Review Article

Sublingual: A Route for Systemic 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 rapid onset of action and better patient compliance than orally ingested tablets. Sublingual verbal meaning is "under the tongue", administrating substance via mouth in such a way that the substance is rapidly absorbed via blood vessels under tongue. The proportion of drug absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes giving acceptable bioavailability. Various techniques are used to formulate the sublingual dosage forms. New sublingual technologies for patient needs enhanced life-cycle management to convenient dosing for geriatric, paediatric and psychiatric patients with dysphagia. This review highlights advantages, disadvantages, different sublingual forms, factors, physicochemical properties of drugs, considerations during sublingual formulation.

Keywords: Sublingual delivery, principle, forms, factors, evaluation, consideration, physicochemical properties, permeability, characteristics of drug.

INTRODUCTION

Sublingual from the Latin for "under the tongue", refers to the pharmacological route of administration by which substances diffuse into the blood through tissues under the tongue. Many drugs are designed for sublingual administration, including cardiovascular drugs, steroids, barbiturates, benzodiazepines, opioid analgesics with poor gastrointestinal bioavailability, enzymes, vitamins and minerals.

PRINCIPLE

When a drugs comes in contact with the mucous membrane below the tongue, it diffuses through it. Because the connective tissue below the epithelium contains a opulence of capillaries, the substance then diffuses into them and enters the venous circulation. In contrast, substances absorbed in the intestines are subject to "first-pass metabolism" in the liver before entering the general circulation. Sublingual administration has positive advantages over oral administration. Being more direct, it is repeatedly faster, and it ensures that the substance will risk degradation only by salivary enzymes before entering the bloodstream, whereas orally administered drugs must survive passage through the inconsistent environment of the gastrointestinal tract, which risks degrading them, either by stomach acid, bile, or by the many enzymes there in, such as monoamine oxidase (MAO). In addition, after absorption from the gastrointestinal tract, such drugs must pass to the liver, where they may be largely altered; this is known as the first pass effect of drug metabolism. Due to the digestive activity of the stomach and intestines and the solubility of the GI tract, the oral route is unsuitable for certain substances, such as salvinorin A.

FORMS

Pharmaceutical preparations for sublingual administration are manufactured in the form of:

- Sublingual tablets—tablets which handily dissolve in the mouth, dissolve rapidly and with little or no residue. Nitroglycerine tablets are an example, the anti-emetic ondansetron is another.
- Sublingual strips—similar to tablets in that they handily melt in the mouth and dissolve rapidly. Suboxone is an example of medication that comes in a sublingual strip.
- Multi-Purpose Tablets—Soluble tablets for either oral or sublingual (or buccal) administration, frequently also suitable for preparation of injections, Hydrostat (hydromorphone) and a number of brands of morphine tablets and cubes.

- Sublingual Drops—a concentrated solution to be dropped under the tongue, as with some nicocodeine cough preparatations,
- Sublingual Spray—spray for the tongue; some human and veterinary drugs are dispensed as such.
- Lozenge—consequence a metred and patient-controlled-rate combination of sublingual, buccal, and oral administration, as with the Actiq fentanyl lozenge-on-a-stick (lollipop).
- Effervescent Buccal or Sublingual Tablets—this entry drives the drug through the mucous membranes much faster (this is the case in the stomach with carbonated or effervescent liquids as well) and is used in the Fentora fentanyl buccal tablet.

SUBLINGUAL DRUG DELIVERY SYSTEM

Sublingual tablets

They are to be placed under the tongue and produce immediate systemic effect by enabling the drug absorbed directly through mucosal lining of the mouth beneath the tongue. The drug absorbed from stomach goes to mesenteric circulation which connects to stomach via portal vein. Thus, absorption through oral cavity averts first- pass metabolism. The tablets are usually small and flat, compressed lightly to keep them supple. The tablet must dissolve quickly allowing the API to be absorbed quickly. Tablet 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 locality. Swallowing of saliva should also be averted since the saliva may contain dissolved drug. Courteous excipients are used to avoid salivary stimulation.

Advantages

1. First pass - The liver is by-passed by tablet, thus there is no loss of drug by first pass effect for sublingual administration, Bioavailability is higher.
2. Rapid absorption - Because of the good blood purveyance to the reabsorption is usually quite rapid.
3. Drug stability - pH in mouth comparatively neutral, so a drug may be more stable.

Disadvantages

1. Holding the dose in the mouth is discomfortable. If any is swallowed that portion must be regarded as an oral dose and subject to first pass metabolism.
2. Only small doses can be accommodated easily.

Factors affecting the sublingual absorption[2]

***Lipophilicity of drug*:** For a drug to be absorbed radically 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*:** Furthermore 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 preferences the absorption of drugs which remain unionized. Also, the absorption of the drugs through the oral mucosa take place if the pKa is greater than 2 for an acid and less than 10 for a base.

***Binding to oral mucosa*:** Systemic accessibility 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 quicker due to thinner epithelium and also the immersion of drug in smaller volume of saliva.

***partition coefficient*:** Compounds with opportune oil to- water partition coefficients are readily absorbed through the oral mucosa. An oil-water partition coefficient range of 40-2000 is considered righteous for the drugs to be absorbed sublingually

Evaluation[3]

a) General Appearance: The general appearance of a tablet, its visual identity and over all "elegance" is monumental for consumer acceptance. It include tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

b) Size and Shape: The size and shape of the tablet can be dimensionally verbalized, monitored and controlled.
c) Tablet Thickness: Tablet thickness is an important characteristic in reproducing appearance and also in enumerates by using filling equipment. Some filling equipment exerts the uniform thickness of the tablets as accounting mechanism. 10 tablets were taken and their thickness was recorded using micrometer.
d) Wetting Time: A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petri dish (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. 3 trials for each batch and the standard deviation were also determined.
e) Uniformity of Weight: I.P. procedure was followed for uniformity of weight, 20 tablets were taken and their weight was determined individually and collectively on a digital weighing balance. From the collective weight the average weight of 1 tablet was determined. The limit for weight variation.
f) 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, snick 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.
g) In-Vitro Dispersion Time: In-vitro dispersion time was determined by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer (pH 6.8). 3 tablets from each formulation were randomly selected and in vitro dispersion time was performed.
h) In-Vitro Disintegration Test: The In-Vitro disintegration 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
i) Surface pH of the tablet: pH of tablet is determine by allowing the tablet in keeping with the contact with 1ml distilled water for 2hr at room temperature and the pH is measured by bringing the pHmeter electrode, in contact with the surface of the tablet and allowing it to equilibrate for 1min.
j) Content uniformity: The content uniformity is determined by following the assay method for active ingredient.
k) Diameter: PHARMATEST PTB 311 is one of the popular instrument for measuring thickness up to 15mm, diameter up to 40mm, and hardness up to 300N.
l) Friability: the friability was determined by following procedure using Roche friabilator. A preweighed tablet was placed in the friabilator. Fribiator 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 minutes. 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 of tablet / Initial weight of tablet x 100.

Fast disintegrating sublingual tablets

Tablets that disintegrate or dissolve rapidly in the mouth are convenient for young children, elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. Only the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The sublingual medication can be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through sublingual blood vessels bypasses the hepatic first-pass metabolic processes.

Evaluation

a) Surface pH of the tablet
b) Tablet weight variation
c) Content uniformity
d) Hardness
e) Thickness
f) Diameter

g) Disintegration time
h) Wetting time and
i) Friability
(evaluation process of all parameters same as above parameters of sublingual tablet)

Bioadhesive sublingual tablet
Evaluation

a) Bioadhesion
b) Tablet weight variation,
c) Content uniformity,
d) Hardness,
e) Thickness,
f) Diameter
g) Disintegration time
h) Wetting time
(evaluation process of all parameters same as above parameters of sublingual tablet)

4. CONSIDERATIONS BEFORE DEVELOPING SUBLINGUAL TABLETS

Oral mucosal drug absorption is administered by:- (a) the permeability of the oral mucous membrane and the anatomy of the elemental tissues (b) the physicochemical properties of the drugs (c) the formulation design. The focus of this review is on the latter two points, as an understanding of these elements enables the selection of drug candidates suitable for oral mucosal delivery and optimizes drug delivery.

4.1.Permeability of the oral mucosa and drug absorption

The salivary glands present in the oral cavity secrete saliva that has a pH of 5.5-7.0. Saliva comprises of proteins and carbohydrate complexes called mucus and enzymes such as amylase and carboxylesterase. Mucus is negatively charged at the physiological pH, forming a cohesive gelatinous film on all oral cavity surfaces. This cohesiveness on oral cavity surface permits mucoadhesion of the drug to the epithelial tissue leading to drug absorption [(5).] The epithelial membrane thickness in sublingual region is 100–200 µm and in the buccal region is 500–600 µm [(6).] In both regions, the epithelial membrane is non-keratinized. The permeability of the mucosa varies from region to region in the oral cavity depending on thickness and degree of keratinization of the epithelial membrane[7.] Rapidly dissolving sublingual tablets are highly impressive for the emergency treatment of angina, breakthrough cancer pain, or migraine.

4.2.Physicochemical properties of drugs.[8]

For efficient absorption through the oral mucosa, the drug must be hydrophobic enough to partition into the lipid bilayer, but not so hydrophobic, such that once it is in the bilayer, it will not partition out again. Adequate oral absorption of drugs has been observed over a wide range of log P (octanol/water partition coefficient) values of 1 to 5. As the log P value increases beyond 5, the solubility in saliva is usually not enough to provide adequate concentration for diffusion through the lipid bilayer[9]. According to the diffusive model of absorption, the flux across the lipid bilayer is directly proportional to the concentration gradient. Therefore, lower solubility in saliva results into lower absorption rates and vice versa. In general, a drug formulated for sublingual or buccal administration should have a molecular weight of less than 500 (as free base) to facilitate its diffusion. Because drugs diffuse through the lipid bilayer in the unionized form, based on the pH-partition theory, the pKa of drugs also plays a big role in drug transport across the oral mucous membrane. It is important to note that the oral cavity, unlike the gastrointestinal tract has a narrow pH range, usually from 5.6 to 7.6. Thus, the basic drug administered as a salt, principally exists as a free unionized base if the pH is raised above its pKa value and this increase in the unionized fraction of a drug increases its bioavailability[10.] For this reason, the incorporation of a suitable buffer in the formulation of an ionizable drug makes it possible to control the pH of aqueous saliva in a range most appropriate for the optimal absorption of such drugs. Drugs that do not contain ionizable groups are not affected by changes in pH.

4.3. Characteristics of sublingual tablets

In view of the short residence time in the mouth, rapid disintegration and dissolution is crucial for drug absorption following administration of sublingual tablets. For this reason, sublingual tablet formulations should be designed to disintegrate and dissolve rapidly in saliva, without the aid of water to achieve this objective. The physical and mechanical characteristics of a tablet such as size, hardness, porosity and wettability affect its disintegration time. A smaller tablet size with low hardness and high porosity, more rapidly disintegrates than a larger or harder tablet. However, a tablet with a high porosity and low hardness is more friable, and this presents problems in tablet packaging and

handling. During development, all approaches to increase the mechanical strength of tablets should be studied, without compromising disintegration and dissolution.

The amount and type of disintegrants also play a significant role in acomplishing rapid disintegration. Effervescent agents have been used to facilitate disintegration [11]. The incorporation of water-soluble excipients, such as saccharides, helps in achieving rapid dissolution by enhancing the wettability of the tablet matrix. In addition, the manufacturing process and critical process parameters also affect disintegration and dissolution of sublingual tablets.

Sweeteners, flavors and other taste-masking agents are essential components for formulations containing drugs with an disagreeble taste. Sugar-based excipients fastly dissolve in saliva and produce endothermic heat of dissolution. They create a pleasant feeling in the mouth and are most suitable for sublingual tablets along with other flavors. The coating is not an option for bitter drugs to be dissolved in saliva.

MANUFACTURING PROCESSES OF SUBLINGUAL TABLETS

Compression molding

Tablets manufactured by the compression molding process show rapid disintegration and dissolution, which is usually within 5–10 seconds.[12] The formulations for the compression molding process typically contain soluble excipients to confer quick and complete dissolution, and taste modifiers for patient compliance[13]. Molded tablets have also been prepared directly from a molten matrix, in which the drug is dissolved or dispersed (heat molding) or by evaporating the solvent from a drug solution or suspension at room pressure (no vacuum lyophilization)[13].

Direct compression

The direct compression method is commonly used for commercial manufacture of sublingual tablets. It is a simple and cost-effective process, as it employs ingredients that can be mixed well and do not require additional granulation steps prior to lubrication and compression. Sublingual tablets manufactured by the direct compression method show good mechanical strength and acceptably fast disintegration[15]. The directly compressible sublingual tablet formulation comprises directly compressible soluble excipients, a super disintegrant, and lubricant. It may also comprises microcrystalline cellulose, dry binder, buffers, surface-active agents, sweeteners, and flavors. Sugar-based excipients are widely used as bulking agents because of their high aqueous solubility, sweetness, pleasant feeling in the mouth, and good taste-masking. Nearly all sublingual formulations incorporate some saccharide-based material[16]. The choice of a suitable disintegrant and its amount are critical for achieving a fast disintegration and dissolution rate. Sometimes effervescent agents are used to inhance disintegration and dissolution of sublingual tablets.

Freeze drying

The resulting tablets are usually light and have highly porous structures that allow rapid dissolution or disintegration. The freeze-drying process may result in a product with an amorphous structure, leading to an increased dissolution rate. However, tablets manufactured by freeze drying process have poor stability at a higher temperature and humidity[17].

CRITICAL CONSIDERATIONS TO PRODUCT QUALITY

Most of these tests are universal quality determinants of conventional tablet dosage forms and are equally relevant for sublingual tablets. However, the disease management and conditions of use for sublingual tablets require a very short residence time in the oral cavity. This critical determinant particularly calls for very rapid disintegration, dissolution, and absorption of the product resulting in quick onset of action. The drugs that are administered sublingually generally have low solubility. Therefore, to enhance dissolution, it is crucial to reduce and control the particle size of the API.

The *wetting test*, designed by Bi et al., compares favorably with the conditions prevailing in the sublingual region of humans and animals

7. CONCLUSION

In conclusion, this review demonstrates that there are a number of commercially available sublingual formulations manufactured using various technologies. The publically available information on sublingual tablets implies that this dosage form has good potential to enhance drug delivery in treating a number of indications. In most reported cases, it has been shown that the sublingual dosage form not only improves the patient's compliance, but also reduces the time for the onset of the drug action, and increases

the bioavailability of drugs as compared to conventional tablets. The ODTs have potential advantages over conventional oral dosage form as they improved patient compliance; convenience, rapid onset of action and bioavailability which drawn the attention of many manufactures. The pediatric geriatric populations areprimary ones whose problems are easily targets by ODTs as both the groups found it difficult to swallow conventional tablets.

Table 1: Physicochemical properties of drugs

Drug	Molecular weight	Largest dose	Water solubility	pka	Log P
1.Nitroglycerin	227	0.6mg	1.8 mg/ml	-5.6	0.94
2.Fentanyl citrate	336*	0.8mg	0.025 mg/ml (citrate)	8.4	2.9
3.Buprenorphine	467.6	2-8mg	Insoluble in water	8.24,10.0	4.9
4.Asenapine maleate	285.8*	10mg	3.7 mg/mL	8.6	4.9
5.Nicotine	162.234	4mg	Slightly soluble	8.21	0.99
6.Ergotamine tartrate	583.68*	2mg	Insoluble in water	6.3	2.4
* Molecular weight of the base. **Largest dose for sublingual tablet.					

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