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Recent insights, challenges and emerging trends in sublingual drug delivery system

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Abstract

An oral solid dosage form (OSDF) refers to pharmaceutical formulations that are orally administered in a solid form, including tablets, capsules, or powders. These dosage forms are intended to be swallowed and dissolved in the gastrointestinal tract, facilitating the systemic delivery of the active pharmaceutical ingredient to the body. The oral or buccal cavity is a desirable route for drug delivery due to its simplicity and ease of administration. This route enables the administration of medications with both systemic and local effects through mucosal and transmucosal delivery. In the transmucosal route, drug absorption via the mucosal barrier reaches the systemic circulation, whereas in the mucosa scenario, it aims to achieve a site-specific release of the medication on the mucosa. The sublingual area of the buccal cavity is the most favourable site for drug absorption. Greater bioavailability and improved patient compliance result from the drug's fraction that is absorbed by the sublingual blood vessels avoiding the hepatic first-pass metabolism. Various dosage forms are examined in detail, such as sublingual tablets including fast dissolving and bio adhesive formulations—films, sprays, wafers, and emerging vaccine delivery systems. The sublingual dosage form is primarily utilized in managing conditions such as migraines, cardiovascular diseases (e.g., angina), schizophrenia, anxiety, allergies, and for the management of pain. The article illustrates marketed products and current clinical applications, offers insights into future prospects for sublingual delivery, and serves as a valuable resource for pharmaceutical scientists and clinicians seeking to understand and improve sublingual drug delivery technologies.

Keywords: Oral solid dosage form, sublingual drug delivery, dosage forms, FDT, super disintegrants

Introduction

The sublingual drug delivery system involves placing the drug formulation under the tongue, where it disintegrates and dissolves due to the action of saliva. Drugs taken through the oral mucosa reach the systemic circulation directly through the internal jugular vein, avoiding hepatic metabolism and resulting in faster and more effective absorption, making the sublingual area the perfect place to administer drugs. The sublingual route also offers several additional advantages, including ease of administration, convenient access to the delivery site, and a relatively short cellular turnover time (4-14 days), making it a promising option for effective drug delivery^[1].

The pH of the oral cavity is kept close to neutral, usually between 6.2 and 7.4, and there is minimal enzymatic activity. Of the relatively small total mucosal surface area (100-200 cm²), the sublingual and buccal regions comprise around 26.5 cm² ± 4.2 and 50.2 cm² ± 2.9 by area. The epithelium in these regions is non-keratinized and stratified, with the sublingual mucosa being significantly thinner (100µm-200µm, 8-12 cell layers) compared to the thicker buccal mucosa (500µm-800µm, 40-50 cell layers). This difference in epithelial thickness contributes to the more rapid absorption of drugs via the sublingual route⁴.

The order of drug absorption will therefore be as follows: Sublingual > Buccal > Gingival > Palatal. Underneath this epithelium, the lamina propria and submucosa provide structural support through connective tissue, blood vessels, lymphatic channels, and smooth muscle^[2]. The principal mechanism by which the medication is absorbed into the oral mucosa is passive diffusion into the lipoidal membrane³.

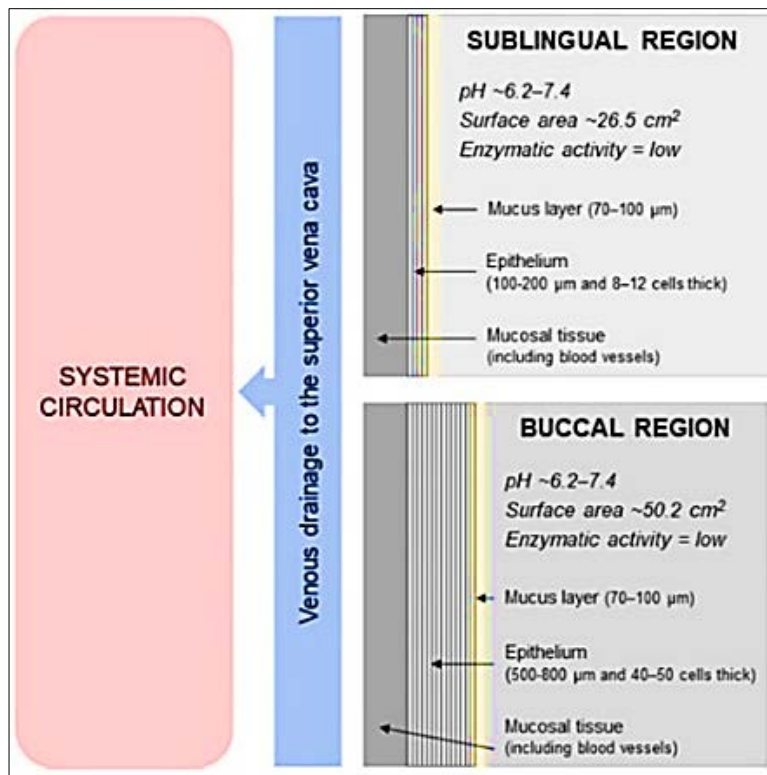
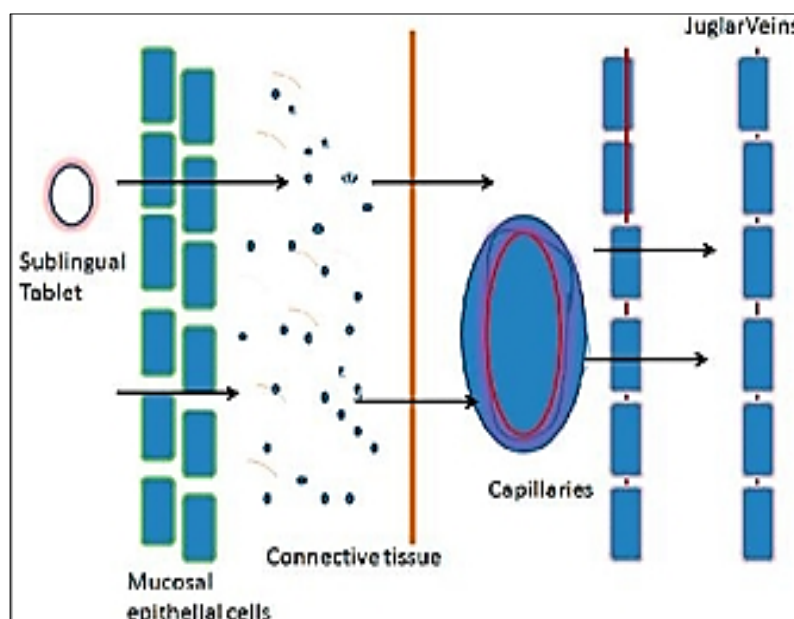


Fig 1: Anatomy of the sublingual and buccal regions in the oral cavity



Fi 2: Mechanism of drug absorption from the sublingual region

Different dosage forms for sublingual drug delivery

1. Sublingual tablets

An oral solid dosage forms designed to be placed under the tongue, where they quickly disintegrate and dissolve [5]. In Oral Solid Dosage Form (OSDF) lots of excipients are used and these excipients influence the drug release [6]

a) Fast disintegrating sublingual tablet

Fast-dissolving tablets (FDTs) are solid dosage forms that contain an active pharmaceutical ingredient and disintegrate quickly, typically within seconds. Following this, the medication is released, dissolved, or distributed in saliva, making it simple to ingest and absorb through the digestive system. Other names for FDT include rapimelts, porous

tablets, mouth dissolving pills, fast dissolving tablets, and quick disintegrating tablets. Water absorption (wicking) and tablet expansion (swelling) are the primary mechanisms by which disintegrants facilitate the breakdown of most sublingual tablets. Water-wicking refers to the capacity of a tablet matrix to absorb and distribute water throughout its structure. Both the amount and speed of water uptake play a crucial role in the disintegration process. When exposed to moisture, certain ingredients expand, generating pressure that disrupts the bonds between particles, leading to tablet breakdown. Sodium starch glycolate is frequently utilized in sublingual tablets to promote the solid dosage form's quick breakdown and disintegration [7]. Some of the commonly used super disintegrants [8,9] are discussed in table 1

Challenges in developing FDTs

- Taste masking is crucial for patient compliance, especially when formulating FDTs with bitter active ingredients.
- Effective moisture barrier strategies are essential to protect hygroscopic FDTs from degradation and maintain their integrity.
- Balancing rapid disintegration with sufficient tensile strength is essential for FDTs success.
- For patient comfort and compliance, it is essential to formulate FDTs that leave little to no residue in the mouth.
- Preventing excessive swelling while ensuring quick disintegration poses a significant challenge [8].

Table 1: Commonly used super disintegrants in FDTs

Super disintegrants	Mechanism	Particle size	Nature
Crospovidone	Both wicking and swelling	Particle size 100µm	Crosslinked homopolymer of N-vinyl-2-pyrrolidone
SSG- Sodium Starch Glycolate	Uptake of water followed by fast and massive swelling	Insoluble in water. Particle size 140 mesh	Cross-linked low-substituted. Carboxymethyl ether of poly glucopyranose
CCS- Croscarmellose Sodium	Swelling action	Insoluble in water. Particle size- 200mesh	Cross-linked form of CMC
Acrylic acid derivatives	Wicking action	Dispersed in cold water, insoluble in organic solvents	Poly (acrylic acid) highly porous hydrogel
Sodium alginate	Swelling action	solubilized slowly in water, hygroscopic characteristics	Sodium salt of the alginic acid
NS-300 (Carboxymethyl cellulose)	Wicking type	Particle size-100µm	Carboxy methyl cellulose (CMC)
Effervescent mixture	Effervescence	Crystalline in nature	Sodium bicarbonate, citric acid, tartaric acid, sodium salt of alginic acid,
L-HPC (Low substituted hydroxypropyl cellulose)	Both wicking and swelling	Particle size 106µm	Low hydroxyl propyl cellulose
ECG-505(Carmellose calcium/ Calcium carboxymethylcellulos11e)	Swelling type	Particle size 106µm	Calcium salt of CM

b) Bio-adhesive tablets

These dosage forms interact with saliva by absorbing moisture, swelling on the mucosal surface, and undergoing solvent loss, ultimately forming a gel-like consistency [13,14,15]. With its negatively charged structure and low resistance to penetration, mucin effectively enhances the absorption of macromolecular drugs through the oral mucosa by promoting mucoadhesion. The cohesive forces between mucoadhesive substances and the mucosal surface bring them into close contact, thereby prolonging the retention of the dosage form at the application site [16,17,18]. The prolonged residence time of the drug at the absorption site minimizes its elimination by saliva, improves absorption efficiency, and contributes to higher systemic drug levels and enhanced therapeutic benefits [11, 12].

Challenges

- The tablet must adhere to the sublingual mucosa long enough to enhance drug absorption but also disintegrate rapidly to allow fast systemic uptake.
- The sublingual epithelium has limited permeability, especially for high molecular weight or hydrophilic drugs.
- High saliva flow can wash away the drug before absorption, leading to oral (GI) absorption instead of sublingual absorption.
- Permeation enhancers or bioadhesive polymers may irritate or harm mucosal tissue.
- Bio-adhesive polymers and even drugs are hygroscopic, affecting tablet integrity and drug stability [12].

2. Sublingual films

Sublingual films are thin, flexible strips that are intended to stick to the sublingual mucosa and dissolve quickly. They are commonly utilized for drugs requiring accurate dosing or taste masking [12]. These films consist of thin, polymer-

based oral sheets that rapidly break down and dissolve upon contact with saliva, enabling efficient Oro mucosal drug absorption without the need for water or chewing. Sublingual films are widely preferred for delivering specific anti-nausea treatments and opioid analgesics [19].

It consists of a non-aqueous solution containing water-soluble polymers that form thin films, such as pullulan, CMC, HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium alginate, polyvinyl alcohol, and polyvinyl pyrrolidone. The formulation includes an active pharmaceutical ingredient (API) and flavoring agents, which create a film upon solvent evaporation. In cases involving coated drug microparticles, bitter drugs, or resin adsorbents, these components contribute to film formation. The key characteristic of this method is the production of ultra-thin films, typically measuring 2x2 inches, which dissolve rapidly within five seconds, leaving no residue and offering a pleasant taste [19].

Challenges

- They cannot accommodate high drug doses
- They are not appropriate for administering medications that are insoluble in water [14].
- Achieving consistent drug loading in the film matrix is crucial for dose accuracy
- The film and its contents may prematurely degrade or disintegrate if exposed to moisture.
- Co-administration of medications can impact the formulation's dissolution rate and disintegration time, making it a highly challenging task in oral film formulation [15].

3. Sublingual sprays

A sublingual drug delivery system includes therapeutically active substances that can be suspended or dissolved in excipients, such as buffering agents, viscosity-modifying or

building agents, and preservatives, in a pressured or non-pressurized dispenser. A spray pump can be used to measure each dose. A spray pump can be made to provide several doses or a single unit dose. Sublingual spray offers both local and systemic action. To regulate the accuracy of medication distribution, several sizes and compositions are employed. These are usually accomplished by pushing the drug formulation from its orifices upon actuation through the sublingual route. A container closure system, comprising a container, closure, pump, and any package protection device, can be used to develop the formulation [20].

Sublingual sprays disperse medication as a fine mist beneath the tongue, ensuring quick uptake through the sublingual mucosa. They are particularly useful for pain relief, including opioid analgesics like fentanyl, and for treating anxiety-related conditions [21]. Some benefits of employing sublingual sprays include the elimination of the requirement for a disintegration process and the potential for a spray formulation to be more effective in dry mouth situations because it dissolves without the need for saliva.

Challenges

- Achieving an optimal droplet size is essential to ensure effective sublingual absorption and prevent unintended pulmonary deposition [22].
- It is crucial that the API in the spray formulation be both soluble and stable because instability over time may result in decreased efficacy, and poor water solubility can impede medication absorption.
- Achieving consistent dosing with each spray actuation is vital for safety and efficacy [23].
- Sprays, unlike tablets or films, do not attach to the mucosa, which may reduce drug absorption time. Viscosity enhancers or bio-adhesive polymers are required to promote retention [24].

4. Sublingual vaccines

However, the majority of currently used vaccines are delivered through injections, such as subcutaneous or intramuscular administration. This approach often results in weak mucosal immunity, whereas vaccines given via mucosal routes have been shown to effectively stimulate both systemic and localized immune responses. Furthermore, mucosal immunization simplifies vaccine delivery and enhances safety compared to parenteral administration methods [25].

When developing sublingual or buccal vaccines, the influence of saliva must be considered. While saliva can facilitate antigen release from certain dosage forms, it also presents challenges due to its variable composition, pH, and flow rate. Excessive salivary secretion and flow can dilute the antigen or cause the dosage form to be swallowed before adequate mucosal absorption occurs, a phenomenon known as 'saliva washout'. Additionally, digestive enzymes present in saliva may contribute to antigen degradation, potentially reducing vaccine efficacy.

Therapeutic sublingual allergy vaccines are currently the most common vaccines delivered through the oral mucosa. These vaccines are used in sublingual immunotherapy (SLIT) to manage allergic hypersensitivity. Delivering

allergens sublingually can stimulate regulatory T cells, which help suppress unwanted immune responses. As a result, several sublingual products for allergy immunotherapy have been approved, including SLIT one®, Sublivac®, Grazax®, Oralair®, and AllerSlit@forte [26].

Challenges

- Understanding the Pharmacokinetics and Pharmacodynamics of Mucosal vaccines: Absorption, Distribution, and Immune Response Kinetics
- Mechanisms of Mucosal Immunity: The Role of Secretory IgA, MALT Activation, and Cross-Protection Against Pathogen
- Formulation Strategies for Mucosal Vaccine Optimization: Enhancing Stability, Bioavailability, and Immune Potentiation
- Development and Validation of Assays for Assessing Mucosal Immunity: Measuring Secretory IgA and Cellular response [27].

5. Sublingual wafers

Wafers generally refer to a porous, often more structured dosage form that might be produced via processes like lyophilization (freeze-drying), while sublingual films are typically thin, flexible strips made from polymer matrices that dissolve quickly upon contact with saliva [28].

Oral sublingual wafers that dissolve quickly have a 2- 3year shelf life. Saliva dissolves these small strips in the mouth, rapidly releasing the drug. Since they don't need water to be consumed, they are a convenient dose form for travel. Wafers increase the medication's effectiveness, decrease the dosage, and improve its onset of action. They are stable, durable, and quicker than other conventional dosage forms, enhance drug bioavailability, improve dosing accuracy, and can allow the use of bitter-tasting drugs [29].

Challenges

- Formulating such wafers involves ensuring the stability of the active ingredient
- Because the formulation dissolves in the mouth, it effectively masks flavor.
- Maintaining mechanical integrity during handling and storage [28].
- Achieving optimal mucoadhesion is crucial for maintaining the wafer in place long enough for drug absorption without causing discomfort [29].

Drawbacks of Sublingual Drug Delivery

1. An effective drug candidate should exhibit solubility in human saliva and possess sufficient lipophilicity to facilitate permeation through the epithelial layer of the oral mucosa
2. Drug loading capacity is low, so the drug candidates should be of high potency to achieve successful therapeutic efficacy.
3. The microenvironment pH alteration is a viable tactic to improve medication absorption through sublingual formulations; the primary obstacle is the possibility for tooth erosion and localized irritation of the oral mucosa as a result of the oral cavity's pH shift [3]

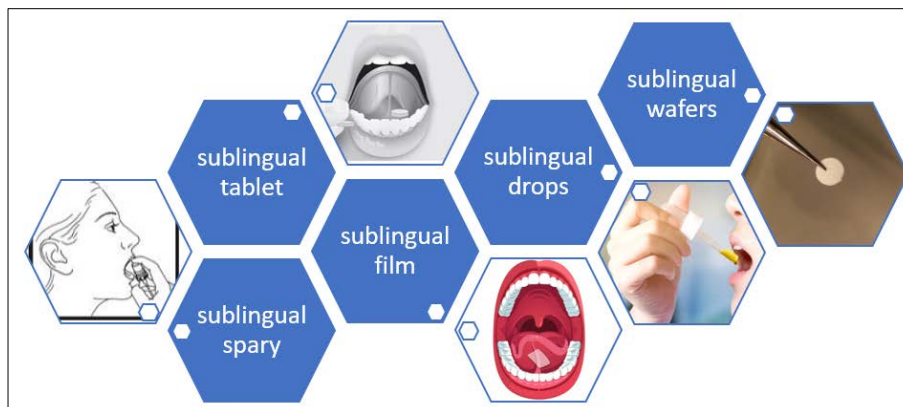


Fig 3: Various dosage forms in sublingual drug delivery



Fig 4: Marketed products for sublingual delivery system

The table 2 lists a few of the commercially available sublingual dosage forms [4, 31]

Table 2: Marketed products of sublingual dosage forms

S.no	Dosage form	Active pharmaceutical ingredient	Management of disease	Brand name/ Manufacturer name
1	Tablet	Lorazepam	Anxiety	Atirvan / Pfizer
2	Tablet, spray	Nitroglycerin	Angina pectoris	Nitrostat®/ Pfizer
3	Tablet, film, spray	Fentanyl	Pain	Abstral/ Novartis(tablet) Subsys / Insys therapeutics(spray)
4	Tablet, spray, oral liquid	Vitamin B12	Vitamin deficiency	Marketed (Sublingual Vitamin B12)
5	Sublingual immunotherapy	Allergen (grass pollen, milk, peanut, ragweed, artemisia annua)	Atopic dermatitis, allergic rhinitis, allergic conjunctivitis, food hypersensitivity	GREER® Extracts/ Greer Laboratories HAL Allergy manufactures
6	Film	Buprenorphine and Naloxone	Narcotic addiction	Suboxone/Indivior (Reckitt Benckiser)
7	Tablet, wafer	Asenapine	Schizophrenia	Saphris / Merck Asenapt / Sun pharma
8	Film, spray	Insulin	type 1 diabetes, Type 2 diabetes	Pivot Park
9	Spray	Sildenafil	Erectile dysfunction	Aetos Pharma
10	Tablet	Isosorbide dinitrate	Angina	Isordil / Ipcalaboratories Sorbitrate / Abbott
11	Wafer	Desmopressin	Diabetes insipidus	Minirin melt / Ferring pharmaceuticals
12	Tablet	Allergen extract	Allergic rhinitis	Odactra / ALK Abello

Advancements in sublingual drug delivery system

A sublingual patient controlled analgesic system, the Sufentanil Sublingual Microtablet System (Zalviso®) is non-invasive and features a pre-defined, non-modifiable program that was established by a medical professional. For moderate-to-severe postoperative pain, Zalviso is advised. It has been shown that analgesia combined with SSTS is a

successful pain management technique following major abdominal and orthopaedic surgery [32]. AcelRx Pharmaceuticals' Zalviso administration device was designed to deliver a single 15 microgram sublingual tablet of sufentanil as needed by the patient over a maximum of 72 hours, which is the suggested treatment duration, with an idle period of 20 minutes (lockout period) between doses.

The Internet of Things is made up of networks of sensors, data collectors, and transmitters that relay information from

various points of entry into a central location via the cloud [33].



Fig 5: Zalviso sublingual device

Future recommendation

During the past few years, the market for buccal drug delivery systems has expanded dramatically. It is anticipated to rise at a compound annual growth rate (CAGR) of 10.3%, from \$3.55 billion in 2024 to \$3.91 billion in 2025. The market is predicted to continue its robust expansion in the upcoming years, reaching \$5.97 billion by 2029 at a compound annual growth rate (CAGR) of 11.1%. Patient-centric drug delivery, the growing elderly population, the need for targeted therapies, the delivery of biologics and peptides, regulatory support and approvals, and R&D expenditures can all contribute to the increase in the projected time. Major trends in the projection period include patient convenience and compliance, innovations in medication formulations, the rise in chronic diseases, paediatric and geriatric care, and enhanced bioavailability [34]. Through taste masking, formulation modification, and patient education, patient compliance issues such as unpleasant taste, local irritation, difficulty in administration, and choking have been resolved [35]. Future potential of sublingual delivery encompasses the administration of biologics such as peptides and proteins, Vaccines, cannabinoids, and other bioactive, as well as hormones administered sublingually. Novel Formulation Strategies comprising of 3D printing of customized dosage forms, Nanoparticles, and integration with smart technologies, including dose-tracking smart packaging and biosensor utilization for feedback-based dosing, enhances personalized and precise medication management.

Conclusion

In summary, sublingual drug administration presents a compelling alternative to traditional oral and parenteral routes, offering rapid absorption, improved bioavailability, and enhanced patient compliance. This method bypasses first-pass metabolism, making it particularly advantageous for drugs with poor gastrointestinal stability or extensive hepatic metabolism. While sublingual delivery has clear benefits, challenges such as formulation limitations and patient variability must be addressed through ongoing research and technological advancements. As pharmaceutical development continues to evolve, sublingual administration remains a promising approach for optimizing drug efficacy and patient outcomes.

Conflict of interest

The authors have no conflicts of interest regarding this investigation.

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