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Review article *Medical research*

Short introduction of sublingual drug delivery system

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ABSTRACT

Onset of action is needed in the case of some acute diseases. Hence the Sublingual drug delivery can be best promising route of administration for a faster and direct absorption of drug into systemic circulation. The most permeable region for a drug absorption in buccal cavity is the Sublingual region. Absorption of a drug through the sublingual blood vessels bypasses the hepatic first-pass metabolism that makes better bioavailability along good patient compliance. Such sublingual approaches present numerous pharmaceutical and patient needs those are enhanced life-cycle management to suitable dosing for children as well as elderly along psychiatric patients with dysphagia. This review is to give a brief and complete overview of sublingual technologies along new and old approaches.

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

INTRODUCTION

Sublingual route of drug delivery proffer systemic drug delivery for immediate onset of curative action. In the case of difficulty in swallowing sublingual drug delivery system is allied with all age groups, particularly for the old age patients and children also the patients those are psychologically retarded even nauseated patient. 17,22
In sublingual drug delivery system absorption of drugs particles get done by passive mechanism into the reticulated vein of sublingual region which lies underneath the oral mucosa and then it is transported via the facial veins and the internal jugular vein and at the end reaches to systemic circulation.8
The sublingual route has higher absorption as 3 to 10 time superior than the oral route. The very small volume of saliva is generally sufficient for such formulations to outcome in tablet disintegration in the oral cavity. Rapid onset of action occurs in sublingual absorption and reflects with short acting in period. 21
Products with sublingual drug delivery have been developed for many indications those range from migraines to psychological illness.15

What are the Advantages and disadvantages of sublingual drug delivery systems

There are certain advantages and limitation of each technology hence the sustained drug delivery also has some advantages and limitation as described below,

Advantages of sublingual drug delivery systems:12

There are many advantages of the sublingual drug delivery system as given below,

Ease of administration	• Patients who refuse to swallow a tablet • Pediatric and geriatric • Psychiatric patients
Rapid onset of action	A relatively rapid onset of action can be achieved compared to the oral route

Rapid and extensive drug absorption	The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
Bypass the first pass metabolism	Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
Faster dissolution and disintegration	The system provides fast dissolution or disintegration in the oral cavity

Limitation of the sublingual drug delivery systems

- Not well suited to sustaineddelivery system
- Medication cannot be used when a patient is uncooperative or unconscious
- This route is unsuitable for prolonged administration as well.

What are the Sublingual glands: 11,19

The Sublingual glands are well known for its secretion as they are also known for their binding and lubricating functions, food get slippery after binding with the saliva and can easily swallowed.

The secretion of sublingual gland has main function in shaping the principle physiological environment of oral cavity in conditions of pH, fluid volume and the composition.

The main 3 salivary glands promote the saliva secretions which are as, parotid, submaxillary and the sublingual glands. The oral microbial flora is regulated by saliva maintain the oral pH and the activity of enzymes.

The salivary gland secretes nearby 0.5 to 2.0 liter of saliva. But only 1.1 ml saliva is constantly present in mouth cavity that provides relatively low fluid volume available for drug release from sublingual drug delivery systems when compared with GI tract. The saliva flow rate is depends on 3 different factors like as the time of day, the type of stimulus and the degree of stimulation.

Physiological Anatomy mucosa:18

The mucosa is about 100-200 µm thick. Generally mucosa is formed with neutral but polar lipid like as cholesterol sulfate, glucosyl ceramide. The saliva have around 99.5 % of water, proteins, glycoprotein, high potassium and bicarbonate, calcium, phosphorous, chloride, low sodium as well. The sublingual gland contain only 5 % saliva with pH 5.6-7.0.

The drug selection for preparation of sublingual tablets: 18,19

The following criteria shall be followed by the drug to be formulated into sublingual drug delivery are as below,

- 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.
- Other drug properties can also potentially change the performance of sublingual tablets are like
  - solubility,
  - crystal morphology,
  - particle size,
  - hygroscopicity,
  - compressibility and bulk density of drug.

The drugs those are unstable in parenteral preparation are suitable for sublingual dosage form.

Sublingual drug delivery absorption mechanism:10

The buccal mucosal absorption potential can influenced by the lipid solubility and consequently the permeability of the solution by osmosis method and the ionization (pH), and the molecular weight of the drug substances. The oral epithelium cells and the epidermis are as well capable of absorbing by phenomena known as endocytosis.

For diffusion through its wall such engulf particles are typically too large.It is very doubtful that this mechanism is used across the whole stratified epithelium. Active transport processes operate only within the oral mucosa. But it is strongly believed that acidic stimulation and uptake into the blood.

Suitable Drugs for sublingual administration: 10,13

The following drugs are most suitable in the sublingual drug administration are as below,

- Cardiovascular drugs,
- Steroids
- Barbiturates and enzymes as well.
- Vitamins and minerals

Factors those affects the sublingual absorption:3,6,14

- Solubility in salivary secretion.
- Binding to oral mucosa
- pH and pKa of the saliva
- Lipophilicity of drug
- Thickness of oral epithelium

Different method of preparation of sublingual formulations:2,16

Sublingual Tablets	Films
Direct compression: ➢ It is incorporated of a super disintegrant into the formulation	**Solvent casting:** A process comprises of casting a dope from a casting die onto a casting support.

➢ With use of highly water soluble excipients to achieve fast tablet disintegration. ➢ The best ideal method for moisture and heatlabile medications. ➢ The high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. ➢ Direct compression method, the tablet's disintegration and solubilisation depend on single or combined action of disintegrating agents ➢ Excipients those are water soluble along with effervescent agent. ➢ Disintegration time depends on tablet size and hardness	Drying the cast dope on the casting support form film and then stripping off the film from the casting support. Next, drying the film while conveying the film with carrying it at both side edges of the film by a pin tenter. Where remaining volatile component content of both side edges of the film being carried by the pin tenter with 30 to 320 mass % of the whole solid matter at the beginning of being cared by the pin tenter. **Then solvent evaporation technique:** It is used instead of solvent casting for the formulation of sublingual films. The sublingual sprays that improves the time to reach maximum plasma concentration as compared to other types of sublingual dosage forms.

Evaluations parameters of sublingual formulation 5,9,20

For tablets

Following evaluation parameters shall be evaluated for tablet formulations as given below,

General appearance	Visual identity, Overall "elegance" Tablet's size, shape, colour, presence, odour, taste, surface texture, physical flaws, consistency.
Size and Shape	Tablets size and shape shall be dimensionally described, monitored and controlled
Tablet thickness	Thickness is a very important characteristic in reproducing appearance. It is measured by micrometer of vernier caliper instrument.
Wetting time	Witting time test performed with a piece of tissue paper (12 × 10.75 cm) folded twice and placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. Then a tablet was put on the paper, and the time for complete wetting was measured.
Uniformity of weight	As per I.P. the uniformity of weight was followed with twenty tablets taken and their weight was determined individually and collectively on a digital analytical weighing balance. An average weight of one tablet was determined from the collective weight
Friability	It is the mechanical strength of a tablet. Here Roche friabilator can used to determine the friability. Tablets with an average weight of 650 mg or above = whole 10 tablets taken and for tablets having average weight below 650 mg equivalent to 6.5 gm tablets shall taken. And put into plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in thefriabilator for 4 min. After the test completed tablets were dusted and reweighed. Now the loss in theweight of tablet is the measure of friability and it is expressed in percentage as %Friability = loss in weight / Initial weight × 100. The percentage loss should be less than 1 %
Tablet hardness	Tablet hardness defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance to break, chipping, abrasion under condition of storage transformation and handling before usage depends on its hardness. Hardness of tablets determined using Monsanto Hardness tester
***In-vitro* dispersion time**	It is measured by droppinga tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation shall randomly selected and in vitro dispersion time was performed
In-vitro disintegration test	The test can carried out on 6 tablets using the disintegration apparatus specified in I.P. distilled water at 37ºC ± 2ºC shall used as a media and the time in minutes and second taken for complete disintegration of the tablet with no retention mass remaining in the apparatus was measured in seconds.

Evaluation Test for film

Tensile Strength	It is the maximum stress applied to a point at which the film specimen breaks down and can calculated by the applied load at rupture divided by the cross-sectional area of the film as given below. Tensile strength = $\frac{\text{Load at failure} \times 100}{\text{Film thickness} \times \text{film width}}$
Percent elongation	A sample of film stretches when stress is applied and it is referred as strain. Strain is just the deformation of film that divided by original dimension of the sample.

	Elongation of film Increases along content increases. Percent Elongation = [(L-Lo)/Lo] × 100 Where, L = Increase in length of film. Lo = Initial length of film.
Young's modulus	This modulus is also known as elastic modulus which is the measureof stiffness of film. Represented as the ratio of applied stress over strain in the region of elastic deformation as follows. Young's Modulus = Slope × 100 Film thickness
Folding endurance	This 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 with no dry breaking is computed as the folding endurance value
Thickness	Polymer films thickness shall measured by using screw gauge. The thickness of every strip at six different areas was determined by using standard procedure
Disintegration time	Disintegration time is determined visually in a glass dish of 25 ml distilled water with swirling every 10 second. The disintegration time is the time when the film starts to break into small parts or disintegrates.
Uniformity of drug content	The film section with dimension 1×1 cm^2 shall cut and dissolved in 6.8 phosphate buffer solution and made up to 100 ml in a volumetric flask. After that 1 ml was withdrawnfrom the solution and diluted to 10 ml. The absorbance of the solution shall taken at λmax and concentration was calculated by using UV-Visible spec- trophotometer.
***D*issolution studies**	Dissolution test shall carried out in USP paddle type apparatus using 900 ml of stimulated salivary fluid (pH 6.8) as a dissolution medium at 50 rpm at 37±0.5ºC. Samples of 5ml shall withdrawn at 4 minutes interval then filtered (through 0.45µ) and replaced with 5 ml of fresh dissolution medium. The Samples were suitably diluted and estimated spectrophotometrically at λmax by using UV-Visible Spectrophotometer.

Sublingual tablets in new trends 1,7

Sublingual fast disintegrating tablets

Generally sublingual fast dissolving tablets offers improved convenience and are frequently preferred over conventional solid oral dosageforms.
Oro-dispersible tablet may have significant enhancement over current treatment options for specific patient group like for instance pediatric patients.

Sublingual Bioadhesive tablets

These are sublingual tablet concept presented based on interactive mixtures consisting of a water soluble carrier covered with fine drug element and along with bioadhesive component.
By using this approach it is probable to obtain a quick dissolution in combination with bioadhesive retention of the drug in the oral cavity.

Sublingual spray

These formulations 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 required dose of the drug will be delivered through the valve.

Lipid matrix sublingual tablets

These lipid matrix sublingual tablets are bioavailable and quick, convenient, consistent dosage forms for many particularly nutraceuticals those are frequently taken orally.

Sublingual vitamin tablets

For long time sublingual immunotherapy frequently for one year surrounding to mast cell stabilizers, antihistamines and sometimes local steroids.

Sublingual immunotherapy

It is a form of immunotherapy that engage putting drops of allergen extracts beneath the tongue.

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