

## “Review on sublingual dosage form”

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**ABSTRACT :** The Fast Dissolving Drug Delivery Systems units a brand new benchmark became an enlargement that got here into life withinside the early 1980's and fight over using the one-of-a-kind dosage shape like pills, suspension, syrups, tablets which can be the opposite oral drug shipping systems, Fast Dissolving Drug Delivery System (FDTS) has a first-rate gain over the traditional dosage bureaucracy because the drug receives hastily disintegrated and dissolves withinside the saliva with out using water In spite of the disadvantage loss of on the spot onset of action; those oral dosage bureaucracy have precious functions which include self medication, elevated affected person compliance, ease of producing and shortage of pain. Hence Fast Disintegrating Tablets (FDTS) era has been gaining significance now-a-days with huge range of medication serving many functions. Fast Disintegrating Tablets (FDTS) has ever elevated their call for withinside the closing decade considering that they crumble in saliva in much less than a minute that progressed compliance in pediatrics and geriatric patients, who've problem in swallowing pills or liquids. As rapid dissolving pill offer instant disintegration after setting it on tongue, thereby fast drug absorption and instant bioavailability, while Fast dissolving oral movies are used as sensible opportunity to FDTS These movies have a capacity to supply the drug systemically via intragastric, sublingual or buccal path of management and additionally has been used for neighborhood action. In gift overview article one-of-a-kind factors of rapid dissolving pills and movies like approach of preparations, modern day technologies, assessment parameters are discussed. This observe can be beneficial for the researchers for his or her lab

**KEYWORD :**Sublingual dosage form, systemic circulation, salivary gland, Tongue, sublingual drug delivery

### I. INTRODUCTION

The meaning of SUBLINGUAL is located or administered under the tongue. Drug delivery via the sublingual route arose from a desire to provide an immediate pharmacological effect. Dysphasia (difficulty swallowing) is a common problem in all age groups, particularly geriatric, pediatric and mentally retarded, uncooperative, nauseated or dehydrated patients/dieters who have difficulty swallowing these dosage forms. Drugs administered sublingually

Enter the systemic circulation directly through the ventral surface of the tongue and the floor of the mouth.

The drug is rapidly absorbed in the reticulated vein under the oral mucosa and transported via the facial veins, internal jugular vein and brachiocephalic vein, and then enters the systemic circulation. Permeable part of the oral cavity is sublingual, buccal (cheek) area, then palatal area. The order is generally based on the relative thickness And amount of blood supply to each part

- Sublingual: under the tongue
- The sublingual dosage form can be defined as a dosage form that is placed under the tongue where it dissolves and the drug is absorbed directly through the sublingual mucosa.
- The dosage form is not intended to be swallowed or chewed.
- Sublingual administration of the drug means that the drug is placed under the tongue and the drug enters the bloodstream directly through the ventral surface of the tongue and the floor of the mouth.
- Dissolved active ingredients of Drug Are rapidly absorbed in the reticulated vein under the buccal mucosa and transported via the facial veins, internal jugular vein and brachiocephalic vein, and then discharged into the systemic circulation



### Why sublingual path are used?

The sublingual path is one of the early modes of management for systemic drug transport. This path avoids first pass metabolism and provides brief drug access into the systemic circulation (3)

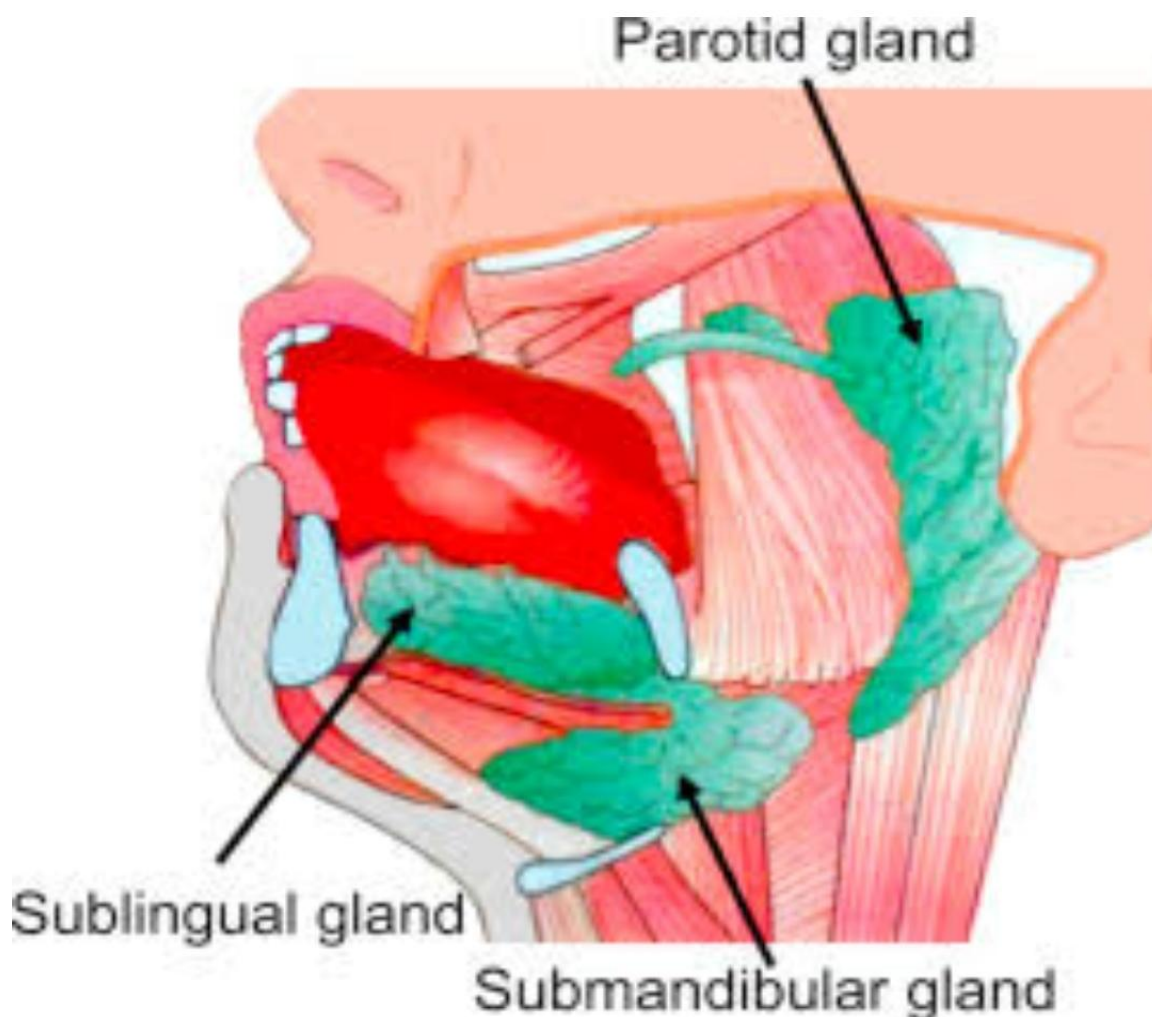
### Sublingual Glands-

Another call of sublingual gland is salivary glands which can be found within the ground of the mouth, below the tongue. Drugs having quick transport and rare dosing routine might be brought correctly through sublingual path due to excessive permeability and wealthy blood supply, the sublingual path produces a fast onset of action. A right oral hygiene might be promoted with the assist of sublingual glands. Sublingual glands also are recognized for his or her binding

and lubricating functions, and sublingual gland secretion makes the meals slippery and without problems swallowable. High content material of saliva within the masticated meals enables the meals to transport with none difficulty. Saliva secretion performs a first-rate position in shaping the precept physiological surroundings of oral hollow space in phrases of pH, fluid extent and Composition. Saliva secretion has been promoted through three essential salivary glands which might be parotid, submaxillary, sublingual glands. However minor salivary or buccal glands also are concerned in saliva secretions which might be located in or right away underneath the mucosa. Saliva regulates oral microbial vegetation through retaining the oral pH and enzyme pastime. Sublingual glands are acknowledged for his or her

viscous saliva with constrained enzymatic pastime while parotid and submaxillary gland produces watery secretion. Saliva enables in lubricating the oral cavity; it allows swallowing and forestalls demineralization of the teeth. Approximately 0.5-2.0L of saliva has been secreted through salivary gland. However the extent of saliva that's to be had continuously is round 1.1ml, hence offering a

incredibly low fluid extent to be had for drug launch from shipping structures as compared to GIT. If we evaluate the GI fluid and saliva, saliva is incredibly much less viscous. The go with the drift price of saliva which relies upon on three elements just like the time of day, the form of stimulus and the diploma of stimulation (6,7)



**Sublingual drug delivery –**

Drug delivery occurs under the tongue through the sublingual mucosa directly into the bloodstream. Dissolved active ingredients are quickly absorbed in the reticulated vein below the oral mucosa and transported through the facial veins. V. Jugularis interna and V. Brachiocephalica and are then transferred to the systemic circulation.

**Buccal Drug Delivery-**The management of medicine via buccal mucosa without delay enters into the systemic circulation [8].

**Onset of Action:**

Determine the onset of action of the different routes of administration as follows: Intravenous: 30 to 60 seconds

Inhalation: 2 to 3 minutes

Sublingual: 3 to 5 minutes

- Intramuscular: 10 to 20 minutes
- Subcutaneous: 15 to 30 minutes
- Rectal: 5 to 30 minutes
- Oral: 30 to 90 minutes Topical/transdermal: minutes to hours [9].

#### **ADVANTAGES OF SUBLINGUAL DRUG DELIVERY -**

• Avoid first-pass effect, enters the system circulation directly and improves its bioavailability [10].

The sublingual route is often used in emergency situations. For example a heart attack. Patients who have difficulty swallowing tablets, particularly pediatric, geriatric, and psychiatric patients, use sublingual oromucosal administration. They are easy to use. No water is required when swallowing the solid dosage form, it is suitable for patients who travel and do not have immediate access to water [11].

- Faster onset of action can be achieved compared to oral administration
- Improves patient compliance due to ease of administration. Recreates the benefits of liquid formulations in a solid dosage form. The passage of the metabolism is avoided and side effects are reduced. The large contact surface of the oral cavity allows for a quick transfer of the drug into the bloodstream, there is a better and faster and wider absorption of the drug.
- Rapid dissolution or decomposition in the oral cavity through the mucosa without the need for water [12].

#### **DISADVANTAGES OF SUBLINGUAL DRUG ADMINISTRATION:**

With sublingual drug delivery, eating, drinking and speaking are not allowed, and this route is not suitable for prolonged administration. The patient is uncooperative or unconscious [13]

The sublingual drug delivery is not allowed to sustain release drug

#### **Ideal drug properties in the sublingual drug delivery system:**

- The drug should not taste bitter
- The dose should be less than 20 mg, e.g. egnedipine.
- Small to medium molecular weight.
- Good stability in water and saliva.
- Experiencing the first pass effect of E.ketotifen fumarate.
- Drug should not ionize at oral pH.

• Many drug properties can affect tablet performance. Sublingual factors such as solubility, crystalline morphology, particle size, hygroscopicity, apparent density and compressibility of the drug.

• Some drugs undergo extensive first-pass metabolism resulting in poor bioavailability in their oral dosage forms, this type of drug is amenable to sublingual dosage form.

• Parenterally unstable drug formulations are amenable to sublingual dosage form

• Aerosol: The term aerosol is used to denote various systems ranging from colloidal in nature to systems composed of pressurized sachets. Aerosol has been defined as a colloidal system consisting of very finely divided

Solid or liquid particles dispersed and surrounded by a gas. Dosing valves are important for medicinal aerosols.

These valves allow for the delivery of aerosol quantities ranging from 25 to 100  $\mu\text{L}$  per actuation [14]

#### **Sublingual Absorption:**

Sublingual media, generally “under the tongue” refers to a process in which drug substances are delivered through the mouth in this way that substances are quickly absorbed through the blood under the tongue instead of through the digestive tract. There is evidence that with sublingual absorption by simple diffusion; the sublingual area acts more like litmus paper

And easily absorbs substances. Therefore, not all substances are accessible and permeable to the oral mucosa.

One of the well-known drugs that is commonly used with great success is glyceryl trinitrate, a powerful coronary vasodilator used to quickly relieve the symptoms of angina. It has been shown to be effective when administered sublingually, becoming pharmacologically active after just 1-2 minutes. Aerosol administration has been found to provide rapid symptomatic relief with a first-pass metabolism.

When compared to the level of first pass metabolism compared to the sublingual spray, it drops from % to 48% with sublingual tablets and 28% with the oral dose. Sublingual verapamil (38 calcium channel antagonist, prescribed to treat angina, hypertension) was effective in controlling ventricular rate.” Experiments with some analgesics show much faster absorption from the mouth than less fat-soluble morphine. Remarkable absorption was achieved with the sublingual

administration of deoxycortisone acetate, morphine, nifedipine and 17-B-estradiol.

#### **Sublingual absorption mechanism:**

The absorption potential of the oral mucosa is influenced by the lipid solubility and thus the permeability of the solution (osmosis), the ionization (pH) and the molecular weight of the substances. For example, absorption of some drugs across the buccal mucosa has been shown to increase as the pH of the carrier decreases (more acidic) and decreases with a decrease in pH (more basic). Cells of the oral epithelium and epidermis are also able to absorb by endocytosis.

It is unlikely that this mechanism is used in all stratified epithelia. It is also unlikely that active transport processes take place within the oral mucosa. However, it is believed that acid stimulation of the salivary glands with concomitant vasodilation facilitates absorption and uptake into the circulatory system. The mouth is lined with a mucous membrane covered with squamous epithelium containing mucous glands. The tissue of the sublingual mucosa resembles that of the buccal mucosa.

41 The salivary glands are made up of lobules of cells that secrete saliva through the salivary ducts into the mouth. There are three pairs of salivary glands namely sublingual, parotid and submandibular which are located on the floor of the mouth. The more sour the taste, the more saliva production is stimulated; Serves to prevent possible damage to acid-sensitive tooth enamel by bathing the mouth in copious amounts of neutralizing liquid. The sublingual artery travels anteriorly to the sublingual gland.

Supplies the gland and branches of adjacent muscles and the mucous membranes of the mouth, gums and tongue. Two symmetrical branches run behind the lower jaw below the tongue to meet and connect at its tip. Another branch anastomoses with the submental branches of the facial artery. The sublingual artery arises from the lingual artery, the body's main blood supply to the floor of the mouth and tongue, which arises from the external carotid artery. Hemisphere

#### **Osmosis:**

Successful drug absorption via the sublingual route requires the ability to travel through the buccal mucosa through a method of diffusion known as osmosis. Which applies to all forms of absorption by the body; that regulate intestinal and sublingual absorption. The distribution of water through the cell walls depends

on the osmotic difference in the blood between the extracellular fluid and the intracellular fluid. Small particles that dissolve easily in water are rarely a problem in the Permeability and diffusion and can move freely between body tissues. Active transport into cells leads to rapid drug metabolism. Molecules such as amino acids and glucose are essential to cellular metabolism and have evolved to facilitate their rapid diffusion and permeation through cell membranes.

#### **Factors Affecting Sublingual Absorption” –**

##### **Lipophilicity of the drug –**

In order for a drug to be fully absorbed sublingually, the drug must have greater lipid solubility, which is essential for passive permeation.

##### **Solubility in Salivary Secretion –**

i. e In addition to high lipid solubility, the drug must be soluble in oral fluids, ie biphasic solubility of the drug should be soluble In aqueous buccal fluids drug is required for absorption.

##### **Salivary pH and pKa:**

Since the average pH of saliva is 6.0, this pH favors the absorption of drugs that remain syndicated.

The absorption of drugs through the oral mucosa occurs when the pKa value is greater than 2 for an acid and less than 10 for a base.

##### **Binding to the oral mucosa:**

The systemic availability of drugs that bind to the oral mucosa should be low.

##### **Oral epithelium thickness:**

The thickness of the sublingual epithelium is 100-200  $\mu\text{m}$ , which is less compared to the buccal thickness. Therefore, drug absorption is faster due to thinner epithelium and also due to drug immersion in smaller volume of saliva.

##### **In Vivo Evaluation:**

Analysis of Pharmacokinetic Data and Evaluation of Bioavailability Rabbits have been described as one of the animals lacking keratinized mucosa and therefore closely resembling human sublingual mucosal tissue. The maximum plasma concentration ( $C_{\text{max}}$ ) and the time to reach the maximum plasma concentration ( $T_{\text{max}}$ ) can be obtained directly from the plasma data. The

Area under the plasma concentration curve (AUC) can also be calculated using the trapezoidal rule and then bioavailability.

#### **PRINCIPLE:**

When a chemical comes into contact with the mucous membrane under the tongue, it diffuses

through it. Since the connective tissue under the epithelium contains an abundance of capillaries, the substance then diffuses into them and enters the venous circulation. Instead, substances absorbed in the gut undergo “first-pass metabolism” in the liver before entering the general circulation. Sublingual administration ensures the substance is at risk of degradation only through Salivary enzymes before they reach the bloodstream, while orally administered drugs must survive passage through the hostile environment of the gastrointestinal tract, which puts them at risk of being destroyed by either gastric acid or bile, or by the many enzymes that they contain, like monoamine, to be degraded oxidase (MAO). In addition, after being absorbed in the gastrointestinal tract, such drugs must reach the liver, where they can be extensively modified;(17)

**Historical development of the sublingual dosage form:**

Difficulty swallowing (dysphagia) is a common problem in all age groups, especially in

the elderly and children, due to the physiological changes associated with these age groups. Carrying small device used to crush tablets, allowing for easy swallowing. Other categories that have problems using conventional oral dosage forms are mentally ill, uncooperative and nauseous patients, those with dizziness, sudden episodes of allergic attacks and coughing.

Sometimes it can be difficult to swallow conventional products due to lack of water. These problems led to the development of a new type of solid oral dosage form called dissolvable tablets, which rapidly dissolve and dissolve in saliva without the need for water. They are also known as fast-dissolving tablets, orodispersible tablets, and rapimelts, porous, melt-dispersible, fast-dissolving or fast-disintegrating tablets. Highlights the contribution of various Researchers in the field of sublingual tablets and highlights the patented technology in the field of sublingual technology.(15, 16)

3	2003	In vitro and in vivo evaluation of a new sublingual tablet system for rapid Oromucosal absorption using fentanyl citrate as the active
4	2006	Formulation and optimization of sublingual tablets of rabeprazole sodium.
5	2009	Development and optimization of a sublingual Tablet formulation for physostigmine salicylate.
6	2011	Sublingual route for the systemic delivery of ondansetron
7	2012	Formulation and in-vitro evaluation of fast disintegrating Rosiglitazone sublingual tablets.
8	2012	formulation and evaluation of sublingual tablets of losartan potassium.
9	2012	Development and characterization of sublingual tablet of lisinopril.
10	2013	formulation and evaluation of immediate release tablets of linezolid.

**Table-1 The Patented Technology in the field of Sublingual Technology**

		optimal design.
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**FORMULATIONS**

Sublingual Tablets  
 Sublingual Films  
 Multipurpose tablets

Sublingual drops  
 Sublingual spray  
 Lozenge  
 Effervescent sublingual tablets

### Sublingual Tablets

Sublingual tablets are solid unit dosage forms intended to be placed under the tongue for immediate action by avoiding the first pass effect of the drug through the liver. The tablets are usually small and flat and slightly compressed to keep them soft. The tablet should dissolve quickly so that the API can be absorbed quickly. It dissolves in a small amount of saliva.

After the tablet is placed in the mouth under the tongue, the patient should avoid eating, drinking, smoking and possibly speaking to keep the tablet in place. You should also avoid swallowing saliva as saliva can contain dissolved medication. Mild excipients are used to avoid salivary stimulation. Nitroglycerin tablets and Ondansetron (Zopran) tablets are examples of sublingual tablets.

### Sublingual Films

Films or strips that dissolve in the mouth, a new drug delivery system for oral drug delivery based on transdermal patch technology has been developed. On the patient's tongue or any other tissue of the oral mucosa, the film is immediately wetted with saliva, quickly hydrates and adheres to the application site. It then rapidly breaks down and dissolves to release the drug for oral absorption or FormulaThe modifications will retain the fast-dissolving aspects and allow for gastrointestinal absorption if swallowed. Sublingual strips are similar to tablets in that they melt easily in the mouth and dissolve quickly. Suboxone is an example of a medication that comes in a sublingual form. Drag.

### Multi-Purpose Tablets-

Soluble drugs for both oral or sublingual administration, frequently additionally appropriate for education of injections, Hydrostat (hydromorphone) and some of manufacturers of morphine drugs and cubes.

### Sublingual drops

Concentrated solutions to put under the tongue, like some nicocodeine cough drops

### Sublingual spray

Spray for the tongue; certain human and veterinary medicinal products are supplied as such.

### Pills

As with Actiq Fentanyl Stick Lollipop, performs a patient-controlled, metered combination of sublingual, buccal, and oral deliver

### Sublingual Effervescent Tablets

This method propels the drug through the mucous membranes much faster (this is also the case in the stomach with carbonated or effervescent liquids) and is used in the Fentora Fentanyl tablet.

### Drugs used in the formulation of sublingual dosage forms:

Physostigmine salicylate-Anti-Alzheimer's  
Scopolamine-Opioid analgesic Spray  
Furosemide Diuretic Tablet  
Nifedipine, Nitro-glycerine Anti-anginal Tablet  
VinpocetineNeutropic Agent Tablet  
Terbutaline sulphate-Bronchodilator Tablet  
Amlodipine besylate, Captopril-Anti hypertensive Tablet  
Ondansetron Hydrochloride- Anti emetic Film  
Salbutamol sulphate Anti-asthmatic agent

## II. CONCLUSION:

As per number of reviews article Sublingual drug delivery has several advantages like rapid onset of action, liver is bypassed, low dose give high efficacy, provides fast dissolution and disintegration, hence it can be used for emergency conditions.

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