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Review on Sublingual Drug Delivery System

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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 administered drugs. In terms of permeability, the sublingual area of the oral cavity is more permeable than the buccal area, which in turn is more permeable than the roof of the mouth area. The portion of drug absorbed through the sublingual blood vessels avoids hepatic first-pass metabolic processes giving good bioavailability. Sublingual technology for patients need enhanced lifecycle management to convenient dosing for geriatric, pediatric and patient with dysphagia. This review highlights the introduction of sublingual drug delivery,mechanism ,factors affecting sublingual absorption, advantages, disadvantages,methods of preparation(tablet,films),drug administered by this route and conclusion.

Keywords: Improvedbioavailability,Sublingualdelivery, Dysphagia, Technique.

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INTRODUCTION

Systemic drug delivery through the sublingual route had emergedfrom 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 retarted, uncooperative, nauseated or on decreased liquidintake/ dietshave difficulties in swallowing these dosage forms[1]. Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream throughthe ventralsurface ofthetongueandfloorof 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[2]. The main mechanismfor theabsorption ofthedrugintooral mucosaisvia passive diffusion into the lipoidal membrane[3]. 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

MECHANISM OF SUBLINGUAL DRUG DELIVERY

The absorption potential of the buccal mucosa is affected by thelipidsolubilityandhencethepermeabilityofthesolution, the ionization (pH), and the molecular weight of the substances. For example, absorption of some drugs via the buccal mucosa is shown to increase when carrier pH is lowering (more acidic) and decrease with a lowering of pH (more alkaline).[4,5]

The absorption is effected by the lipid solubility and hence the permeability of the solution commonly known as osmosis, the ionization,andthemolecularweightofthedrug.Thecellsof oral epithelium adsorb the drug by the process of endocytocis. It is unlikely that the same mechanism is observed throughout the stratified epithelium. However, it is believed that acidic stimulation of the salivary glands, with the accompanying vasodilatation, 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 mucosa[6,7] The salivary glands consist of lobules of cells which secrete saliva through the salivary ductsintothemouth.Thethreepairs of salivary glands are the parotid, the submandibular and the sublingual which lies on the floor of the mouth. The more acidic the taste is, greater the stimulation of salivary output; serving to avoidpotentialharmto acid-sensitive tooth enamel by bathing the mouth in copious neutralizingfluid.The sublingualartery 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.

Twosymmetricalbranchestravelbehindthejawboneunderthe 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[8,9].

FACTORS AFFECTING THE SUBLINGUAL ABSORPTION[10]

1. **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.
2. **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.
3. **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.
4. **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.
5. **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 OF SUBLINGUAL DRUG DELIVERY SYSTEM

- ✓ Easy to administered to the patients who are unable to swallow a tablet, such as pediatric, geriatric patients and psychiatric patients.
- ✓ A relatively fast action can be achieved compared to the oral route.
- ✓ The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
- ✓ First pass metabolism is avoided and the drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
- ✓ They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

DISADVANTAGES OF SUBLINGUAL DRUG DELIVERY SYSTEM

- ✓ Although this site is not well suited to sustained delivery Systems.
- ✓ Sublingual medication cannot be used when a patient is unconscious.
- ✓ Sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.

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 disintegrats, water soluble excipients and effervescent agent. Disintegration efficacy is strongly affected by the 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.[11,12]

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 tenter[13]. 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 minutes when compared with immediate release oral tablets (1.3 hours), intramuscular (1 hour),and intranasal oxycodone (0.42 hour) in healthy volunteers[14].

EVALUATION PARAMETER

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.[15]

Water absorption ratio

A piece of tissue paper folded twice is placed in a small Petri dish Containing 6 ml of water. A tablet is put on the tissue paper and allowed to completely wet.The wetted tablet is then weighted. Water absorption ratio, R was determined using following equation.

R = 100 × Wa –Wb/Wa

Where,

Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption. [16]

Disintegration test

The test was carried out on 6 tablets using the apparatus specified in I.P. 1996 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. [17]

Drug Content

Randomly ten tablets are selected from formulation, finely powdered and powder equivalent mg of drug is accurately weighed and transferred to 100 ml volumetric flasks containing solution of desired pH. The flask is shaken to mix the contents thoroughly. The volume is made up to the mark with solution and filtered. One ml of the filtrate is suitably diluted and drug content is estimated using a double beam UV-visible spectrophotometer. This procedure is repeated thrice and the average value is calculated. [18]

In-vitro dissolution studies

Dissolution study was carried out in USP paddle type apparatus using 300 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 minute interval, filtered (through 0.45µ) and replaced with 5ml of fresh dissolution medium. The samples were suitably diluted and estimated spectrophotometrically at 276 nm by using ELICO- 164 double beam UV-Visible spectrophotometer. The dissolution experiments were conducted in triplicate. Dissolution rate was studied for all designed formulations and dissolution parameters were calculated. [19]

DRUGS ADMINISTERED BY SUBLINGUAL ROUTE

Table 1: 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

Table 2: Drugs used in the formulation of sublingual dosage forms

Drug	Category	Dosage form
Physostigmine salicylate	Anti-Alzheimer's	Tablet
Scopolamine	Opioid analgesic	Spray
Captopril	Anti-hypertensive Agent	Tablet
Furosemide	Diuretic	Tablet
Nifedipine	Anti-anginal	Tablet
Nitroglycerine	Anti-anginal	Tablet
Vinpocetine	Neutropic Agent	Tablet
Terbutaline sulphate	Bronchodilator	Tablet
Amlodipine besylate	Anti hypertensive	Tablet
Ondansetron Hydrochloride	Anti emetic	Film
Salbutamol sulphate	Anti-asthmatic agent	Film

CONTRIBUTION

Table 3: Contribution in the field of Sublingual Medications

S.No.	Year	Contribution
1.	1986	Freeze drying process converts the mixture of active water dispersible carrier materials into open matrix network that disintegrates rapidly.[20]
2.	1994	Regular compression method that produces tablet with higher mechanical strength.[21]
3.	2001	Formulation and optimization of captopril sublingual tablet using d-optimal design.[22]
4.	2003	In vitro and in vivo evaluation of a new sublingual tablet system for rapid Oromucosal absorption using fentanyl citrate as the active substance.[23]
5.	2006	Formulation and optimization of sublingual tablets of rabeprazole sodium.[24]
6.	2009	Development and optimization of a sublingual Tablet formulation for physostigmine salicylate.[25]
7.	2011	Sublingual route for the systemic delivery of ondansetron.[26]
8.	2012	Formulation and in-vitro evaluation of fast disintegrating Rosiglitazone sublingual tablets.[27]
9.	2012	formulation and evaluation of sublingual tablets of losartan potassium.[28]
10.	2012	Development and characterization of sublingual tablet of lisinopril.[29]
11.	2013	formulation and evaluation of immediate release tablets of linezolid.[30]

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.

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