SUBLINGUAL SPRAY: A BOOST TO NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Sublingual dosage form is 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 which is very reach to vascular blood supply. Here the sublingual spray is to be sprayed for faster onset of action. The absorption of drug through sublingual route is 3-10 times greater than that given oral route. Main advantages include elimination of first pass effect, rapid drug absorption, high efficacy, large surface area, drug stability, ease of termination of therapy and many more. Drug directly go to the arterial circulation by sublingual vein and capillaries and then to jugular vein and then to the Superior vena cava. Pharmaceutical preparations for sublingual administration are manufactured in the forms of: tablets, drops, film, and sprays. Therefore current write up is focused on anatomical structure of sublingual route, its blood supply, mechanism of drug absorption, advantages and disadvantages of sublingual spray with their marketed formulation has been discussed.

Key Words: sublingual, spray, novel drug delivery

INTRODUCTION

Drugs have been applied to the mucosa for topical application for many years. However, recently there has been interest in exploiting the oral cavity as a portal for delivering drugs to the systemic circulation. Notwithstanding the relatively poor permeability characteristics of the epithelium, a number are offered by this route of administration. Sublingual drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularized, drugs that are absorbed through the oral mucosa directly enter to the systemic circulation, by passing the gastrointestinal tract and first-pass metabolism in the liver. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route than the intravenous route. Sublingual sprays are to be sprayed under the tongue and produce immediate systemic effect by enabling the drug absorbed directly through mucosal lining of the mouth beneath the tongue. The absorption of drug through sublingual route is 3-10 times greater than that given oral route.

Advantages:-

✓ Sublingual spray formulation has a faster onset, longer duration, and fewer adverse events, compared to sublingual tablet. Ease of administration to patients who refuse to swallow a tablet.

✓ In patients who experience dry mouth, the spray formulation may be a better alternative, since the dissolution of the spray is not dependent upon patient saliva.

✓ No requirement of drug disintegration.

✓ Water is not required for swallowing the dosage form; elimination of first pass metabolism, Good mouth feels property.

✓ Some drugs are absorbed from the mouth pharynx and esophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
Disadvantages:-

- This site is not well suited to sustained-delivery systems.
- Generally not applicable for drugs that require high blood levels or large Doses.
- Drugs which are not absorbed by passive diffusion or irritating to oral mucosa are also not applicable to this drug delivery system.
- Taste masking is main problem associated with this formulation.

The Mechanism of Sublingual Absorption:-

The salivary glands consist of lobules of cells which secrete saliva through the salivary ducts into the mouth. The three pairs of salivary glands are the Parotid, the Sub mandibular and the Sublingual which lies on the floor of the mouth. The more acid the taste the greater the stimulation of salivary output, serving also to avoid potential harm to acid sensitive tooth enamel by bathing the mouth in copious neutralizing fluid. With stimulation of salivary secretion oxygen is consumed and vasodilator substances are produced, and the glandular blood flow increases, due to increased glandular metabolism.

The sublingual artery 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. Two symmetrical branches travel behind the jaw bone under the tongue to meet and join at its tip. Another branches meets and anastomoses with the sub mental branches of the facial artery. The sublingual artery system 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.

Mechanism of drug release:-

Drug directly go to the arterial circulation by sublingual vein and capillaries and then to jugular vein and then to the superior vena cava to blood vessels.

Sublingual sprays deliver drug-containing aqueous droplets to the mouth. The velocity and size of the droplets are monitored in order to ensure delivery to the oral cavity rather than to the lungs. Rapid Mist technology is also currently been evaluated for the buccal delivery of morphine and fentanyl. On actuation, the drug-containing mist is sprayed in the oral cavity and deposits in the buccal and sublingual mucosal membranes.

Factors Affecting Drug Absorption:-

1. Degree of Ionization, pH, and Lipid Solubility

The permeability of unionizable compounds is a function of their lipid solubility, determined by their oil–water partition coefficients. The absorption of drug through a membrane depends upon its lipophilicity, which in turn depends on its degree of ionization and partition coefficient. Generally small molecules that are predominantly lipophilic, with a log P of 1.6–3.3, are absorbed most rapidly; above 3.3, limited water solubility restricts their absorption.

2. Molecular Size and Weight

The permeability of a molecule through the mucosa is also related to its molecular size and weight, especially for hydrophilic substances. Molecules that are smaller in size appear to traverse the mucosa rapidly. The smaller hydrophilic molecules are thought to pass through the membrane pores, and larger molecules pass extracellularly. Increases in molar volume to greater than 80 mL/mol produced a sharp decrease in permeability.

3. Permeability Coefficient

To compare the permeation of various drugs, a standard equation calculating the permeability coefficient can be used. One form of this equation is

\[ P = \frac{\% \text{ permeated} \times V_d}{A \times t \times 100} \]

Where, \( P \) is the permeability coefficient (cm/s), \( A \) is the surface area for permeation, \( V_d \) is the volume of donor compartment, and \( t \) is the time.

This equation assumes that the concentration gradient of the drug passing through the membrane remains constant with time, as long as the percent of drug absorbed is small.

Composition of Sublingual Spray:-

A spray formulation consists of two essential components:

1. Product concentrate
2. Propellant.

Product concentrate:-

The product concentrate consist of active ingredients, or a mixture of active ingredients and other necessary agents such as Penetration enhancers, solvents, antioxidants, flavoring agents, sweeteners, hydrophilic polymers, preservatives, acidifying agents, co solvent.
Penetration enhancers:-
Enhancers have been used to increase the permeation of drugs through the membrane, and thus increase the subsequent bioavailability. Some examples of penetration enhancers and their mechanisms are bile salts (micellization and solubilization of epithelial lipids), fatty acids such as oleic acid (perturbation of intracellular lipids), azone (1-dodecylazacycloheptan-2-one) (increasing fluidity of intercellular lipids), and surfactants such as sodium lauryl sulfate (expansion of intracellular spaces).

Propellants:- The propellant provides the force that expels the product concentrate from the container and additionally is responsible for the delivery of the formulation in the proper form (i.e., spray, foam, semisolid). When the propellant is a liquefied gas or a mixture of liquefied gases, it can also serve as the solvent or vehicle for the product concentrate.

Ideal properties of propellants,
1. It should be non-toxic.
2. It must be pure.
3. It should be free from irritation effect.
4. It should have good solvent action on numbers of therapeutically active ingredients.
5. It should be chemically inert and non-reactive.
6. It should be non-flammable.

Marketed Preparation:-

<table>
<thead>
<tr>
<th>API</th>
<th>Brand name</th>
<th>Company name</th>
<th>Composition</th>
</tr>
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<tbody>
<tr>
<td>Glutathione</td>
<td>White Light Glutathione</td>
<td>AIM global</td>
<td>Glutathione- 2,500mg Vitamin C-1,000mg</td>
</tr>
<tr>
<td>Glyceryl trinitrate</td>
<td>Glytrin spray</td>
<td>AFT Pharmaceuticals Ltd. Takapuna AUCKLAND</td>
<td>The propellant is CFC free. Excipients: peppermint Oil, propellant 1,1,1,2-tetrafluoroethane (HFC 134A), ethanol BP</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Isocard spray</td>
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<tr>
<td>Nitroglycerin</td>
<td>Nitrolingual, Nitroquick,</td>
<td>W Lambert-P Davis– P.zer Pharmaceuticals</td>
<td></td>
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<tr>
<td>Zolpidem tartrate</td>
<td>Zolpimist</td>
<td>ECR pharmaceuticals (Manufacturer-NOVADEL)</td>
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Oral spray formulations containing sumatriptan for the treatment of migraine, ondansetron hydrochloride (Zensana) for chemotherapy- or radiotherapy-induced nausea and vomiting and, sildenafil (Duromist), for erectile dysfunction, are currently either at preclinical stage or at phase I or II clinical trials.

Evaluation of sublingual sprays:-

- Physiochemical test:-

1. Vapor pressure: The pressure can be measured simply with pressure gauges or elaborately through use of water bath, test gauges and special equipment.
2. Density: the density of system may be accurately determined through the use of a hydrometer or pycnometer.
3. Moisture content: Karl Fischer method has been accepted to a great extent. Gas Chromatography has also been used.

4. Identification of propellant: Gas chromatography and infrared spectroscopy have been used to identify the propellants and also to indicate the proportion of each component in a blend.

5. Concentrate: propellant ratio.

- Performance test:-

1. Leak test: Leak is done by checking the crimping of valve must be available to prevent defective container. This is accomplished by measuring the crimps dimensions and ensuring that they meet specifications. Final testing of valve closure is done by passing the filled containers through water bath.
2. **Particle size Determination:** Cascade impactor and light scatter decay methods are mostly used.

3. **Delivery rate:**
Determine the exact flow required from the nozzles by calculating:
\[
\text{L} / \text{min} = \frac{\text{l/ha x km/h x nozzle spacing (m)}}{600}
\]

4. **Spray pattern:** A method is based on the impingement of the spray on a piece of paper that has been treated with a dye-talc mixture. The particles that strike the paper cause the dye to go into solution and to be absorbed onto the paper. This gives a record of the spray, which can be then used for comparison purpose.

5. **Net content:** The tared cans that have been placed onto the filling line are reweighed, and the difference in weight is equal to the net content.

6. **Dosage with metered valves:** Several points must be considered. 1) Reproducibility of dosage each time the valve is depressed and 2) Amount of medication actually received by the patient. Reproducibility of dosage may be determined into by assay techniques whereby one or two doses are dispensed into a solvent or onto a material that absorbs the active ingredients determined.

- **Stability testing**
There are two types of stability testing: electrochemical testing and long term static testing. Electrochemical testing provides a limited amount of information but is an effective screening tool. Long term static testing provides the most significant information such as: weight loss, concentrate/propellant saturation changes (vapor pressure measurement), maintaining original spray characteristic, corrosion, and concentrate stability (separation, coagulation, chemical change, color, and odor change). Long term static testing is normally done at a temperature of 120°F, over a period of three months to a year.

**Patented Technology:**
Blondino et al., (2011) has got us patent on stable anti-nausea oral spray formulations and methods. Stable formulations of selective 5-hydroxytryptamine receptor antagonists for oral spray administration for absorption by the oral mucosa and related methods of preparation and administration are provided. A preferred composition includes ondansetron in a concentration of about 5.1 to about 5.2% w/w; propylene glycol in a concentration of about 60.1 to about 60.3% w/w; water in a concentration of about 5.3 to about 5.4% w/w; and ethanol in a concentration of about 27.1 to about 27.3% w/w. Additional preferred excipients are preservative free and/or non-aqueous or primarily non-aqueous.

**Future prospective:**
The sublingual spray technology offers formulation of many pharmacological agents making it preferred mode of delivery in diseases like angina, diabetes, and cardiovascular diseases. It allows more rapid absorption into the bloodstream than is possible with oral administration to the gastrointestinal tract. Oral spray administration is non-invasive, non-technical and convenient for patients. In patients requiring rapid onset of action for therapeutic drugs, this route is more comfortable and convenient than intravenous drug administration.

![Sublingual Spray Technology](image)
REFERENCES