



REVIEW ARTICLE

Design of Sublingual Drug Delivery System: A Review

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ABSTRACT

Therapeutic efficacy of a drug is not simply function of its intrinsic pharmacological activity but also depends upon the drug delivery system or route of administration. The most common route of drug administration is oral route in which drug is swallowed and absorbed in systemic circulation through membrane gastrointestinal track. But due to common problem of dysphasia number of population finds difficulty in swallowing the conventional dosage form. In this case it is essential to go for an alternative route of drug administration. Among the various alternative routes available for drug delivery the Oromucosal route of drug delivery is the most preferred one because it offers several advantages such as ease of administration, rich vascularized mucosal linings offering better absorption. Oromucosal route of drug delivery includes sublingual route and buccal route. The sublingual route provides rapid onset of action while buccal route is preferred for sustained drug delivery. The current review highlights the rationales of drug for sublingual drug delivery, various sublingual dosage forms and their evaluation parameters.

KEYWORDS

Oral Mucosa, Sublingual Route, Rationales of Sublingual Drug Delivery, Evaluation Parameters

INTRODUCTION

The term sublingual, meaning literally 'under the tongue' refers to a method of administering drug substances via mouth in such a way that the drug substances are rapidly absorbed in systemic circulation via highly vascularised oral mucosa under the tongue rather than digestive tract. The route of absorption of drug through highly vascularised oral mucosa allows direct access of drug substance to the blood

Circulation, thus providing rapid onset of action.¹

It is estimated that 25% of the population find difficulty in swallowing conventional solid dosage forms like tablets and capsules and therefore do not take their medication as prescribed by the physician resulting in high incidence of non-compliance and ineffective therapy. Mainly this difficulty is experienced in particular by pediatrics and geriatric patients. It also applies to people who are bedridden and to those active working patient who are busy travelling, especially those who have no access to water.² In order to overcome all these problems related to administration of drug by

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oral route it is essential to develop alternative routes for administration of drug.³

Alternative absorptive mucosa are being considered as potential sites for drug administration include the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity. These transmucosal routes of drug delivery offer distinct advantages over peroral administration for systemic drug delivery such as possible bypass of the first pass effect and avoidance of presystemic elimination within the gastrointestinal tract.⁴

Advantages of Transmucosal Route over Per-Oral Route of Drug Administration^{5,6}

- The drug is not exposed to destructive acidic environment of the stomach.
- Therapeutic plasma concentration of the drug can be achieved more rapidly.
- The drug enters directly to the systemic circulation and bypasses the first pass.
- With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated.
- Delivery of drug can be terminated more easily when compared to other dosage forms.

Among the various transmucosal routes, the oral mucosa represents the most popular route of drug administration due to high patient compliance and unique physiological features of oral mucosa like highly vascularised structure with excellent permeability. Because of this drugs that are absorbed through the oral mucosa directly enter into the systemic circulation and give rapid onset of action. It also bypasses the gastrointestinal tract and first pass hepatic metabolism.⁷

Drug delivery via the membranes of the oral cavity can be subdivided as sublingual delivery, buccal delivery and periodontal, gingival, and odontal delivery. Sublingual delivery means the administration of the drug via the sublingual mucosa (the membrane of the ventral surface of

the tongue and the floor of the mouth) to the systemic circulation; buccal delivery means the administration of the drug via the buccal mucosa (the lining of the cheek and area between the gums and upper and lower lips) to the systemic circulation; and periodontal, gingival, and odontal delivery, for the local treatment of conditions of the oral cavity, principally aphthous ulcers, bacterial and fungal infections, and periodontal disease. These oral mucosal sites differ greatly from one another in terms of anatomy, permeability to an applied drug, and their ability to retain the delivery system for the desired period of time.⁸

As the oral mucosa is highly vascularized any drug diffusing across the oral mucosal membrane has direct access to the systemic circulation via capillaries and venous drainage and it bypasses the hepatic first pass metabolism. The rate of blood flow through the oral mucosa is substantial, and is generally not considered to be the rate limiting factor in the absorption of drugs by this route. For oral delivery through the gastrointestinal tract, the drug goes through a rather hostile environment before absorption. This includes a drastic change in gastrointestinal pH (from pH 1–2 in the stomach to 7–7.4 in the distal intestine), unpredictable gastrointestinal transit, the presence of numerous digestive enzymes and the intestinal flora. In contrast to this harsh environment of the gastrointestinal tract, the oral cavity offers relatively consistent and favorable physiological conditions for drug delivery. This is maintained by the continuous secretion of saliva. Compared to secretions of the gastrointestinal tract, saliva is a relatively mobile fluid with less mucin, limited enzymatic activity and virtually no proteases. Enzyme degradation in the gastrointestinal tract is a major concern for oral drug delivery. In comparison, the buccal and sublingual regions have less enzymes and lower enzyme activity, which makes it favorable especially to protein and peptide delivery.⁹

Drug permeability through the oral (e.g. buccal/sublingual) mucosa represents the major

Table 1: Characteristics of Oral Mucosa¹⁰

Tissue	Structure	Thickness (µm)	Turnover Time (Day)	Surface area(cm ²) ±SD	Permeability	Residence time	Blood flow*
Buccal	NK	500-600	5-7	50.2± 2.9	Intermediate	Intermediate	20.3
Sublingual	NK	100-200	20	26.5±4,2	Very good	Poor	12.2
Gingival	K	200	-	-	Poor	Intermediate	19.5
Palatal	K	250	24	20.1±1.9	Poor	Very good	7.0

NK is non-keratinized tissue, K is keratinized tissue, * In rhesus monkeys (ml/min/100g tissue).

physiological barrier for oral transmucosal drug delivery. The oral mucosal thickness varies depending on the site as does the composition of the epithelium. The characteristics of the different regions of interest in the oral cavity are shown in Table 1.

The oral mucosa which are subjected to mechanical stress (the gingiva and hard palate) are keratinized while the mucosa of the soft palate, sublingual, and buccal regions, are not keratinized. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function.

These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and have only small amounts of ceramides. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides.

Thus these epithelia are considerably more permeable to water than keratinized epithelia.^{4,11} Sublingual drug delivery is more commonly used to get immediate onset of pharmacological effect to treat acute disorders, whereas the buccal route is chosen when a prolonged release of drug is needed as in case of chronic disorders.³

Suitability of Drugs for Sublingual Drug Delivery

Although the oral sublingual mucosa is rich in

vascularature, but not all drugs, however, can be administered by the oral sublingual mucosal route. The absorption of administered drug via sublingual route is influenced by the characteristics of the oral mucosa and the physicochemical properties of the drug.¹ There are certain criteria's which are to be fulfill by drug to get absorbed by sublingual route given in Table 2.

Table 2: Physicochemical Criteria for Sublingual Drug Delivery^{9,12,13,14,15,16,17}

Physicochemical Properties of Drug	Accepted Range
Dose	< 20 mg
Taste	Not intensely bitter
Stability	Good stability in water & saliva
Molecular weight	Small to moderate (163.3-342.3)
pKa	>2 for acidic Drug < 10 for basic Drug
Log p	1.6 to 3.3
Lipophilicity	lipophillic
No. of hydrogen bond acceptor site	1 to 5 (2.93)
No. of hydrogen bond donar site	0 to 2.5 (1.26)
Polar surface area	13.0 to 66.0 (38.1)
Number of Ratable bonds	0.5 to 6 (3.30)

Mechanisms Involved in Drug Absorption across the Oral Mucosa

The main mechanism involved in drug transfer across the oral mucosa is passive diffusion, although facilitated diffusion has also been shown to take place for some drug substances primarily with nutrients. Passive diffusion involves the movement of a drug from the region of higher concentration to the region of lower concentration across biological membrane. Then the drug further diffuses into the venous capillary system and eventually reaches to the systemic circulation via the jugular vein. The physicochemical characteristics of a drug are very important for the diffusion process. Although passive diffusion is undoubtedly the major transport mechanism for drugs, the absorption of nutrients from the oral cavity has been shown to involve carrier systems (facilitated diffusion), which lead to a more rapid absorption than the concentration gradient (Passive diffusion).¹⁸

Advantages of Sublingual Drug Delivery¹²

- A relatively rapid onset of action can be achieved compared to the oral route.
- Ease of termination of therapy if required.
- Bypasses first pass effect and improve bioavailability.
- Protect the drug from hostile environment of gastrointestinal tract.
- Improved patient compliance due to ease of administration.
- Rapid and extensive drug absorption due to rich vasculature.
- Most preferred route in emergencies.
- Fast disintegration or dissolution in the oral cavity, without need for water.

Disadvantages¹²

- Administration of drugs interferes with eating, drinking, and talking.
- Generally unsuitable for prolonged administration.

- Not well suited for sustained drug delivery systems.

Sublingual Formulations

These formulations are designed to administer through the sublingual mucosa i.e. through mucosal lining of oral cavity beneath the tongue to give immediate systemic effect. Various Sublingual formulations can be classified as Sublingual Tablet, Sublingual film, Sublingual spray and Sublingual capsules.

Sublingual Tablets

The sublingual tablets are usually small, flat and compressed lightly to keep them soft. These tablets are designed in such a way that they must dissolve quickly in small quantity of saliva and allow the drug to be absorbed through the sublingual mucosa. The various types of sublingual tablets commonly used are Fast disintegrating sublingual tablets, Bioadhesive sublingual tablets and Lipid matrix sublingual tablets.

Fast Disintegrating Sublingual Tablets

These tablets disintegrate or dissolve rapidly in the mouth. The small volume of saliva is usually sufficient to result in rapid tablet disintegration in the oral cavity. The medication can then be absorbed into the systemic circulation from blood vessels in the sublingual mucosa. The sublingual route usually produces a faster onset of action than orally ingested conventional tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes. Various Techniques can be employed are heat based technologies like cotton candy process, melt extrusion process, tablet molding technique and sublimation process or technologies like lyophilization, direct compression method and effervescent system.¹⁹

Bioadhesive Sublingual Tablets

Bioadhesion is usually defined as the bond formation between two biological surfaces or between a biological surface and a synthetic surface. Problem associated with sublingual tablet formulations is the swallowing parts of

the dose of the drug by patient before it has been released and absorbed into the systemic circulation through sublingual mucosa. Addition of a bioadhesive component to the formulation is a well-known approach of increasing the probability of a more site-specific drug release. However, this concept is normally applied to non-disintegrating tablets or discs in order to extend the release of the active substance hence such a system may not be suitable for an immediate-release formulation. This problem can be overcome by dry mixing of carrier particles with fine dry particles of a bioadhesive material to form an interactive mixture. These small, bioadhesive units could then replace the large, bioadhesive, single unit (tablet or disc). It is then theoretically possible to add the active substance to the surface of these carrier particles, resulting in ordered units comprising coarse particles carrying both bioadhesive component and drug. After compression, tablets composed of these units would have the potential to rapidly disintegrate and release the units to adhere to the sublingual mucosa. Provided the drug is instantly dissolved and be able to permeate the mucous membranes easily, it will be rapidly absorbed at the administration site before there is a chance of it being swallowed.^{20,21}

Lipid Matrix Sublingual Tablets

These tablets are 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. The lipid matrix sublingual tablet is a bioavailable, quick, convenient and consistent dosage form for many neutraceuticals that are often taken orally.²²

Sublingual Film Drug Delivery

These are thin films that dissolve when in contact with saliva and release the drug in oral cavity. These films also referred as fast dissolving films or strip. Such film typically designed for oral administration and dissolve within 1 min when placed in the mouth without drinking or chewing. Sublingual films are

prepared for patients having chocking problem with tablet dosage form.^{23,24}

Sublingual Spray

Sublingual sprays are the dosage forms in which the drug is dissolved or dispersed in a vehicle and filled in container with a metered valve. On actuation a desired dose of the drug will be delivered through the valve.²²

Sublingual Capsules

These are the solid dosage forms in which the powder is filled into capsule, it should be cut open and the contents are placed below the tongue.²² In table 3 various sublingual formulations along with some drugs are given.

Table 3: Drugs Used In Formulation of Sublingual Dosage Forms

Drug	Dosage form	Reference No.
Physostigmine salicylate	Sublingual Tablet	25
Scopolamine	Sublingual spray	26
Captopril	Sublingual Tablet	27
Furosemide	Sublingual Tablet	28
Nifedipine	Sublingual Tablet	29
Nitroglycerine	Sublingual Tablet	30
Vinpocetine	Sublingual Tablet	31
Terbutaline sulphate	Sublingual Tablet	32
Amlodipine Besylate	Fast dissolving sublingual tablet	33
Ondansetron HCl	Sublingual Film	17
Salbutamole Sulphate	Sublingual Film	35

Oxycodone	Sublingual spray	36
Fentanyl Citrate	Fast dissolving sublingual tablet	20
Zolmitriptan	Bioadhesive sublingual tablet	37
Ephedrine	Fast disintegrating sublingual tablet	38,39
Buprenorphine	Bioadhesive sublingual tablet	21

Evaluation Tests for Tablets

Weight Variation Test

As per IP weight variation test for sublingual tablet can be carried out by selecting 20 individual units and their average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table 4 and none deviate by more than twice that percentage.⁴⁰

Tablet 4: IP Standards for Weight Variation Test

Dosage form	Average weight	Percentage deviation
Uncoated and film coated tablets	80 mg or less	10.0
	More than 80 mg but less than 250 mg	7.5
	250 mg or more	5.0

Test for Content Uniformity

According to IP test for content uniformity can be carried out by determine the content of active ingredient(s) in each of 10 dosage units taken at random using the method given in the monograph or by any other suitable analytical method. The preparation complies with the test

if individual content of dosage unit is 85 to 115 per cent of the average content. If content of more than one dosage unit is outside these limits or if content of one dosage unit is outside the limits of 75 to 125 per cent of the average content, then the preparation fails to comply with test for content uniformity.⁴⁰

Test for Mechanical Strength

Test for Tablets

Friability test

Test for friability of uncoated tablets is carried out using specified amount of tablets. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Dedust the tablets carefully and weigh accurately the required number of tablets. Place the tablets in the drum and rotate it 100 times. Remove the tablets, remove any loose dust from them and weigh them accurately. Calculate loss of weight by comparing initial weight and final weight. As per IP specifications a maximum loss of weight not greater than 1.0 per cent is acceptable for most tablets. If obviously cracked, chipped or broken tablets are present in the sample after tumbling, the sample fails the test.⁴⁰

Hardness

A diametral compression test is performed according to European Pharmacopoeia method 2.9.8 (resistance to crushing of tablets) using Monsanto Hardness Tester.⁴¹ According to standard literature minimum hardness of sublingual tablet should be 2 kg/cm² for blister packing and 3 kg/cm² for bottle packing.⁴²

Evaluation Parameters for Film

Mechanical properties of films are evaluated Instron using a TA.XT2 texture analyzer equipment equipped with a 5kg load cell. Films are held between two clamps positioned between 3cm. During measurement the strips were pulled at rate of 2mm/sec. The force and elongation were measured when film breaks. Four mechanical properties namely tensile

strength, elastic modulus, percentage elongation and folding endurance are calculated.²³

Tensile Strength

Tensile strength is calculated by formula =
$$\frac{\text{force at break}}{\text{Initial cross sectional area of film in mm}^2}$$

Elastic modulus (Young's Modulus)

Elastic modulus is calculated by formula

Elastic modulus =
$$\frac{\text{force at corresponding strain}}{\text{Cross sectional area (mm}^2\text{) X Corresponding strain}}$$

Percentage Elongation

It is calculated as

$$\% \text{ elongation}^n = \frac{\text{Increase in length}}{\text{Original length}} \times 100$$

Folding Endurance

The folding endurance is expressed as the number of folds (number of times the film is folded at the same place) required to break the specimen or to develop visible cracks. This also gives an indication of brittleness of the film. A strip measuring 2.5 cm X 2.5 cm (6.25cm²) was subjected to folding endurance by folding the patch repeatedly at the same place several times until a visible crack was observed.⁴³

Disintegration Test

According to USP the disintegration test for sublingual Tablets is carried out as per USP disintegration test for uncoated tablet. As per USP sublingual tablet must disintegrate completely within 2 minutes or at within the time limit specified in the individual monograph. To comply test all six tablets have disintegrate completely within specified time. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.⁴⁴ For sublingual film in vitro disintegration time is determined visually in a petri dish with 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates. The disintegration time of

prepared films was recorded in triplicate. Sublingual film must disintegrate completely within 1 minute or at within the time limit specified in the individual monograph.²³

Drug Dissolution Test

Dissolution tests for sublingual tablet are carried out by paddle method using distilled water as dissolution medium with a preset temperature of 37⁰C and paddle rotation of 50 rpm. According to the scientific literature, the amount of drug dissolved from sublingual tablets must exceed 80% in 15 minutes.²⁰

In Vivo Permeation Studies

Goat oral mucosa was used to check the permeation of drug through the mucosa using a Franz diffusion cell at 37 ± 0.5°C. Fresh goat oral mucosa was mounted between the donor and receptor compartments. The sublingual dosage form was placed with the core facing the mucosa, and the compartments were clamped together. The donor compartment was filled with 1 ml of phosphate buffer (pH 6.8). The receptor compartment (45 ml capacity) was filled with phosphate buffer (pH 6.8) and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. Five- milliliter samples were withdrawn at pre-determined time intervals and analyzed for drug content using an ultraviolet (UV) spectrophotometer.⁴⁵

Other Tests

Simulated Wetting Test

The wetting time (WT) of sublingual tablet is measured by a procedure that simulates the physiological conditions under a moist tongue surface. Two layers of absorbent paper fitted into a rectangular plastic dish (11 cm x 7.5 cm) are wetted thoroughly with distilled water & excess water will be drained out of the dish. The tablet is placed at the center of the plastic dish and the time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet (WT) is recorded using a stopwatch.³⁹

Swelling Property

Swelling property of the oral film is checked by using saliva solution. Keep the film on the pre weighed steel mesh one part is placed in the 50 ml saliva solution. Weigh the film after specific time up to constant weight of film is come.²⁴

Sublingual mucosal drug delivery is the most preferred and acceptable route of drug delivery. It provides high patient compliance, rapid onset of action and improved bioavailability. Compare to conventional route like oral or parenteral, sublingual route offers several advantages. Many pharmaceuticals are designed for sublingual administration including cardiovascular drugs, steroids, barbiturates, enzymes, antiemetics, vitamins, minerals and vaccines. The sublingual tablets and films are more popular dosage forms. Along with these newer dosage forms like sublingual sprays and sublingual capsules are also introduced.

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