Sublingual Drug Delivery: A Promising Route for Enhanced Bioavailability and Patient Compliance

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ABSTRACT:

Sublingual drug delivery has gained significant attention in recent years as a promising alternative to conventional oral administration. This route offers several advantages, including enhanced bioavailability, rapid onset of action, and improved patient compliance. The sublingual mucosa, composed of highly vascularized and permeable tissues, provides an ideal site for drug absorption, allowing direct entry into the systemic circulation and bypassing first-pass metabolism.

This review article comprehensively examines the principles and mechanisms underlying sublingual drug delivery. It discusses the anatomical and physiological characteristics of the sublingual mucosa, highlighting its unique properties that facilitate drug absorption. Additionally, various factors influencing sublingual drug absorption, such as drug physicochemical properties, formulation approaches, and dosing considerations, are extensively reviewed.

Furthermore, this article presents a detailed analysis of the advantages associated with sublingual drug delivery. The rapid onset of action, achieved by the rich blood supply and avoidance of gastrointestinal degradation, makes this route particularly suitable for drugs requiring quick therapeutic effects. The improved bioavailability and reduced inter- and intra-individual variability enhance the predictability of drug response and enable precise dosing. Moreover, the sublingual route offers a non-invasive and patient-friendly administration method, potentially improving medication adherence and overall treatment outcomes.

Several case studies are included to illustrate successful sublingual drug delivery, highlighting its efficacy in diverse therapeutic areas, including analgesia, cardiovascular disorders, and hormone replacement therapy. Moreover, the review discusses recent advancements in formulation technologies, such as nano-formulations and mucoadhesive systems, which further optimize drug delivery and enhance therapeutic outcomes.

KEYWORDS: Sublingual drug delivery, bioavailability, patient compliance, mucosal absorption, lipophilicity.

INTRODUCTION :

Sublingual Drug Delivery :

Drug delivery via sublingual route was introduced by Dr. Paulson in the 1800s and 1858, Field demonstrated that when nitroglycerin is placed on the tongue it readily gets absorbed across the oral cavity's mucosa resulting in nausea, fullness in both sides of the neck, and other clinical effects. Since then, several molecules have been developed for sublingual drug delivery owing to the numerous advantages over other routes of administration.

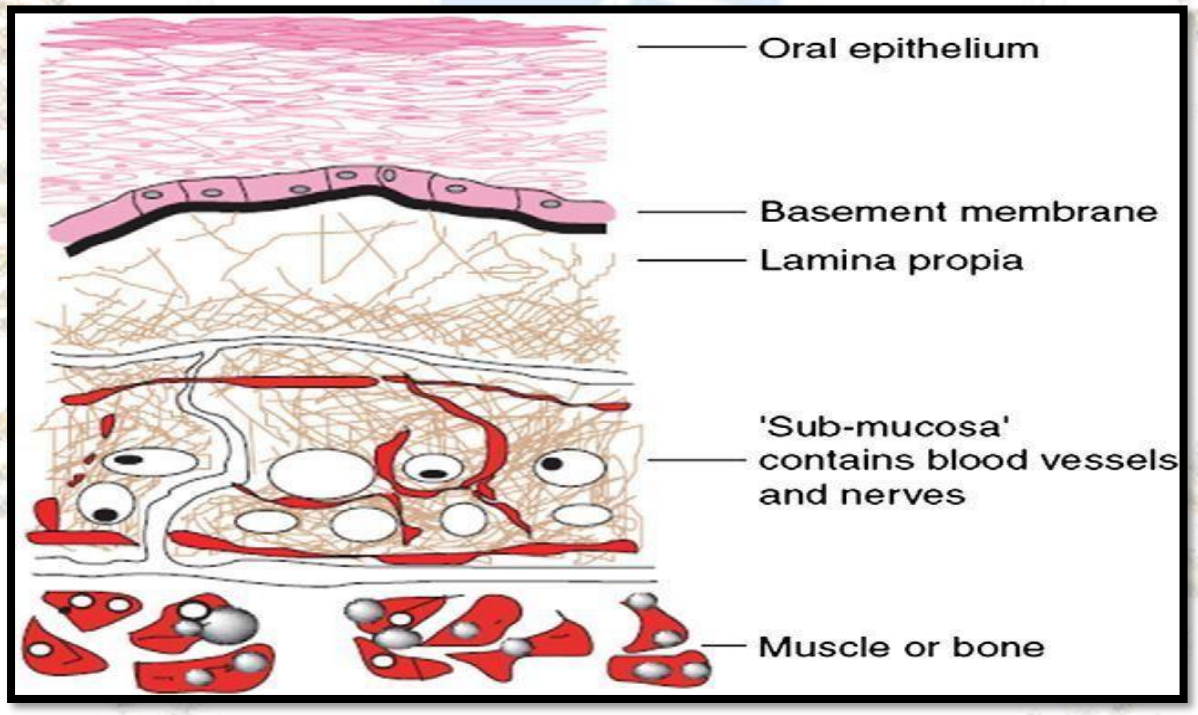
Sublingual products have been designed for numerous indications ranging from migraine (for which, rapid onset of action is important) to mental illness (for which, patient compliance is important for treating chronic indications such as depression and schizophrenia). By selecting the appropriate pharmaceutical excipients in the correct proportion, in combination with optimal manufacturing techniques, the sublingual tablets could be manufactured as small and flat, compressed lightly to keep them soft, and designed to dissolve in small quantities of saliva and absorbed by simple diffusion. (1,2)

Structure of sublingual mucosa

Anatomically, the sublingual region is located in the oral cavity, which is composed of the tongue, bounded by a hard and soft palate and mucous membrane under the tongue. The mucous membrane lining the floor of the mouth and the inferior surface of the tongue is called sublingual mucosa. Sublingual mucosa consists of thin non-keratinized stratified squamous epithelium (~100 µm) with multiple layers of closely packed cells attached to underlying structures through loose fibrous connective tissue called lamina propria. The basal layer of epithelium contains mitotically active cells, which continually undergo mitotic division to produce new cells to migrate to thesurface to replace those that are shed. (3)

The interface between oral epithelium and connective tissue is a structureless layer called the basement membrane. It is about 1-2 µm in diameter and is represented by irregular and upward projections of connective tissue in the epithelium. Lamina propria is followed by a layer of loose fibrous and fatty connective tissue called submucosa. It separates the oral mucosa from underlying bone or muscle and contains major blood vessels, nerves, and a few salivary glands. Sublingual mucosa along with buccal mucosa, lips, and soft palate constitute the lining mucosa, which represents approximately 60% of the total surface area of the oral cavity. The structure of the sublingual mucosa is shown in **Figure.1**(4)

Fig No.1 Schematic representation of sublingual mucosa



The mucosa lining the sublingual cavity has a surface area of 25 cm^2 and an epithelial thickness of approximately 100 µm. anterior branch of the external carotid artery called the lingual artery supplies blood to the tongue and floor of the oral cavity. The sublingual artery, a branch of the lingual artery provides blood to the floor of the mouth and the sublingual gland. The artery runs parallel to the surface of the submucosa and extends several branches that form an extensive capillary network beneath the basal epithelial cells. (5,6)

Blood from the oral mucosa is drained via lingual facial and retromandibular veins opening into the internal jugular vein. Blood supply to sublingual mucosa is shown in **Figure.2**

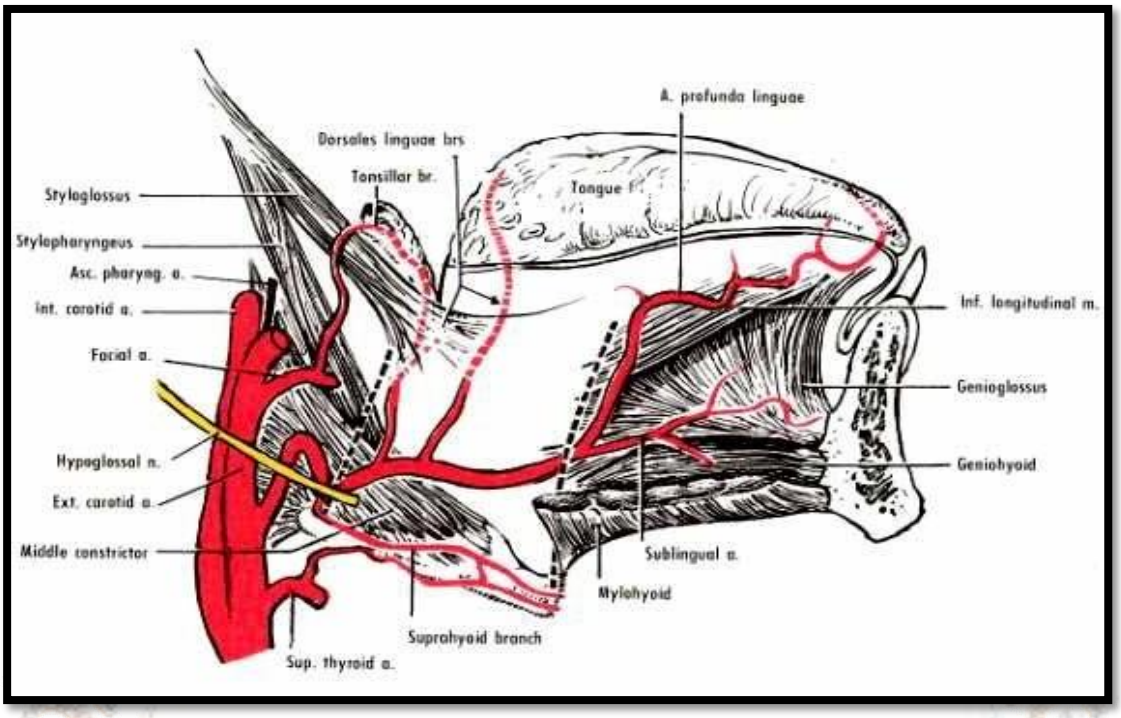


Fig No. 2 Blood supply to the sublingual mucosa

The lining of the oral cavity is referred to as the oral mucosa and includes the buccal, sublingual, gingival, palatal, and labial mucosa In **Table.1**, the thickness and surface area of oral cavity membranes have been shown and compared to other mucosalsystems, sublingual mucosa delivery is a very attractive route for systemic administration of drugs as sublingual mucosa is more permeable due to less thickness and more surface area with rich blood supply. (7)

Oral cavity membrane	**Thickness (µm)**	**Surface area (cm^2)**
Buccal mucosa	500-600	5.2
Sublingual mucosa	100-200	26.5
Gingival mucosa	200	-
Palatal	250	20.1

Table No. 1Thickness and surface area of oral cavity membranes

Mechanism of sublingual absorption

Following sublingual administration, the drugs are majorly absorbed across the mucous membrane by passive diffusion. The rate of diffusion is dependent on the molecular weight, the solubility of the drug, the concentration gradient, temperature, the surface area of the membrane, and the proximity of the molecule to the membrane physical models have been proposed to describe drug absorption from saliva through lipid layer mucous membrane into systemic circulation. The rate of absorption across the mucous membrane is directly related to the partition coefficient. Some compounds, such as glutamic acid, L-ascorbic acid, nicotinic acid, and, thiamine are transported via carrier-mediated process. Mechanism of sublingual tablet absorption by passive diffusion process is shown in below **Figure. Below 3**(8,9)

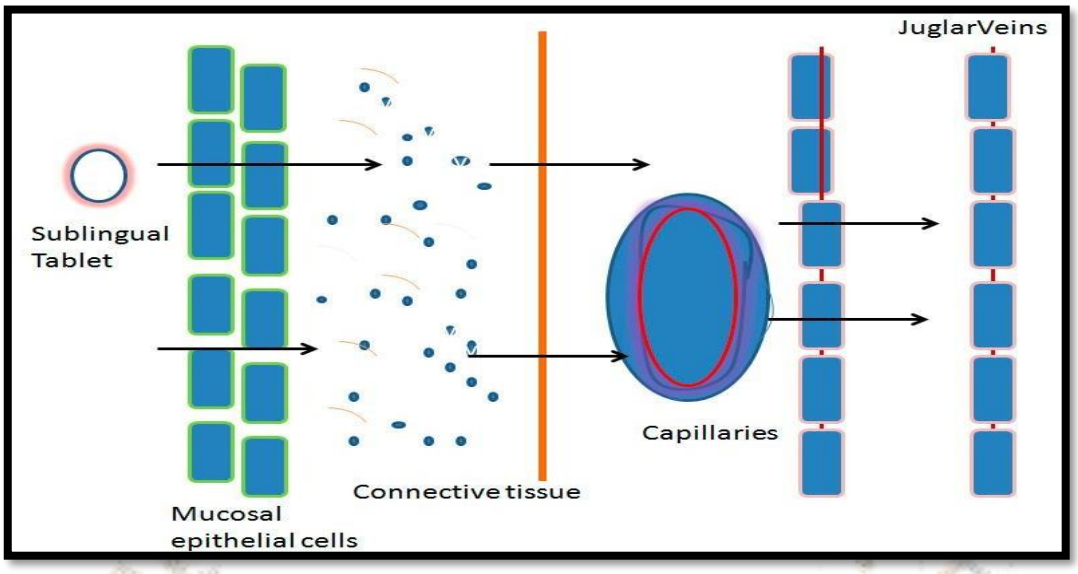


Fig No.3 Mechanism showing sublingual absorption

Factors affecting the sublingual absorption

Different physicochemical properties of a molecule govern the choice of route for transport across oral mucosa mainly lipid solubility, degree of ionization, pK_a of the drug, pH of the drug solution, presence of saliva, membrane characteristics, molecular weight, and size of the drug·

Lipophilicity of drug

For a drug to be absorbed completely through a sublingual route by passive permeation, the drug must have slightly higher lipid solubility than that required for GI absorption. Satisfactory oral absorption of drugs has been observed over a wide range of log P (octanol/water partition coefficient) values of 1 to 5.

Solubility in salivary secretion

In addition to high lipid solubility, the drug should be soluble in saliva i.e. biphasic solubility of the drug is necessary for absorption. As the log P value increases beyond 5, the solubility in the saliva is usually not enough to provide adequate concentration for diffusion through the lipid bilayer. 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 in lower absorption rates and vice versa. (10)

pH and pK_a of the saliva

The pK_a of drugs also plays a crucial role in drug transport across the oral mucous membrane based on the pH-partition theory. The mean pH of saliva is 6.0, usually ranging from 5.6 to 7.6. Thus, a basic drug administered as a salt predominantly exists as a free unionized base if the pH is raised above its pK_a value and this increase in the unionized fraction of a drug, increases its bioavailability. For this reason, the inclusion 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. Also, the absorption of the drugs through the oral mucosa occurs if the pK_a is greater than 2 for an acid and less than10 for a base.

Binding to the oral mucosa

The systemic availability of drugs that bind to oral mucosa is poor.

The thickness of the oral epithelium

The thickness of sublingual epithelium is 100-200 µm which is less as compared to buccal epithelium thickness. Hence, the absorption of drugs is faster due to thinner epithelium and also the immersion of the drug in a smaller volume of saliva.

Oil to the water partition coefficient

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

Advantages of sublingual tablets

The advantages include rapid onset of action, improved bioavailability, and rapid absorption of drugs through pre-gastric absorption of drugs from the mouth, pharynx, and esophagus as saliva passes down, convenience for administration i.e. without water anywhere and anytime, possibility of dose reduction with fewer side effects and improved patient compliance due to the elimination of associated pain with injections. (4)

It also provides new business opportunities like product differentiation, product promotion, patent extension, and life cycle management.

Disadvantages of sublingual tablets

Disadvantages include that, drugs with an unpleasant taste or with obnoxious odor or drugs, which irritate the mucosa are not suitable for sublingual administration.

Eating, drinking and smoking may hamper the absorption of drugs and are not well suited for sustained delivery systems.

Loss of the dose may occur due to salivary flow and swallowing (if the patient is noncooperative or unconscious) and administration of a high dose is not possible due to the relatively smaller surface area, as compared to GIT.

Manufacturing sublingual tablets-technology platforms

In the recent past, several new advanced technologies have been introduced for the formulation of sublingual dosage forms like lyophilization, direct compression, spray drying, sublimation, and nanonization. These techniques are based on the principles of increasing porosity and/or addition of super disintegrants and water soluble excipients in the tablets. The formulations prepared from these techniques differ from each other based on the factors like mechanical strength of the final product, drug and dosage form stability, mouth feel, taste, rate of dissolution of the formulation in saliva, rate of absorption from saliva, and overall drug bioavailability. (3)

Direct compression

The direct compression method is commonly used for the 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 further granulation steps before lubrication and compression. Sublingual tablets manufactured by the direct compression method exhibit good mechanical strength and acceptably fast disintegration.

The directly compressible sublingual tablet formulation containsdirectly compressible soluble excipients, super disintegrants, and lubricants along with dry binders, buffers, surface active agents, sweeteners, and flavors. Sugar-based excipients are widely used asbulking agents because of their high aqueous solubility, sweetness, pleasant feel in the mouth, and good taste masking. Sometimes effervescent agents are used to increasing the disintegration and dissolution of sublingual tablets along with mouth feel.

Freeze drying

It is one of the well-established processes in the industry. The process involves lowering the temperature of the product in an aqueous medium to below freezing under a high vacuum. A gradual temperature rise is applied during the drying process to extract the water in the form of vapor, which is collected as ice on a condenser. The product temperature at the ice sublimation interface and the collapse temperature of the formulation is critical to obtaining a freeze-dried cake of quality structure. This process retains the physical structure and preserves the material for

the storage or transport of biopharmaceuticals.

The freeze-drying process may result in a product with amorphous, usually light, and highly porous structures that allow rapid dissolution or disintegration leading to enhanced bioavailability.

Fluid bed top spray granulation

Emerging innovative technologies like fluid-bed granulation are being explored for improving the granulation process, thereby improving the uniformity, porosity, and disintegration time of low-dose fast dissolving tablets. The drug is dissolved in a granulation solvent and it is sprayed over a diluent during, which the crystalline form of the drug converts to an amorphous form. Improved content uniformity, dissolution, and bioavailability are the advantages of this process. The prepared tablets disintegrate rapidly in contact with saliva in times ranging, from 30 seconds to 3 minutes.

Sublimation technology

The basic principle involved in the sublimation technique is the addition of a volatile salt to the tableting component to obtain a substantially homogenous mixture and the removal of volatilizing salt creates pores in the tablet, which helps in achieving rapid disintegration when the tablet comes in contact with saliva. The tablets were subjected to vacuum at 80°C for 50 minutes to eliminate volatile components and thus create pores in the tablet.

Volatile salts such as camphor, ammonium bicarbonate, naphthalene, urea, etc. are used as sublimable components to prepare porous tablets. (2)

Considerations critical to product quality attributes

To develop a sublingual tablet that can elicit the desired physicochemical and mechanical properties of the drug product at the site of absorption, it is important to understand, control, and monitor the following quality attributes: particle size of active pharmaceutical ingredient (API), wetting time, disintegration and dissolution, content uniformity, hardness, friability, size and weight variation, stability, texture and taste masking, etc.

Applications of sublingual tablets

Sublingual drug administration is applied in the field of cardiovascular drugs, steroids, some barbiturates, and enzymes. It has been a developing field in the administration of many vitamins and minerals, which are found to be readily and thoroughly absorbed by this method. Nutrition, which is absorbed sublingually avoids exposure to the gastric system and liver, which means direct nutritional benefits are particularly important for sufferers of gastrointestinal difficulties such as ulcers, hyperactive gut, coeliac disease, and those with compromised digestion.

Drugs like cardiovascular drugs such as nitrites and nitrates,analgesics such as morphine, anti-hypertensive such as Nifedipine and bronchodilators such as fenoterol could be administered successfully through sublingual routes to show their rapid onset of action.

The sublingual formulations are used for acute analgesia in pre-hospital and hospital emergency department care, and also for pediatric acute pain management. (8)

Treatment of angina pectoris, hypertension, and anti-atherosclerotic activity could be done effectively with the sublingual dosage form because it offers the fast release of the drug from the formulation and it reaches the systemic circulation directly, which bypasses the first pass metabolism of drugs.

The sublingual administration of vaccines may be used against various infectious diseases. Preclinical studies have found that sublingual vaccines can be highly immunogenic and may protect against influenza virus and Helicobacter pylori·

DRUGS ADMINISTERED BY SUBLINGUAL ROUTE:

Table 2: Marketed Products of Sublingual Tablet

Brand Name	Catergory	Srength
Abstral Fentanyl Citrate	Opioid Analgesic	50, 100, 200, 300, 400, 600, 800 µg
Subutex Buprenorphine	Opioid Analgesic	2 and 8mg
Avitan Lorazepam	Antianxiety	1, 2 mg
Edular Zolpidem tartrate	Sedatives/ Hypnotics	5, 10 mg
Isordil Isosorbide dinitrate	Vasodilators	2.5, 5 10mg
Suboxone Buprenorphine hydrochloride	Narcotic + Opioid antagonist	2/0.5, 8/2 mg
Nitrostat Nitroglycerine	Antianginal	0.3 mg , 0.4 mg , or 0.6 mg

CONCLUSION:

In conclusion, sublingual drug delivery represents a promising approach with significant potential for improved drug bioavailability and patient compliance. The comprehensive understanding of the underlying principles and factors influencing sublingual absorption presented in this review can guide the development of optimized formulations and facilitate the translation of sublingual drug delivery into clinical practice.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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