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Review Article

SUBLINGUAL DRUG DELIVERY SYSTEM: A NOVEL APPROACH

Bhabani Shankar Nayak*[1], Subham Sourajit[2], Manaswini Palo[2], Subhasmita Behera[2]

[1]Institute of Pharmacy and Technology, Salipur, Cuttack, Odisha, India
[2]Jeypore College of Pharmacy, Rondapalli, Jeypore – 764002, Koraput, Odisha, India

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Abstract

In some acute disease cases, medication requires rapid onset of action. Sublingual drug delivery is considered to be a promising route for faster and direct absorption of drug into systemic circulation. In buccal cavity, sublingual area is most permeable for drug absorption. The portion of drug absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolism, which leads to greater bioavailability with better patient compliance. New sublingual technologies offers many pharmaceutical and patient needs, that are enhanced life-cycle management to convenient dosing for pediatric, geriatric, and psychiatric patients with dysphagia. The objective of this study to demonstrate a complete approach of sublingual drug delivery system with both conventional and novel approach with its current and future approaches.

Keywords: Sublingual, first pass metabolism, dysphagia, permeability, bioavailability.

INTRODUCTION

Systemic drug delivery through the sublingual route offer immediate onset of therapeutic action. Dysphagia (difficulty in swallowing) is associated with all age groups, especially elderly, children, and patients who are mentally retarded, uncooperative, nauseated patient [1,2]. The drug solutes are rapidly absorbed through passive mechanism into the reticulated vein of sublingual which lies underneath the oral mucosa, and transported through the facial veins and internal jugular vein and finally reaches to systemic circulation [3]. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route. 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 [4]. Sublingual products have been developed for numerous indications ranging from migraines to mental illness (depression and schizophrenia) [5].

Advantages and disadvantages of sublingual drug delivery system:

Sublingual drug delivery system offers several advantages such are ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric patients and psychiatric patients. A relatively rapid onset of action can be achieved compared to the oral route. The large contact surface of the oral cavity contributes to rapid and extensive drug absorption. Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract. The system provides fast dissolution or disintegration in the oral cavity. This system possesses various limitations like not well suited to sustained delivery systems; medication cannot be used when a patient is uncooperative or unconscious and this route is unsuitable for prolonged administration [6].

Sublingual glands:

Sublingual glands are also known for their binding and lubricating functions, and sublingual gland secretion makes the food slippery and easily swallowable. 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. Saliva regulates oral microbial flora by maintaining the oral pH and enzyme activity. 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 GI tract. The flow rate of saliva which in turn depends on 3 factors such as the time of day, the type of stimulus and the degree of stimulation [7,8].

Anatomy and physiology of mucosa:

The thickness of mucosa is 100-200 μm. Mucosa is composed of neutral but polar lipid e.g. cholesterol sulfate, glucosyl ceramide. The saliva is composed of 99.5 % water, proteins, glycoprotein, high potassium (7X Plasma), bicarbonate (3X plasma), calcium, phosphorous, chloride, low sodium (1/10X Plasma). The sublingual gland contain 5 % saliva. The pH of saliva is 5.6-7.0 [9].

Suitability of drug for preparation of sublingual tablet:

The drug should possess following criteria's to be designed as sublingual tablet are lipophilic (pKa > 2 for acidic drug and 10 < for basic drug, Log p is 1.6-3.3), no bitter taste, dose lowers than 20 mg, small to moderate molecular weight (163-342), good stability in saliva, partially no ionized at the oral cavities pH and undergoing first pass effect. Many drug properties could potentially affect the performance of sublingual tablets like solubility, crystal morphology, particle size, hygroscopicity, compressibility and bulk density of drug. Drugs that are unstable in parenteral preparation are suitable for sublingual dosage form [8,9].

The mechanism of sublingual absorption:

The absorption potential of the buccal 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. The cells of the oral epithelium and epidermis are also capable of absorbing by endocytosis. 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 and uptake into the circulatory system. Fig 1 shows mechanism of transportation of drugs through sublingual route into the arterial circulation [10].

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. 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) [10,11].

Factors affecting the sublingual absorption:

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. ***Binding to oral mucosa:*** Systemic availability of drugs that bind to oral mucosa is poor. ***pH and pKa of the saliva:*** As the mean pH of the saliva is 6.0, this pH favours the absorption of drugs which remain unionized. ***Lipophilicity of drug:*** For complete absorption of drug, it must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation. ***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 [12-14].

METHOD OF PREPARATION OF SUBLINGUAL FORMULATIONS:

Sublingual Tablets:

Direct compression is one of the techniques which require the incorporation of a super disintegrant into the formulation, or the use of highly water-soluble excipients to achieve fast tablet disintegration. It is the ideal method for moisture and heat-labile medications. 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 solubilisation depends on single or combined action of disintegrates, water soluble excipients and effervescent

agent. Disintegration efficacy is strongly affected by tablet size and hardness [15-17].

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 to 320 mass % of solid matter at the beginning of being cared by the pin tenter. 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 within 20 min when compare with immediate release oral tablets (1.3 h), intramuscular (1 h), and intranasal oxycodone (0.42 h) in healthy volunteers [16,17].

EVALUATIONS [18-20]:

General appearance:

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape:

The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet thickness:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as accounting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Wetting time:

A piece of tissue paper (12 × 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured.

Uniformity of weight:

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight.

Friability:

It is the measure of mechanical strength of tablets. Roche friabilator can be used to determine the friability by following procedure. A pre-weighed tablet was placed in the friabilator. Fribaiator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 min. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as %Friability = loss in weight / Initial weight × 100. The percentage loss should be less than 1 %.

Tablet hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

***In-vitro* dispersion time:**

In-vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

***In-vitro* disintegration test:**

The test was carried out on 6 tablets using the apparatus specified in I.P. distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of

the tablet with no palable mass remaining in the apparatus was measured in seconds.

Test for film:

Tensile Strength:

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the film as given below.

$$\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Film thickness} \times \text{film width}} \quad \ldots\ldots (1)$$

Percent elongation:

A film sample stretches when stress is applied and it is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample. Elongation of film Increases as the content increases.

$$\text{Percent Elongation} = [(L-Lo)/Lo] \times 100 \ldots\ldots\ldots\ldots (2)$$

Where, L = Increase in length of film. Lo = Initial length of film.

Young's modulus:

Young's modulus or elastic modulus is the measure of stiffness of film. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows.

$$\text{Young's Modulus} = \frac{\text{Slope} \times 100}{\text{Film thickness}} \quad \ldots\ldots\ldots\ldots\ldots (3)$$

Folding endurance:

Folding endurance is determined by drying process repeated folding of the film at the same place till the breaks. The number of times the film is folded without dry breaking is computed as the folding endurance value.

Thickness:

The thickness of the polymer films was measured by using screw gauge. The thickness of each strip at six different areas was determined by using standard procedure.

***In vitro* disintegration time:**

In vitro disintegration time is determined visually in a glass dish of 25 ml distilled water with swirling every 10 s. The disintegration time is the time when the film starts to break or disintegrates.

Uniformity of drug content:

The film of area 1×1 cm^2 was cut and dissolved in 6.8 phosphate buffer solution and made up to 100 ml in a volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at λ_{max} and concentration was calculated by using UV-Visible spectrophotometer.

***In-vitro* dissolution studies:**

Dissolution study was carried out in USP paddle type apparatus using 900 ml of stimulated salivary fluid (pH 6.8) as a dissolution medium at 50 rpm. Temperature of the dissolution Medium was maintained at 37±0.5ºC. Samples of 5ml were withdrawn at every 4 min interval, filtered (through 0.45µ) and replaced with 5 ml of fresh dissolution medium. The Samples were suitably diluted and estimated spectrophotometrically at λ_{max} by using UV-Visible Spectrophotometer.

***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 tissue. 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 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 magnet-

ic bead at 50 rpm. One film of dimension 2 × 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. The percentage of drug permeated was determined by measuring the absorbance using UV-Visible spectrophotometer.

NOVEL SUBLINGUAL TABLETS [21,22]:

Fast disintegrating sublingual tablets (FDT):

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. Oro-dispersible tablet (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 orodipersible 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.

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 cavity.

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.

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:

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 as recommended by WHO. The only sublingual vitamin that all doctors recommend is vitamin

B_{12} (cyanocobalamin).

Sublingual immunotherapy:

Sublingual immunotherapy (SLIT) is a form of immunotherapy that involves putting drops of allergen extracts under the tongue. Sublingual immunotherapy is very much helpful in the case of SAC (seasonal allergic conjunctivitis) and PAC (Perennial allergic conjunctivitis) whom are spreading at a much faster rate among people who are working in industries and 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. 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).

PATENTS:

The detail of various patents on sublingual tablets and films is given in Table 1 [23,24].

MARKETED PREPARATION:

The various marketed formulations of sublingual tablets are tenormin sublingual tablet (isoproterenol), microtab sublingual tablet (nicotine), nascobal sublingual tablet (vitamin B_{12}), subuter sublingual tablet (buprenorphine) and nitroquick sublingual tablet (nitroglycerin) [25].

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 [26].

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 min, 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.

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