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REVIEW ON: SUBLINGUAL DRUG DELIVERY SYSTEM

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ABSTRACT

Sublingual administration is frequently utilized for medications that are metabolized or degraded in the gastrointestinal tract first. Drug administration through the oral mucous membrane is seen to be a promising alternative to the oral route. Sublingual administration offers faster onset of action and more patient compliance compared to oral tablets or pills. Fast disintegrating sublingual tablets release drugs beneath the tongue and breakdown quickly within minutes. The sublingual portion of the oral cavity (the floor of the mouth) has higher permeability than the buccal (cheek) and palatal (roof of the mouth) areas. Sublingual blood vessels absorb the medication, bypassing hepatic first-pass metabolism, resulting in satisfactory bioavailability. Various techniques are utilized to create sublingual dosage forms. New sublingual technologies address a wide range of pharmaceutical and patient demands, from improved life-cycle management and simple dosage for dysphagic pediatric, geriatric, and psychiatric patients. This study covers the benefits, drawbacks, sublingual gland, and factor affecting the sublingual absorption.

KEYWORDS: Sublingual delivery, Oral cavity, Improved bioavailability, Dysphagia.

INTRODUCTION

Over the past two decades, novel drug delivery systems have been in high demand due to improved patient compliance and emergency options. The goal of delivering a rapid start of pharmacological effect gave rise to systemic drug delivery via the sublingual route. Sublingual administration involves placing the drug under the tongue, allowing it to enter the bloodstream through the ventral surface and floor of the mouth. Drug solutes enter

the reticulated vein beneath the mouth mucosa, travel through the facial veins, internal jugular vein, and brachiocephalic vein, and eventually reach the systemic circulation. The highly vascularized buccal mucosa absorbs substances directly into the bloodstream, resulting in systemic delivery.[1]

The amount of medication absorbed by sublingual blood vessels circumvents the liver's first-pass metabolism and has a satisfactory bioavailability. Dysphagia, or difficulty swallowing, is a frequent issue affecting people of all ages. People who drink consumes less liquid often find it difficult to swallow solid food.[2] Drug absorption in the oral mucosa occurs mostly by passive diffusion into the lipoidal membrane.[3]

A reduction in oral pH brought on by salivary gland hypofunction can result in a larger ionized fraction of fentanyl and decreased lipophilicity. Additionally, this disease is linked to a number of abnormalities of the oral mucosa that might alter the mucosa's permeability.[4]

Sublingual medication absorption is 3-10 times higher than oral absorption, and only surpassed by hypodermic injection. Tablets disintegrate easily in the mouth due to the tiny volume of saliva required for dissolution. Sublingual absorption is often quick, but has a brief duration. Nitroglycerine, an excellent antiangina medication, undergoes substantial metabolism when taken orally (>90%). It quickly absorbs through the sublingual mucosa and reaches its maximal plasma level within 1–2 minutes. Sobrero, who discovered nitroglycerin (NTG), detected medication absorption through the oral mucosa in 1847. Sobrero discovered that placing nitroglycerin on the tip of the tongue created a severe headache that lasted many hours.[5]

Overview of the Oral Cavity

The outermost layer of the oral mucosa is made up of stratified squamous epithelium. A lamina propria, the basement membrane, and the submucosa, the deepest layer, are located underneath this. In terms of permeability, the oral mucosa is typically in the middle of the intestine and epidermal mucosa. Since the various oral mucosa have different structures and functions, there are significant variances in permeability between the various oral cavity regions.[6]

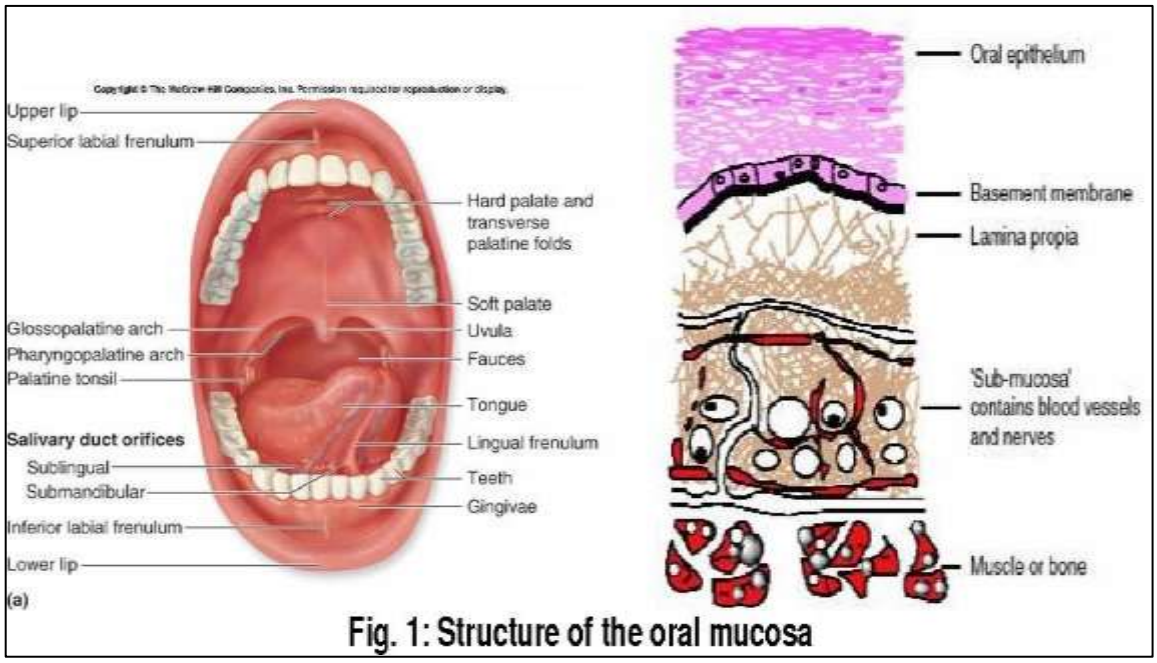

Fig. 1: Structure of the oral mucosa

Sublingual Glands

The sublingual gland is the smallest important salivary gland. Sublingual glands are located on the floor of the mouth, beneath the tongue. These glands create mucin and contribute to saliva production, which is important for medication breakdown.

Glands secrete a substance that mingles with food, aids in chewing, and coats the food to facilitate easy digestion.[6] Insufficient salivation can impede the swallowing process and cause food particles to become lodged in the throat. The drug is absorbed in the oral cavity in the following order: Sublingual > buccal > gingival > palate. The sublingual route has strong permeability and vascularity, resulting in a quick commencement of effect. The medication is diluted in saliva and subsequently adsorbed throughout the mouth.[7,8]

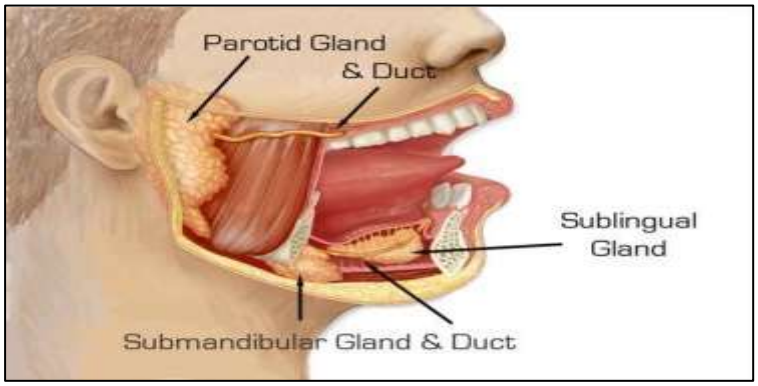

Fig. 2: Sublingual Gland.

Permeability across the sublingual mucosa

Compared to keratinized barriers like the stratum corneum, the nonkeratinized sublingual mucosa is not a conspicuous permeability barrier; rather, the superficial layers of the epithelium constitute a significant barrier to the transport of molecules over the sublingual mucosa. This barrier restricts the amount of potentially hazardous exogenous compounds and medications that can pass through the membrane. The "membrane-coating granules" (MCGs)-derived intercellular substance in the sublingual mucosa is responsible for the permeability barrier. MCGs occur in the epithelium's superficial cell layers.[9]

Saliva that has a pH of 5.5–7.0 is secreted by the salivary glands that are located in the mouth. Amylase and carboxyl esterase are two examples of the enzymes found in saliva, along with protein and carbohydrate complexes known as mucus. A cohesive gelatinous layer forms on all surfaces of the mouth cavity due to mucus's negative charge at physiological pH. Drug absorption is made possible by this cohesiveness, which enables the drug's mucoadhesion to the epithelial tissue.[10] The oral mucosa is a leaky epithelium that sits between the epidermis and the intestinal mucosa. The buccal mucosa's permeability is thought to be 4–4000 times higher than that of the skin. The permeability of the oral mucosa decreases with keratinization, with the sublingual mucosa being thinner and non-keratinized, while the buccal mucosa is thicker and non- keratinized.[11]

The sublingual mucosa functions as a powerful barrier, preventing most chemicals from passing through it and allowing only trace amounts to do so. Therefore, only highly potent compounds can be administered sublingually in order for the few amounts of medication that do get through to produce a therapeutic effect. Consequently, expanding the variety of chemicals that can be supplied sublingually has made it crucial to identify safe and efficient permeation-enhancement techniques.[12]

Sublingual drug absorption mechanism

The permeability of the solution, also referred to as osmosis, the drug's molecular weight, ionization, and lipid solubility all have an impact on absorption.[13] The medication is absorbed by the oral epithelium's cells through the mechanism of endocytosis. It is improbable that the same mechanism occurs throughout the stratified epithelium. Furthermore, it is improbable that active transport mechanisms function within the oral mucosa.[14] Acidic stimulation of salivary glands, together with

vasodilation, is thought to improve absorption and uptake into the bloodstream. The mucous membrane lining the mouth has mucous glands and is covered with squamous epithelium. The buccal mucosa and sublingual mucosal tissue are comparable.[15,16] The salivary ducts allow saliva to be secreted into the mouth by lobules of cells that make up the salivary glands. Salivary glands are divided into three pairs: Parotid, Submandibular, and Sublingual, located on the mouth's floor. The more acidic the taste, the more salivary flow is stimulated. This also helps to protect acid-sensitive tooth enamel by providing adequate neutralizing fluid. Salivary secretion stimulates oxygen consumption and vasodilator production, leading to enhanced glandular blood flow and metabolism. The sublingual artery proceeds forward to supply the sublingual gland, as well as the surrounding muscles and the mucous membranes of the tongue, gums, and mouth. Two symmetrical branches connect behind the jawbone and under the tongue, joining at the tip. Another branch forms an anastomosis with the submental branches of the facial artery. The lingual artery, which originates from the external carotid artery and provides the body's primary blood supply to the tongue and the floor of the mouth, gives rise to the sublingual artery. The internal carotid artery, which supplies the majority of the cerebral hemisphere, is easily accessible due to its close proximity.[17,18]

Osmosis

A nutrient must be able to pass through the buccal mucosa membranes in order to be absorbed sublingually. This is accomplished via a process of diffusion called osmosis, which regulates all forms of absorption by the body, including intestinal and sublingual absorption. Water distribution across cell membranes is determined by the osmotic difference between intracellular and extracellular fluids in the blood. The total outward hydrostatic pressure and the in-vivo osmotic pressure of the plasma control the distribution of water across the blood vessel walls. The capillary wall allows tiny molecules to pass through it quickly and freely, in contrast to the cell membrane. Water diffusion across a water-permeable membrane is determined by the particle's molecular weight. Small particles dissolve easily in water, allowing them to travel freely between biological tissues. Substances are rapidly metabolized after active translocation into cells. Cell metabolism relies on molecules like glucose (fructose) and amino acids, which require particular processes for fast diffusion across cell membranes.[19]

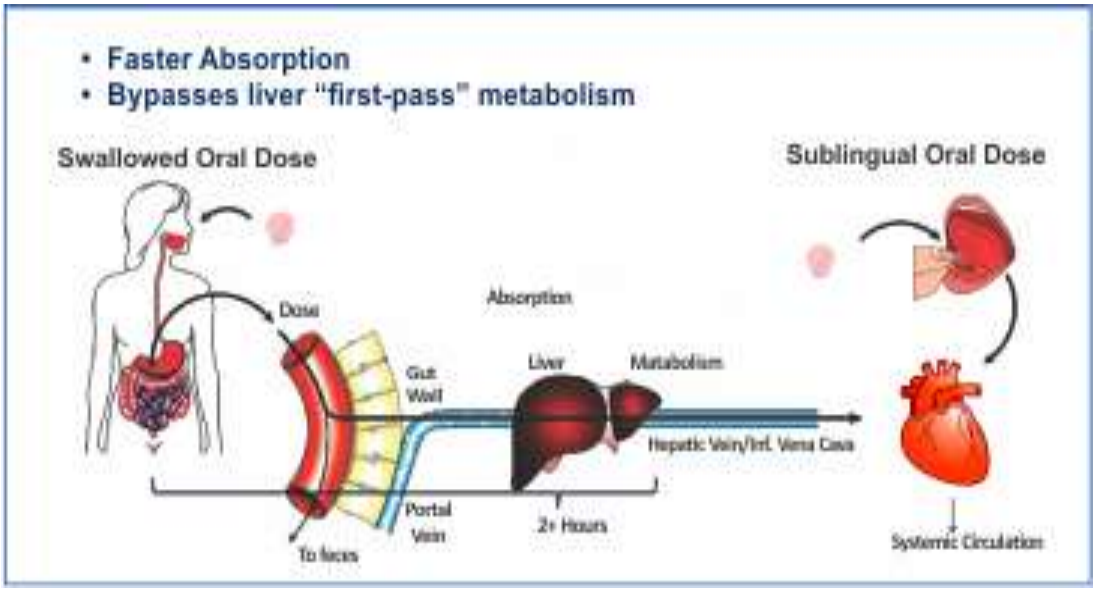

Fig.3: Sublingual drug absorption.

Drugs for sublingual administration

Sublingual medication delivery is used in medicine for certain barbiturates, enzymes, hormones, and cardiovascular medicines.[20] The administration of several vitamins and minerals has been a growing field, and it has been discovered that this method absorbs them quickly and completely. Sublingually absorbed nutrition provides direct nutritional benefits without exposing the stomach or liver.[21] This is especially beneficial for people with digestive issues, ulcers, coeliac disease, hyperactive gut, elderly people, and invalids. The nutritional benefit is also not influenced by the digestive system. delivered this way include antianginals like nitrites and nitrates, antihypertensive like nifedipine, analgesics like morphine, and bronchodilators like fenoterol. Certain hormones like estradiol and peptides like oxytocin can also be provided, for example, fentanyl citrate, apomorphine, prochlorperazine dimaleate (PRO), and hydrazine HCl (HYD).[22]

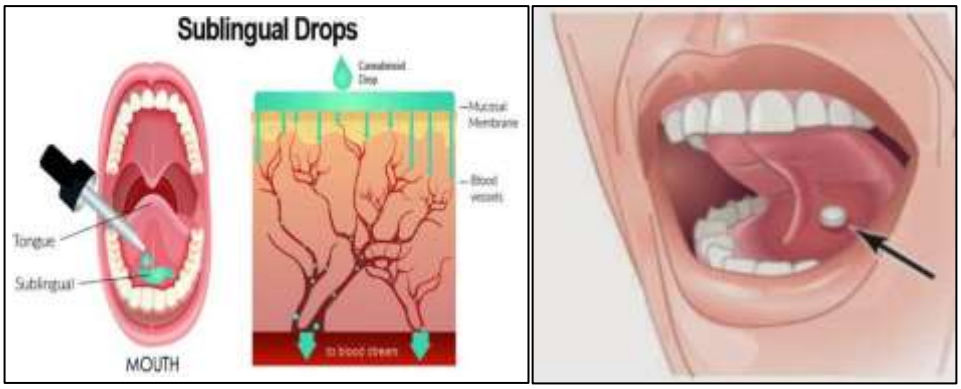

Fig. 4: Sublingual drug administration.

Ideal Properties of Drug in Sublingual Drug Delivery System[23]

- Drug should not bitter flavor.
- Lower doses than 20mg, such as nifedipine.
- Low to intermediate molecular weight.
- Excellent stability in water and saliva.
- Ph is partially non-ionized in the oral cavity.
- Undergoing the first pass effect, such as ketotifen fumarate.
- Sublingual tablet performance may be affected by many pharmacological qualities such as solubility, crystal shape, particle size, hygroscopicity, bulk density, and compressibility
- Some medications have low bioavailability in oral dose forms due to substantial first-pass metabolism. These pharmaceuticals are better suited for sublingual administration.
- Drug preparations that are parenterally unstable can be taken sublingually.

Factor affecting Sublingual absorption

Drug absorption through the buccal or sublingual mucosa depends on various parameters.

1. Solubility

For the medication to have biphasic solubility which is required for absorption it must have high lipid solubility and be soluble in aqueous buccal fluids. Oral mucosa-binding medications have little systemic availability.[24]

2. Thickness of epithelium

The oral epithelium's thickness influences how well drugs are absorbed. Compared to the buccal epithelium, the sublingual epithelium has a thickness of 100–200 μm. As a result of the thinner epithelium and the medication's immersion in a smaller volume of saliva, drug absorption occurs more quickly.[25]

3. Lipophilicity of drug

To fully absorb a medicine through the sublingual route, it must have somewhat higher lipid solubility compared to GI absorption. This is necessary for passive penetration.[26]

4. pH and pKa of the saliva

Saliva has a typical pH of 6.0, which promotes medication absorption while remaining

unionized. Drugs are absorbed through the oral mucosa with pKa values greater than 2 for acids and less than 10 for bases.[27]

5. Binding to oral mucosa

Poor systemic availability characterizes medications that bind to the mouth mucosa.[28]

6. Oil to water partition coefficient

Favorable compounds have high oil-to-water partition coefficients and are easily absorbed by the oral mucosa.

An oil-water partition coefficient of 40-2000 is optimum for sublingual medication absorption.[29]

Advantages[30,31]

1 Sublingual methods provide quick absorption of medications by placing them directly in the mouth

2 In addition to avoiding the liver, the medication is protected from breaking down by the intermediate gastrointestinal tract's pH and digesting enzymes.

3 Due to the avoidance of hepatic first-pass metabolism and the decreased likelihood of side effects, low dosages yield excellent efficacy.

4 Sublingual dose forms are often used in emergency situations, like as asthma, due to their quick action.

5 The mouth's vast contact surface aids in the thorough and quick absorption of drugs.

6 Easy to administer to people who cannot swallow tablets, including children, psychiatric patients, and the elderly.

7 Improved patient compliance by eliminating discomfort from injections, allowing for drug administration in asleep or debilitated patients, and providing convenience over injections or oral meds.

8 Improved drug delivery efficiency and dosage accuracy.

Disadvantage[31]

1. Unsuitable for formulations with sustained release.
2. Small doses: Because of the mouth cavity's restricted size, sublingual administration may call for lesser doses.
3. Sublingual medication administration might be unpleasant as it requires

prolonged oral retention.

4. Some medications may have an unpleasant taste in the tongue, posing a difficulty for patients.

Different formulation for Sublingual drug delivery system[32-37]

1. Fast –disintegration sublingual tablet

Tablets that dissolve fast in the mouth are beneficial for older patients, youngsters with difficulty swallowing, and situations when consumable liquids are unavailable. A last-disintegrating tablet is a solid drug administration device that dissolves swiftly beneath the tongue without requiring water. The drug enters the salivary flow, dissolves, spreads, and absorbs in the sublingual area. These dose forms are preferred over standard oral solids because of their convenience. Sublingual tablets have the potential to create new economic opportunities in the pharmaceutical industry, including product differentiation, line expansion, distinctiveness, and patent protection. According to the European Medicines Agency Committee of Medicinal Products for Human Use (CHMP), sublingual tablets offer significant benefits for children. Faster disintegration minimizes the risk of choking and makes it more difficult to split the dose. Sublingual medicines primarily disintegrate due to water-breathing and swelling properties.[32]

2. Bioadhesive sublingual tablet

The latest sublingual tablet concept involves combining a water-soluble carrier with small particles of substances and a bio-adhesive polymer. These compounds have the potential to create high-dissolution tablets by combining bio-adhesive polymers. Bioadhesive sublingual tablets have longer retention duration in the oral cavity, leading to more effective drug administration.[33]

3. Thin film drug delivery

A novel drug delivery method for oral drug administration, mouth dissolving films or strips, was created utilizing the transdermal patch's technology. The delivery system consists of a very thin oral strip, which is simply placed on the patient’s tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. Sublingual strips, similar to tablets, dissolve quickly in the mouth.

Suboxone is a medicine that comes in a sublingual strip.

4. Lipid matrix sublingual tablet

Lipid sublingual tablets use advanced liposomal and sublingual technology to provide faster and more complete absorption than traditional oral drug delivery methods. Oral dose is convenient and dependable for many medications.

5. Sublingual immunotherapy

Drops of the dose form are administered under the tongue. This technique produces various dosage forms of mast cell stabilizers, antihistamines, and local steroids. This method is more effective than subcutaneous immunotherapy for treating allergic rhinitis safely. Compared to traditional dosing forms, it is more clinically effective and safer.

6. Sublingual vitamin tablet

One of the most commonly utilized sublingual pills is vitamin B12. It helps to maintain our body's metabolism and is advised to be taken orally.

7. Multi-purpose tablets

Soluble tablets that can be taken orally or sublingually, frequently used for injectable preparation, morphine tablets and cubes available in several brands; Hydrostat (hydromorphone).

8. Sublingual drops

Concentrated solutions to be administered sublingually, similar to several cough preparations containing nicocodeine.

9. Sublingual spray

The formulation involves dispersing or dissolving a drug in a solvent, filling a container with a metered valve, and delivering a sufficient dose through the valve into the sublingual area.

10. Lozenge

A combination of sublingual, buccal, and oral administration, similar to the Actiq fentanyl lozenge-on-a-stick (lollipop), has been shown to have measured and patient-controlled effects.

11. Effervescent Sublingual Tablets

The Fentora fentanyl tablet uses this technique, which allows the drug to pass through mucous membranes considerably more quickly (this also occurs in the stomach with carbonated or effervescent beverages).

Manufacturing technique used in sublingual tablet formulation[38-44]

1. Direct Compression

Direct compression is a popular method for producing tablets as it is simple and straightforward. The procedure involves combining the active drug with excipients including fillers, binders, and lubricants to create a homogeneous blend that can be compacted into tablets.

2. Tablet Molding

Wet granulation is a popular method for quickly disintegrating and dissolving tablets, as it improves their solubility. However, it can cause issues with mechanical strength and flavor masking.

3. Spray Drying

Spray drying creates fine, porous powder by evaporating the processing solvent. It's commonly utilized in pharmaceutical and biological procedures. Spray drying can be used to create rapidly disintegrating tablets by incorporating a support matrix (e.g., hydrolyzed or non-hydrolyzed gelatin), bulking agents (e.g., mannitol), disintegrants (e.g., sodium starch glycolate and cross-carmelose sodium), acidic materials (e.g., citric acid), and alkali (e.g., sodium bicarbonate) to improve disintegration and dissolution.

4. Taste Masking

Fast dissolving tablets require effective taste masking, which can be achieved through several approaches. Drugs can be microencapsulated using pH-sensitive acrylic polymers such as Eudragit E, Eudragit L-55, and Eudragit RL by solvent evaporation or extraction. To disguise the bitter taste, tiny granules of the medication and disintegrant can be coated with ethylcellulose, a water-insoluble polymer.

5. Freeze Drying

A method called lyophilization can be used to create tablets with an open matrix network that is porous and quickly disperses in the mouth. To make the tablet, the medication is

encapsulated in a water-soluble matrix and freeze-dried. To optimize the process or raise the caliber of the product, additional excipients such as colors, flavors, suspending agents, wetting agents, preservatives, and antioxidants can be added.

6. Mass Extrusion

This method softens the active blend with a solvent mixture of water-soluble polyethylene glycol and methanol. The softened substance is extruded through an extruder or syringe to form a cylinder, which is then sliced into even segments using a hot blade to create tablets. The dried cylinder can conceal the flavor of harsh medications by coating them.

7. Sublimation

To generate fast-dissolving tablets, the sublimation technique includes adding a volatile salt to the tableting component. This creates pores in the tablet upon removal.

When a tablet comes into touch with saliva, it quickly disintegrates. Common volatile salts include camphor, ammonium bicarbonate, naphthalene, and urea. The tablets are vacuumed at 80°C for 30 minutes to remove volatile components and generate pores.

Table 1: Marketed Preparation of Sublingual tablet.

Brand Name	Active Ingredient	Category	Manufacturer
Saphris	Asenapine	Antipsychotic agent	Merck
Ergomes	Ergoloid mesylates		Cipla
Subutex	Buprenorphine HCL	Narcotic + Opioid Analgesic	Sun pharma
Ergomar	Ergotamine tartrate		Rosedale pharmaceuticals
Abstral	Fentanyl citrate	Opioid Analgesic	Galena Biopharmaceuticals
Imdur	Isosorbide dinitrate	Vasodilators	Astrazeneca
Nitrostat	Nitroglycerin	Antianginal	Pfizer
Intermezzo	Zolpidem tartrate	Sedatives/Hypnotics	Purdue Pharma

Table 2: Drugs used in the formulation of sublingual dosage forms.

Drug	Category	Dosage form
Physostigmine Salicylate	Anti-Alzheimer's	Tablet
Captopril	Anti-hypertensive agent	Tablet
Nitroglycerine	Anti-anginal	Tablet
Nifedipine	Anti-anginal	Tablet
Scopolamine	Opioid analgesic	Spray
Fuosemide	Diuretic	Tablet
Vinpocetine	Neutropic agent	Tablet

Amlodipine besylate	Anti-hypertensive	Tablet
Salbutamol sulphate	Anti-asthmatic agent	Film
Ondansetron Hydrochloride	Anti emetic	Film
Terbutaline sulphate	Bronchodilator	Tablet

Recent Developments

Nitrolingual spray is a metered-dose spraying pump that delivers nitroglycerine as a sublingual aerosol using propellants. The product sprays nitroglycerine droplets over or under the tongue, enhancing absorption and bioavailability. Rapid action is necessary for hypertension.

Future Prospects

Sublingual tablets are ideal for delivering medications with low bioavailability, such as proteins and peptides. Patients tend to avoid injections unless they can use sophisticated auto-injectors. ODTS-enhanced oral protein delivery systems show promise for delivering high-molecular-weight proteins and peptides.

CONCLUSION

The study found that sublingual tablets improved patient compliance and drug delivery for both pediatric and geriatric patients. Sublingual drug delivery is commonly employed for fast-acting medications. These tablets are designed to be easier to swallow. The target population now includes individuals seeking quick pills without water. The medicine in tablets enters the bloodstream through glands in the sublingual cavity. Sublingual administration typically results in peak blood levels within 10 -15 minutes, compared to oral administration. Sublingual absorption is efficient. Thus rapid onset of action is achieved. Sublingual absorption is faster and more efficient than traditional oral dose forms like tablets and capsules. There are various sublingual dose forms available in the market, including pills, films, and sprays.

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