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Sublingual Drug Delivery System

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Abstract:
Sublingual route is the most popular route for systemic effects for its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. For drug absorption in oral cavity, sublingual area is most permeable to drugs. The drug delivered by the sublingual route bypasses the hepatic first-pass metabolism and providing acceptable bioavailability. Dysphagia (difficulty in swallowing) is common problem for all age or on reduce liquid intake have difficulties in swallowing the solid dosage forms. This review highlights the mechanism of sublingual absorption, factors affecting sublingual absorption, advantages, disadvantages and evaluation parameters.

Keywords: Sublingual, Market view, Dysphagia, Sublingual absorption.

I. INTRODUCTION

For the last twenty years, there has been an enhanced demand for more patient compliant dosage forms. As a result, there are now approximately 350 drug delivery corporations and 1000 medical device companies. The demand for their technologies was approximately $14.20 billion in 1995 and, according to industry reports; this is expected to grow to $60 billion annually[1,2] . Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance. Electrostatic drug deposition and coating[3] , and computer assisted three-dimensional printing (3DP) tablet manufacture have also recently become available[4] . Fast-dissolving drug-delivery systems were first developed in the late 1970's as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid-dosage forms. The novel technology of oral fast-dispersing dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar. By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules[5] . Dysphagia is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy[6] . The most common complaint was tablet size, followed by surface, form and taste. The problem of swallowing tablets was more evident in geriatric and pediatrics patients, as well as travelling patients who may not have ready access to water[7, 8] .

Salient features of fast dissolving drug delivery systems[9] :

- Ease of administration for patients who are mentally ill disabled and uncooperative.
- Require no water
- Over comes unacceptable taste of the drugs.
- Can be designed to leave minimal or no residue in the mouth after administration and also provide a pleasant mouth feel.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging
- Cost effective

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Need for fast dissolving drug delivery systems:
Fast dissolving drug delivery systems can improve acceptance and compliance in patients with dysphagia. Similarly, from market point of view, introduction of FDDS will assist life cycle management of drug especially if the drug is patent protected.

Dysphagia[10]:

Dysphagia, or difficulty in swallowing, is common among all age groups. According to a study dysphasia is common in about 35% of the general population, as well as an additional 30-40% of elderly and 18-20% of all persons in long term care facilities. Common complaints about the difficulty in swallowing tablets due to size, surface, form, and taste of tablets. Geriatric and pediatric patients and traveling patients who may not have ready access to water are in need of easy swallowing of dosage forms. These studies show an urgent need for a new dosage form like FDDS that make tablets disintegrate in the mouth without chewing or additional water intake and thus improve patient compliance.

Market view[11]:

The need for non-invasive delivery systems continues due to poor patient compliance with existing delivery regimens, limited market size for drug companies and drug uses, coupled with high costs of disease management. Pharmaceutical marketing is one reason for the increase in available fast-dissolving /disintegrating products. As a drug entity reaches the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A dosage form allows the manufacturer to extend the market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. In this regard, fast dissolving /disintegrating formulations are similar to many sustained release formulations that are now commonly available. An extension of market exclusivity, which can be provided by a fast dissolving/ disintegrating dosage form, leads to increased revenue, while also targeting underserved and under-treated patient population.

SUBLINGUAL TABLETS:

Tablets that disintegrate or dissolved rapidly in the patients mouth are convenient for young children, the elderly and patients with swallowing difficulties and in situation where potable liquids are not available. For these formulations the small volume of saliva is usually sufficient to result in tablets disintegration in oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa or it can be swallowed as a solution to be absorbed from gastrointestinal tract. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through sublingual blood vessels bypass the hepatic first pass metabolic process. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological action, dysphagia (Difficulty in swallowing) is a common problem of all age groups, especially elderly, children and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid intake diets have difficulties in swallowing these dosage forms[12,13]. The sublingual administration of the drug means placement of drug under the tongue and drug reaches directly into the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into reticulated vein which lies underneath the oral mucosa and transported through the facial veins, internal jugular vein and braclocephalic vein and then drained into systemic circulation. The main mechanism for the absorption of the drug into oral mucosa via passive diffusion into the lipoidal membrane[14] . The absorption of the drug through the sublingual route is 3-10 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.

Fig-1 : Route of sublingual drug administration

In terms of permeability, the sublingual area of the oral cavity is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (Route of the mouth)

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area. The differences in permeability are based on the relative thickness, the blood supply and degree of keratinization of these membranes. In addition to the differences in the permeability of the various mucus membranes, the extent of drug delivery is also affected by the physiochemical properties of the drug to be delivered[15] . Sublingual products have been developed for numerous indications ranging from migraines(for which rapid onset of action is important) to mental illness(for which patient compliance is important for treating chronic indications such as depression and Schizophrenia[16] .

Sublingual glands:

Sublingual glands are also known as the salivary glands which are present in the floor of the mouth underneath the tongue. These glands produce mucin and help to promote the production of saliva. Because of the secretions of the glands the interior area of the mouth is kept lubricated which is necessary for chewing and swallowing. Absorption means transfer of drug from its site of administration to the systemic circulation, so it is obvious that absorption is directly proportional to the membrane layer thickness. Sublingual > Buccal > Gingival > Palatal having mucosa thickness of 100- 200, 200,250,500-600 respectively. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action which makes it an appropriate route for drugs with short delivery period and frequent dosing regimen. The drug is released into saliva and its subsequent spreading may cause the drug to be absorbed across the oral cavity[17] .

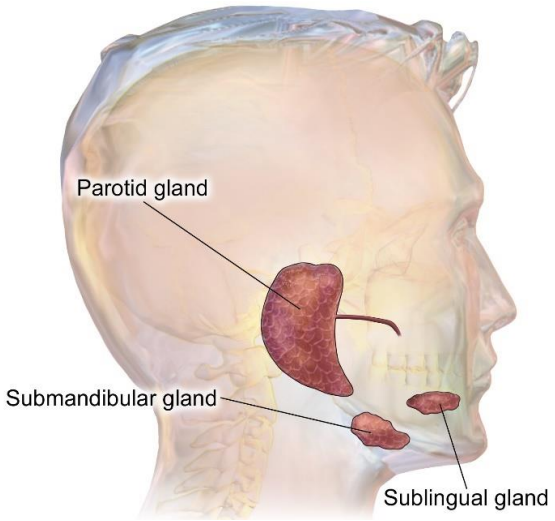

Fig-2 : Sublingual gland

Structural features of oral mucosa structure:

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium.

Mechanism of sublingual absorption:

The absorption potential of oral 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. Absorption of some drugs via oral mucosa is shown to increase by carrier pH is lowering (more acidic) and decrease with a lowering of pH(more alkaline)[18,19] . The cells of the oral epithelium and epidermis are also capable of absorbing by endocytosis (the uptake of particles by a cell as if they hollowly wrapping itself around it. 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 process operate within the oral mucosa. However, it is believed that acidic stimulation of the salivary glands with the accompanying vasodilation, facilitates absorption and uptake into the circular system. The mouth is lined with a mucus membrane which is covered with squamous epithelium and contains mucus glands. The sublingual mucosal tissue is similar to that of buccal mucosa[20] .

The salivary glands consists of lobules of cells which secretes saliva through the salivary ducts into the mouth. The three pairs of salivary glands are the Parotid, Submandibular and sublingual which lies on the floor of the mouth. The more acid the taste, the greater the stimulation of salivary output; serving to avoid potential harm to acid-sensitive tooth enamel by bathing the mouth in copious neutralizing fluid. The sublingual artery travels forward to the sublingual gland, it supplies the gland and branches to the neighboring muscles and to the mucus membranes of the mouth, tongue and gums. Two symmetrical branches travel behind the jawbone under the tongue to meet and join at its tip. Another branch meets and anastomoses with the submental branches of the facial artery. The

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sublingual artery stems from the lingual artery-the bodies 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 routes applying the greater part of the cerebral hemisphere[21,22] .

Criteria to formulate sublingual tablets:

- No bitter taste
- Dose lowers than 20mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non-ionized at the oral cavities pH
- Undergoing first pass effect

Factors affecting the sublingual absorption[23]:

1. Lipophilicity of drug
2. Solubility in salivary secretion
3. pH and pKa of the saliva
4. Binding to oral mucosa
5. Thickness of oral epithelium
6. Oil-water partition coefficient

1.Lipophilicity of drug: For a drug to be absorbed completely through sublingual route the drug must behave 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 favours the absorption of drug 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 for a base.

4. Binding to oral mucosa: Systemic availability of drugs that bind to oral mucosa is poor.

5. Thickness of oral epithelium: As the thickness of sublingual epithelium is 100- 200µm which is less as compared to buccal thickness. So, the absorption of the drug is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva.

6. Oil- water Partition coefficient: Compounds with favourables O/W partition coefficients are readily absorbed through the oral mucosa. An O/W partition coefficient range of 40-2000 is considered optimal for the drugs to be absorbed sublingually.

Advantages:

- A relatively rapid onset of action can be achieved compared to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
- Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious are incapacitated patients; convenience of administration as compared to injections are oral medications.
- Low dosage gives high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects.
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
- Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions.
- Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of anti- angina drugs.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

Disadvantages:

- Since sublingual administration of drugs interferes with eating, drinking and talking, this route is generally considered unsuitable for prolonged administration.
- Although this site is not well suited to sustain-delivery systems.
- Sublingual medications cannot be used when a patient is uncooperative or unconscious.
- The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the blood vessels. This will decrease the absorption of the medication.

II. Conclusion :

In conclusion, sublingual drug delivery is a promising alternative to traditional oral drug administration routes. The sublingual route offers a number of advantages, including rapid onset of action, avoidance of first-pass metabolism, and improved bioavailability. Sublingual drug delivery can be particularly beneficial for drugs that are poorly soluble or have low bioavailability when taken orally. Furthermore, the ease of

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administration and reduced risk of adverse effects make it an attractive option for patients who have difficulty swallowing or are unable to take medications orally. While sublingual drug delivery has shown great potential, further research is needed to optimize the design and development of sublingual drug formulations. Future studies should focus on identifying the optimal drug candidates, optimizing formulation parameters such as the choice of excipients and the drug dosage, and evaluating the safety and efficacy of sublingual drug delivery in different patient populations. Overall, sublingual drug delivery has the potential to revolutionize the way we administer medications and improve patient outcomes.

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