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Sublingual Drug Delivery System: A Promising Route For Systemic Drug Delivery

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ABSTACT

The delivery of drugs through the mucous membrane of the mouth is thought to be a promising substitute for oral administration. Sublingual literally meaning is “under the tongue”. Administrating substances is rapidly absorbed via blood vessels under tongue. The portionof drug absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolism processes giving acceptable bioavability. Sublingual tablet dissolve instantaneously, releasing the drug within a few second without the need of water and chewing. The objectives behind this reviewwere to summaries the benefits of sublingual formulation, mechanismof action, advantages of route of administration, factor affecting permeability of drug, variousin vitro evaluation parameters and commercially available sublingual dosage from. Sublingual tablet disintegrates rapidly and the small amount of saliva present is usually sufficient for achieving disintegration of the dosage form coupled with better dissolution and increased bioavability.Different sublingual technologies address pharmaceutical industries and patient need to enhanced lifecycle and appropriate dosing for pediatric, geriatric, psychiatric patients also patients with dysphagia.

Keyword: Sublingual tablets, patient compliance, Bioavailability, Oral route.

INTRODUCTION

Oraladministration is route where a pharmaceutical ingredient or substance will be taken through the mouth. Many medicinal products are taken by mouth. when administering certain medications locally and systemically, the sublingual route is the recommended method. In terms of a plentiful blood supply, quick beginning of action, enhanced bioavailability, avoidance of hepatic first-pass metabolism, influence from food, better patient compliance, and easy self-medication, this route is beneficial for oral medications. Compared to drug dosage, it offers a few clear benefits. Sublingual drug delivery has been effectively used by numerous innovative drug delivery systems in recent years, and they have been brought to market. The drug's physicochemical characteristics, the dosage form's design, and the permeability of the sublingual membrane all affect a drug's sublingual distribution and subsequent absorption.[1]

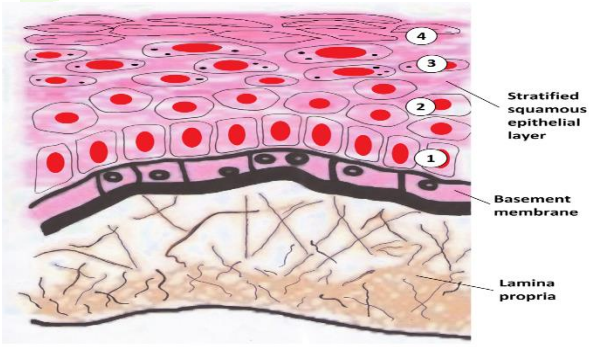
The physicochemical characteristics and formulation design are the main topics of this review article since it is only by understanding these aspects that drug molecules appropriate for sublingual delivery can be chosen and the final formulation can be optimized. When a medication is administered sublingually, it is inserted beneath the tongue and enters the bloodstream through the bottom of the mouth and the ventral surface of the tongue.[2]

Through the internal jugular, brachiocephalic, and facial veins, the dissolved medication is quickly absorbed into the vascular veins beneath the oral mucosa and then released into the systemic circulation. Direct systemic administration is made possible by the substance's direct access to the bloodstream via the highly vascularized oral mucosa absorption pathway. Sublingual medication delivery is utilized in medicine for certain barbiturates, enzymes, hormones, and cardiovascular medicines. This is an emerging field in the administration of numerous vitamins and minerals, which this way has been discovered to absorb entirely and with ease Under the tongue" and describes the process of giving medication orally such that the blood vessels beneath the tongue quickly absorb it. When oral tablets are not preferred due to their slower onset of action, sublingual delivery can be helpful. Sublingually given medications directly reach the systemic circulation through the floor of the mouth and the tongue's ventral surface. Acceptable bioavailability is achieved by circumventing the hepatic first-pass metabolic pathway for a portion of the drug absorbed through the sublingual capillaries. [3]

Since most people these days need immediate relief, the sublingual version is the most appropriate dosage type. Novel sublingual technologies address a broad spectrum of pharmaceutical and patient needs, such as easier dosage administration for small patients, the elderly, and mentally ill people who have swallowing difficulties, as well as more efficient lifecycle management. For medications with short half-lives, the sublingual route is highly suitable. [1,2]

The anatomy of the oral mucosa

The four sections of the oral cavity—the sublingual, buccal, gingival, and palatal—are where drug absorption can take place. These regions vary from one another in terms of their biochemical makeup, histological makeup, and capacity to hold the dose form long enough to for full medication absorption. The sublingual membrane, situated beneath the tongue at the floor of the mouth, is frequently utilized for both local and systemic medication administration**.** Mucous membranes consist of three separate layers. The epithelium, which forms a protective barrier and is made up of stratified squamous epithelial cells, is the outermost layer. The epithelial membrane's innermost layer is known as the basement membrane. The submucosa lies beneath the lamina propria, which is situated beneath the epithelium. Collagen and elastic fibres make up the hydrated, low-density layer of connective tissue known as the lamina propria. The oral submucosa has an abundant blood vascular supply. Following absorption from the sublingual mucosa, the medication diffuses straight into the venous circulation, which then flows into the superior vena cava through the internal jugular, subclavian, and brachiocephalic veins in the trunk. Unlike oral delivery, venous return from these regions enters the systemic circulation and avoids hepatic metabolism. Drugs that are directly injected into the bloodstream have better bioavailability and a quicker time to start working therapeutically. [4,5]



Represents the Anatomical Structure of oral mucosa

Drug Absorption through the Sublingual Region

Saliva has a pH between 5.5 and 7.0 and is primarily made up of mucus and enzymes like amylases and carboxylesterases that create a sticky, gelatinous film on every surface of the mouth cavity. Drug absorption and mucoadhesion are caused by sublingual membrane aggregation. The sublingual area's epithelium is between 100 and 200 µm thick and is not keratinized. Unlike other parts of the oral cavity, the sublingual lining's epithelial cells are permeable to drug absorption due to the presence of glucosylceramide, cholesterol, and cholesterol esters. After sublingual administration, several medications have faster

absorption and greater bioavailability due to their relative thinness and high permeability. When a quick start of action is needed, the sublingual area is thus a particularly practical place to obtain therapeutically appropriate concentrations of medications in a short amount of time. Saliva and tongue motions regularly wash out the sublingual area, making it unsuitable for the long-term storage of dose forms. [1,3]

Mechanism of drug absorption from the sublingual region:

Through a process called endocytosis, which is the ingestion of particles by cells, the cells of the oral epithelium and epidermis can also absorb particles. Usually, these absorbed particles are too large to permeate through their wall. Nonetheless, it's thought that stimulating the salivary glands acidically and causing extra vasodilatation helps with absorption and uptake into the circulatory system. Saliva is produced by lobules of cells in the salivary glands and enters the mouth through the salivary ducts. There are three pairs of salivary glands: the sublingual, which is located on the floor of the mouth, the parotid, and the submandibular. The more acidic the flavour, the greater the stimulation of saliva production, protecting acid-sensitive tooth polish by rinsing the mouth with an abundance of killing liquid. The mucous membrane that lines the mouth has mucous glands and is covered in squamous epithelium. Buckling mucosa and sublingual mucosal tissue are comparable. For a drug to be absorbed sublingually, it must be able to pass through the buckle mucous membranes by a diffusion mechanism called osmosis, which regulates both intestinal and sublingual retention.[5]

Drugs for sublingual administration

It is advised for those with gastrointestinal issues, such as ulcers, hyperactive bowel syndrome, celiac disease, individuals with digestive difficulties, the elderly, and those with disabilities, to absorb nutrients sublingually and to avoid interaction with the stomach system and liver. denotes immediate nutritional benefits, which are especially significant because they are unaffected by gastrointestinal side effects. Antianginal medications like nitrites and nitrates, antihypertensive medications like nifedipine, analgesics like morphine, and bronchodilators like fenoterol are a few examples of medications administered in this manner. It is also possible to inject some peptides, like oxytocin, and steroids, like estradiol. G. Hydrazine hydrochloride, apomorphine, prochlorperazine dimaleate {PRO}, and fentanyl citrate.The sublingual drug could be used to treat, Migraine, angina pectoris, hypertension, and antiatherosclerotic action dose form since it provides a quick release of the medication from the formulation and goes straight to the systemic circulation, avoiding the initial pass metabolism of medicines. [1,3]

Factors affecting the sublingual absorption [6,7]

Solubility in salivary secretion: The drug must be soluble in aqueous buccal fluids in addition to having a high lipid solubility; in other words, the drug must be biphasic in order to be absorbed.

Binding to Oral Mucosa: Drugs that bind to the oral mucosa have low systemic availability. The 100-200 μm thickness of the oral epithelium is the thickness of the sublingual epithelium, not exactly the buccal thickness. This results in faster absorption of drugs through thinner epithelia and also enables drug immersion in small amounts of saliva.

pH and pKa of the saliva: The saliva's PH is 6.0; this pH Favors the absorption of drugs which remain unionized. Also, if the pKa is greater than 2 for an acid and less than 10 for a base, the absorption of the drugs through the oral mucosa occurs.

Lipophilicity of Drug:Drugs that are absorbed sublingually must have a lipid solubility that is marginally higher than that of GI absorption in order to allow for passive permeation and full absorption.

Mouth epithelial mucosa thickness: Due to thickness of epithelial mucosa (100-200μm) is minimum, permeability of drugs is better due to thin epithelial mucosa. Hence, absorption of drug in low volume of saliva is easy.

SUITABILITY OF DRUG FOR PREPARATION OF SUBLINGUAL TABLET:[7]

- Mask the bitter taste of drugs which influence the patient compliance.
- Dose like 10 to 50 mg are suitable for this area.
- Having less molecular weight of drug.
- Stable at hydrated region like mouth.
- Practically non ionized at neutral pH.
- Drugs have metabolized by liver which results in poor bioavailability are suitable for sublingual dosage form.
- Drugs not given in parenteral preparation.
- Should have lower bioavailability.

SUBLINGUAL FORMULATION: [8,9,10,11]

Fast disintegrating sublingual tablets:

Tablets that dissolve quickly in the mouth are useful for elderly patients, small children who have trouble swallowing, and situations where drinkable liquids are unavailable. A fast-disintegrating tablet is a solid medication delivery system that dissolves quickly under the tongue without the need for water. The medication entered the salivary flow, dissolved, spread, and was absorbed in the sublingual area. These dosage forms are more convenient and often chosen over traditional solid oral forms. In terms of the pharmaceutical industry, sublingual tablets may open up new business opportunities in the form of product discrimination, line addition with life cycle supervision, uniqueness, and patent life safety. The European Medicines Agency Committee of Medicinal Products for Human Use (CHMP) described sublingual tablets as having great advantages for children. The size, disintegrating time, and taste play important roles in the commercial potential of formulation. A fast-disintegrating time reduces any choking hazard and will also make it harder to split out the dose. Water-breathable and swelling are the two most important for disintegration action for most of the sublingual medications.

Bio adhesive sublingual tablets:

This latest concept of sublingual tablet based on collective mixtures consisting of water-soluble carrier covered with small particles of substances and bio adhesive polymer. By these substances it may be easy to make tablets of high dissolution rate with combination of polymers of bio adhesive property.

Sublingual mouth spray:

Formulation which given drug in dispersed or dissolve in solvent form, filled in the container with metered valve and on deposition a suitable dose of drug delivered through valve in a sublingual area.

Lipid matrix sublingual tablets:

Lipid sublingual tablets represent a dosage form that leverages advancements in liposomal and sublingual technologies to produce a medication with a faster and more comprehensive absorption rate compared to other conventional oral drug delivery methods. For many drugs taken orally, this dosage form is quick, easy, and reliable.

Sublingual vitamin tablets:

The sublingual vitamin that all doctors offer is vitamin B12 (cyanocobalamin). Vitamin-B12 is very helpful in our body's metabolism only taken by mouth.

Sublingual immunotherapy:

Immunotherapy known as sublingual immunotherapy suggested extracting a liquid drop of allergen under the tongue. For those with severe allergic conjunctivitis or asthma, sublingual immunotherapy is very helpful in treating seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), which are spreading more quickly among people who work in industries. Allergen-specific immunotherapy (SIT)

requires monthly vaccinations for three years and can have negative side effects, including anaphylactic reactions. This immunotherapy is one of the safest and most effective treatments for allergic rhinitis, and it has an advantage over subcutaneous immunotherapy.

ADVANTAGES:

- Rapid onset of action is achieved as it different from other routes. In case of elimination of required therapy, the formulation has to be removed.
- Liver is surpassed and drug protected from acid attack with digestive enzymes of the middle gastro intestinal tract.
- Increase patient compliance because of cancelation of pain due to injections.
- Intake of drug to senseless condition of patients is easy for administration other than these medications.
- Ease to administered to those patients who are unable to swallow a tablet, e.g., paediatric, geriatric and psychiatric patients.
- The main advantage of this dosage form it protect drug from degradation which occur due to pH and digestive enzyme in GIT.
- The main advantage of this dosage form it protect drug from degradation which occur due to pH and digestive enzyme in GIT.
- Low dosage gives high efficacy and also decreases risk of side effects.
- The wide contact surface area gives fast and extensive drug absorption. Hence, instant action in urgent situations like, asthma.

METHODS OF PREPARATION [7]

The subsequent techniques might be used to make sublingual tablet

1. Direct compression Method
2. Compression moulding
3. Sublimation method
4. Spray drying method

Direct compression Method

This method is commonly used in commercial manufacturing industries of sublingual tablets because of easy and low-cost process, because of basic substances which mixed properly and no requirement of additional granulation steps to lubricate and simple compress of tablet. This process involves better strength and promotable instant disintegrate. The immediate compressed sublingual medicated formulation having quickest soluble super disintegrants, binders and lubricants. They also involve dried binder, surface active agent, artificial sweeteners, and flavouring agents. Sugar-based excipient is widely used as bulked agent due to their heavy water solubility, sweet property and appreciable oral feel. Almost all sublingual formulations involve some saccharide-based material. The suitable amount of disintegrant is critical situation to get a fast disintegration and dissolution rate.

Advantages:

1. Reduced production cost and time.
2. Product stability can be improved.
3. Less number of equipment's are required, less process validation.
4. Suitable for the process of water and moisture sensitive APIs.
5. The chances of batch-to-batch variation are negligible.
6. Dry process.
7. Low labour inputs.
8. Lower consumption of power.

Compression moulding

Tablets are made with hydrophilic components to maximize drug disintegration. A powder mass is moistened with a hydroalcoholic solvent and then crushed into a dosage form. After that, time is allowed for the solvent system to evaporate. The flavor of the drug particles is produced by spray-congealing a molten mixture of sodium carbonate, lecithin, hydrogenated cottonseed oil, polyethene glycol, and an active ingredient into lactose-based tablet triturate. One of the benefits of the moulding process is its very porous mass, which promotes rapid disintegration because solvents are removed through drying. The active ingredient is usually mixed with lactose, dextrose, sucrose, mannitol, or another appropriate diluent that can serve as the base to create moulded tablets. This base ought to dissolve in water with ease.

Sublimation method

Sublingual tablets dissolve quickly primarily due to a pore in the tablet's structure. Because conventional tablets lack pores, highly water-soluble ingredients may not dissolve as quickly in them. Therefore, the sublimation process uses volatile materials to create a porous matrix.

Spray drying method

This method produces a free-flowing support matrix by spraying an aqueous solution comprising matrix (Gelatin, either hydrolysed or unhydrolyzed), along with other components, into a spray dryer. After combining with the active ingredient, this free-flowing support matrix was compacted to create a tablet that dissolves quickly. It is composed of the bulking ingredient mannitol and the disintegration agent sodium starch glycolate or croscarmellose sodium. Two effervescent agents, citric acid and sodium bicarbonate, improve dissolving and disintegration. In an aqueous media, sublingual tablets produced with this method dissolve in less than 20 seconds.

Evaluation of sublingual tablets: [4,9,10,11]

There are two types:

1. Pre - compression

2. Post – compression

1.PRE-COMPRESSION

Angle of repose:This method will be performed by funnelling method; the powdered blend will be poured through the funnel fixed at a position 2 cm above the plane. And powder will be poured until the upper tip of blend touch the lower tip of funnel.

$$\theta = \text{Tan}^{-1}\, h / r,$$

Where,

h is the height of the powder cone

r is the radius of the powder cone

Bulk density: All amount of powder will be precisely weight and will be transferred in measuring cylinder. Value will be measured by volume occupied by powder without any tapping on cylinder hence, the formula is given below:

Bulk Density = Weight of the powder/Volume of the bulk

Tapped Density:The procedure will be same as bulk density after that the measuring cylinder will be tapped for 100 times then tapped volume occupied by blend powder will be measure.

Tapped Density =Weight of the powder/Volume of the tapped

Compressibility Index or Carr's Index: Calculated by this formula

CI= (TD-BD) ×100 / TD.

Where,

TD is tapped density of powder blend;

BD is bulk density of powder blend

Hausner's Ratio:

This will measure the indirect flow of powder. This formula is used to compute it :

Hausner's Ratio (HR) = Tapped Density \ Bulk Density

POST-COMPRESSION

Weight Variation:

Twenty pills will be ingested and their individual and collective weights will be calculated on an electronic weighing scale in accordance with the I.P. protocol for uniformity of weight. One tablet's average weight will be determined using the entire weight.

Thickness and Diameter: By verniar caliper. Vernier Caliper will be used to measure diameter of each tablet. It will be measured by simply placing the tablet in between the jaws of verniar caliper and slide the scale arm to press the tablet against the stationary arm then the reading displayed will be noted.

Hardness: The hardness of the tablet could be determined using the Monsanto hardness tester (cadmach). The tablet will be placed diagonally between the 2 plungers of the tablet hardness tester; and then pressure will be applied until the tablet breaks down into two pieces; and the reading on the scale will be noted down.

Friability:20 tablets of each batch will beweighed and then tested by friabilator at speed 25 rpm for 4 min. Then weigh will be checked and calculated.

Disintegration Time:

The disintegration apparatus will be used to conduct the test. The time it will take for the tablet to completely disintegrate, leaving no palpable mass in the apparatus, in phosphate buffer (pH 6.8) maintained at 37°C 2°C will be measured.

Wetting Time:

A small petridish filled with 6ml of distilled water will be placed with a piece of tissue paper that has been folded twice. The time it will take for water to reach the tablet's upper surface will be measured after a tablet is carefully placed on the paper. If wetting time witnessed will be lessthat means the tablet will be more porous.

In vitro Drug Release Studies:

The in vitro drug release will be examined using a USP Dissolution Apparatus II (paddle type) at 50 rpm in 900 ml of phosphate buffer (pH 6.8) at 370.5oC. 10 ml of the sample will be removed and filtered repeatedly. After each withdrawal, an identical volume of the medium will be added back into the container to keep the volume steady. UV light will determine the samples' absorbance. Spectrophotometer will be set to maximum value The median drug release values will be displayed as time-dependent cumulative% medication will release.

Conclusion: The study revealed that the sublingual tablet has proved to be better patient compliance and better way of drug delivery for pediatric and geriatric patients. This analysis shows the range of commercially available sublingual formulation made using various production techniques. The sublingual tablet offers numerous significant advantages over conventional dosage forms because of improved

efficacy, bioavailability, and rapid onset of action, better patient compliance and acceptance. It can be prepared in several ways and product performance depends upon the drug suitability and excipients selection in the delivery system.

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