evaluation

Pharmacokinetic data analysis and bioavailability evaluation

Rabbits have been described as one of the few laboratory animals that do not have keratinized mucosa, thus closely resembling human sublingual mucosal tissue²⁵.

The maximal plasma concentration (C_{max}) and the time to reach maximum plasma concentration (T_{max}) can be directly obtained from the plasma data. The area under the plasma concentration-curve (AUC) can also be calculated using the trapezoidal rule and then the bioavailability.

Permeation studies

Ex vivo permeation studies through porcine oral mucosa is carried out using the modified Franz diffusion cell of internal diameter of 2.5 cm. The buccal mucosa was excised and trimmed evenly from the sides and then washed in isotonic phosphate buffer of pH 6.6 and used immediately. The membrane was stabilized before mounting to remove the soluble components. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 200 ml of isotonic phosphate buffer of pH 7.4 which was maintained at 37±0.2°C and hydrodynamics were maintained by stirring with a magnetic bead at 50 rpm. One film of dimension 2 cm X 2 cm and previously moistened with a few drops of simulated saliva. The donor compartment was filled with 1ml of simulated saliva of pH 6.8. Samples were withdrawn at suitable interval replacing the same amount with fresh medium^{26, 27}. The percentage of drug permeated was determined by measuring the absorbance in a UV-Visible spectrophotometer.

Recent developments

Nitroglycerine-delivering sublingual aerosol formulation (nitroglycerine in propellants) in a metered-dose spraying pump, Nitrolingual spray, was developed. It delivers nitroglycerine by spraying onto or under the tongue in the form of spray droplets, which ultimately increase the absorption and hence the bioavailability of nitroglycerine. The rapid onset of action is always required in case of hypertension.

CONCLUSION

Recently many drugs have been formulated for sublingual drug delivery with an objective of rapid drug release and restricting the region of drug release to mouth. Compared to commonly used tablets, capsules and other oral dosage forms, sublingual absorption is generally much faster and more efficient. Sublingual dosages are convenient for young children, the elderly and patients with

swallowing difficulties, and in situations where potable liquids are not available. Peak blood levels of most products administered sublingually are achieved within 10-15 minutes, which is generally much faster than when those same drugs are ingested orally. Sublingual absorption is efficient. The percent of each dose absorbed is generally higher than that achieved by means of oral ingestion. Various types of sublingual dosage forms are available in market like tablets, films and sprays.

Table 1: Drugs used in the formulation of sublingual dosage forms

Drug	Category	Dosage form	References
Physostigmine salicylate	Anti-Alzheimer's	Tablet	28
Scopolamine	Opioid analgesic	Spray	29
Captopril	Anti-hypertensive Agent	Tablet	30
Furosemide	Diuretic	Tablet	31
Nifedipine	Anti-anginal	Tablet	32
Nitroglycerine	Anti-anginal	Tablet	33
Vinpocetine	Neutropic Agent	Tablet	34
Terbutaline sulphate	Bronchodilator	Tablet	35
Amlodipine besylate	Anti hypertensive	Tablet	36
Ondansetron Hydrochloride	Anti emetic	Film	19
Salbutamol sulphate	Anti-asthmatic agent	Film	37

Table 2: Some marketed sublingual tablets

Brand Name	Drug	Category	Strength
Abstral	Fentanyl Citrate	Opioid Analgesic	50, 100, 200, 300, 400, 600, 800 µg
Subutex	Buprenorphine	Opioid Analgesic	2 and 8mg
Avitan	Lorazepam	Antianxiety	1, 2 mg
Edular	Zolpidem tartrate	Sedatives/ Hypnotics	5, 10 mg
Isordil	Isosorbide dinitate	Vasodilators	2.5, 5 10mg
Nicorette Microtab Lemon	Nicotine bitartrate		2m
Suboxone	Buprenorphine hydrochloride+ naloxone	Narcotic + Opioid antagonist	2/0.5, 8/2 mg
Saphris	Asenapine	Antipsychotic agent	5, 10mg
Prohealth Melatonin	Melatonin	Hormone	2mg
Nitrostat	Nitroglycerine	Antianginal	0.3 mg (1/200 grain), 0.4 mg (1/150 grain), or 0.6 mg (1/100 grain)
Temgesic	Buprenorphine	Opioid Analgesic	200 µg

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