WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 5, 33-48. Review Article ISSN 2277–7105

PHARMACOKINETICS OF SUBLINGUAL FILMS: AVOIDANCE OF FIRST-PASS METABOLISM

Miss. Sakshi Sanjay Dighe*, Mrs. Snehal Santosh Pendbhaje, Miss. Akanksha Bhagwaan Ghadge, Miss. Sejal Rohidas Kanade

India.

Article Received on
12 January 2025,

Revised on 02 Feb. 2025,
Accepted on 22 Feb. 2025

DOI: 10.20959/wjpr20255-35441

***Corresponding Author**
Miss. Sakshi Sanjay Dighe
India.

ABSTRACT

Sublingual drug administration is widely employed for medications susceptible to degradation or extensive first-pass metabolism in the gastrointestinal tract. Delivering drugs through the oral mucosa presents a promising alternative to conventional oral routes. Sublingual films, as an advanced dosage form, offer rapid onset of action and improved patient compliance compared to tablets or capsules. These films dissolve quickly beneath the tongue, allowing drug absorption through the highly permeable sublingual mucosa, which is more efficient than buccal or palatal areas. The sublingual route bypasses hepatic first-pass metabolism, resulting in enhanced bioavailability. Various innovative techniques are used to formulate sublingual films, addressing diverse pharmaceutical needs, including ease of use for pediatric, geriatric, and dysphagic patients. This review explores the pharmacokinetics of sublingual films, their advantages, limitations, and the factors influencing sublingual absorption, emphasizing the role of avoiding first-pass metabolism in achieving therapeutic efficacy.

INTRODUCTION

In recent decades, there has been an increasing demand for novel drug delivery systems due to their ability to enhance patient compliance and provide effective options for emergencies. The need for rapid pharmacological effects has driven the development of systemic drug delivery through the sublingual route. This approach involves placing the drug beneath the tongue, where it is absorbed into the bloodstream via the highly vascularized ventral surface and floor of the mouth. The drug solutes pass through the reticulated veins under the oral mucosa, traveling via the facial, internal jugular, and brachiocephalic veins to reach systemic circulation.

The sublingual route allows for direct absorption into the bloodstream, bypassing hepatic first-pass metabolism and ensuring improved bioavailability. Dysphagia, or difficulty swallowing, is a common problem across all age groups, particularly for individuals who consume less liquid and struggle with solid oral dosage forms. Drug absorption through the oral mucosa primarily occurs via passive diffusion into the lipoidal membrane.

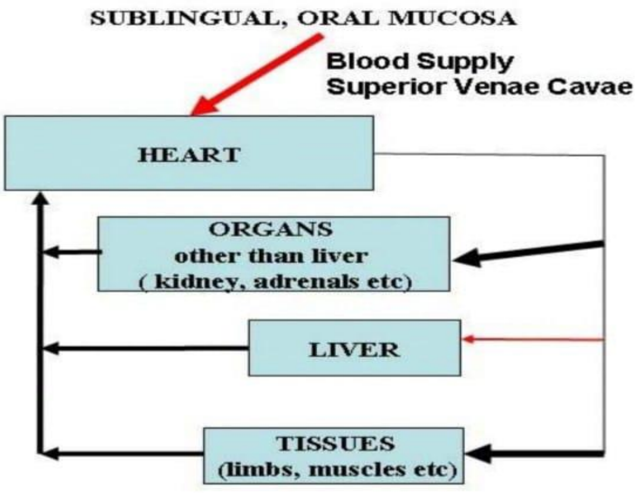
Changes in oral pH, often due to salivary gland dysfunction, can result in an increased ionized fraction of lipophilic drugs like fentanyl, reducing their absorption efficiency. This condition is also associated with altered oral mucosal permeability, further affecting drug absorption.

Sublingual absorption is 3–10 times more efficient than oral absorption and is second only to hypodermic injections in rapidity. The minimal volume of saliva required for dissolution allows sublingual tablets to disintegrate quickly in the mouth. Although sublingual absorption is fast, its effects are often short-lived. For instance, nitroglycerin, a widely used antianginal medication, undergoes significant first-pass metabolism when administered orally (>90%). However, when delivered sublingually, it reaches peak plasma levels within 1–2 minutes. The potential of sublingual drug delivery was first observed in 1847 by Sobrero, who noted that placing nitroglycerin on the tongue caused an intense headache lasting several hours, demonstrating its rapid absorption through the oral mucosa.

Mechanism of Sublingual Absorption

Extensive first-pass metabolism in the liver makes oral administration unsuitable for certain drugs. However, sublingual administration, where the drug is placed under the tongue, can bypass this issue. Drugs absorbed through the oral mucosa are transported to the superior vena cava and directly enter the systemic circulation without passing through the liver initially. This prevents them from undergoing first-pass metabolism in the liver. Once in systemic circulation, only a portion of the drug passes through the liver during each cycle, while the rest is distributed to other organs and tissues that may not metabolize the drug.

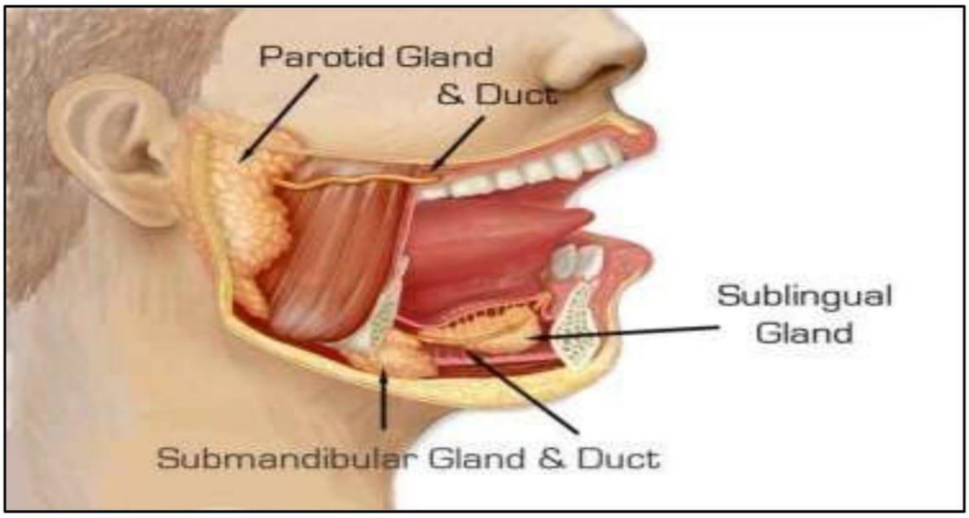
Thus, the sublingual route enhances the bioavailability of drugs that would otherwise be extensively metabolized by the liver.



Sublingual glands

The sublingual gland, the smallest but significant salivary gland, is located on the floor of the mouth beneath the tongue. These glands produce mucin and contribute to saliva, which plays a vital role in breaking down medications. The secretions from these glands mix with food, aid in chewing, and coat the food to facilitate smoother digestion. A lack of adequate saliva can hinder swallowing and cause food particles to become stuck in the throat.

Drug absorption in the oral cavity follows this order: sublingual > buccal > gingival > palate. The sublingual route is highly effective due to its strong permeability and vascularity, enabling a rapid onset of action. Medications are diluted in saliva and then absorbed throughout the oral cavity.

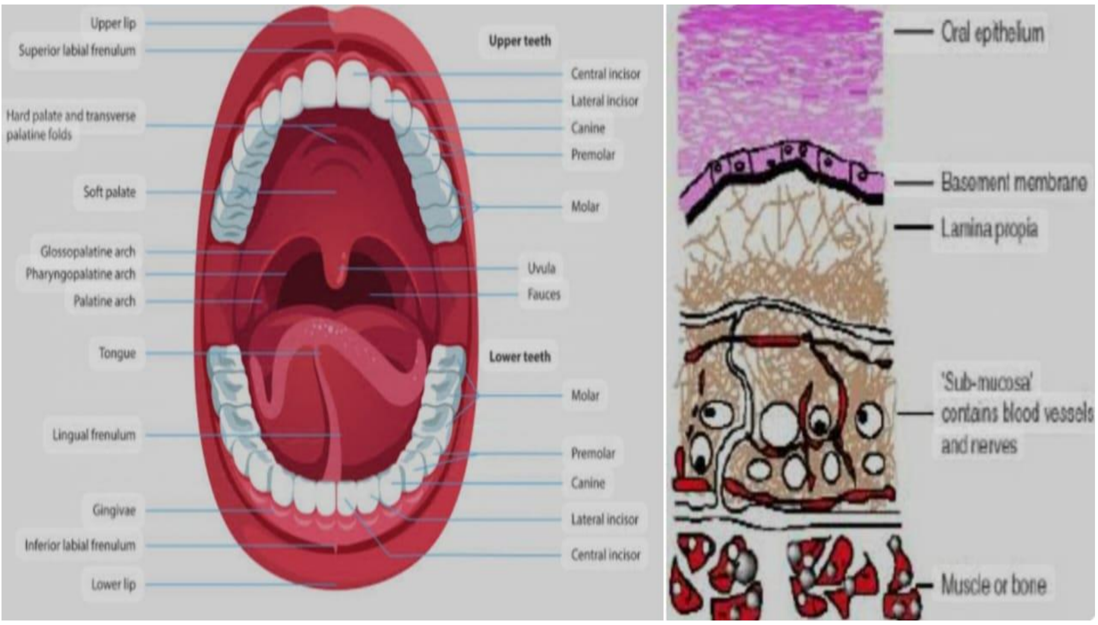


Anatomy of sublingual mucosa

The sublingual mucosa lines the underside of the tongue and the floor of the mouth, playing a vital role in the direct absorption of substances into the bloodstream, particularly for sublingual medications. Its structure consists of a thin, non-keratinized stratified squamous epithelium, which is highly vascularized. This rich network of capillaries allows for the rapid absorption of drugs. The underlying connective tissue contains glands, including minor salivary glands, that produce mucus.

The sublingual glands, situated beneath the tongue, secrete mucus to lubricate and moisten the mucosa. Salivary glands, as exocrine glands, produce saliva—a critical fluid for digestion, lubrication, protection, immunity, taste enhancement, and wound healing.

The sublingual region receives blood supply mainly from the sublingual artery, a branch of the lingual artery, which ensures the rapid uptake of sublingually administered substances. The lingual nerve, a branch of the mandibular nerve (V3), provides sensory and parasympathetic innervation. Parasympathetic fibers are responsible for stimulating saliva secretion.



Physiology of Sublingual Mucosa

The sublingual region in the mouth is constantly kept moist by saliva, a fluid composed of 99% water and 1% organic and inorganic materials. Saliva is secreted by three primary salivary glands: submandibular, parotid, and sublingual, along with several smaller glands within the oral cavity. Its pH ranges from 5.5 to 7, influenced by diet and habits. Saliva plays a vital role in protecting oral tissues, combating bacteria, and aiding in food digestion by softening it. The average daily production of saliva is about 0.5 to 2 liters.

Additionally, mucus, another critical component in the mouth, is produced by salivary glands. Mucus contains mucins, specialized proteins with carbohydrate chains. These mucins contribute to lubrication, food softening, and initiating the digestion process. Saliva includes two types of mucins: MG1, which has a very high molecular weight, and MG2, which has a lower molecular weight. Both types are crucial in maintaining oral health and performing essential functions.

Mechanism Sublingual drug absorption

The permeability of a solution, often referred to as osmosis, along with the drug's molecular weight, ionization, and lipid solubility, significantly influences absorption. The drug is absorbed by the cells of the oral epithelium through endocytosis. However, it is unlikely that the same mechanism operates uniformly throughout the stratified epithelium. Additionally, active transport mechanisms are not typically active within the oral mucosa.

Acidic stimulation of the salivary glands, accompanied by vasodilation, is believed to enhance absorption and uptake of the drug into the bloodstream. The mucous membrane lining the oral cavity is covered with squamous epithelium and contains mucous glands. The buccal and sublingual mucosal tissues share similar structures. Saliva is secreted into the mouth via the salivary ducts, which originate from lobules of cells in the salivary glands. These glands are classified into three paired groups: parotid, submandibular, and sublingual, located on the floor of the mouth.

Acidic tastes increase salivary flow, which not only aids in digestion but also protects acid-sensitive tooth enamel by providing sufficient neutralizing fluid. Salivary secretion stimulates oxygen consumption and the production of vasodilators, resulting in increased glandular blood flow and metabolism.

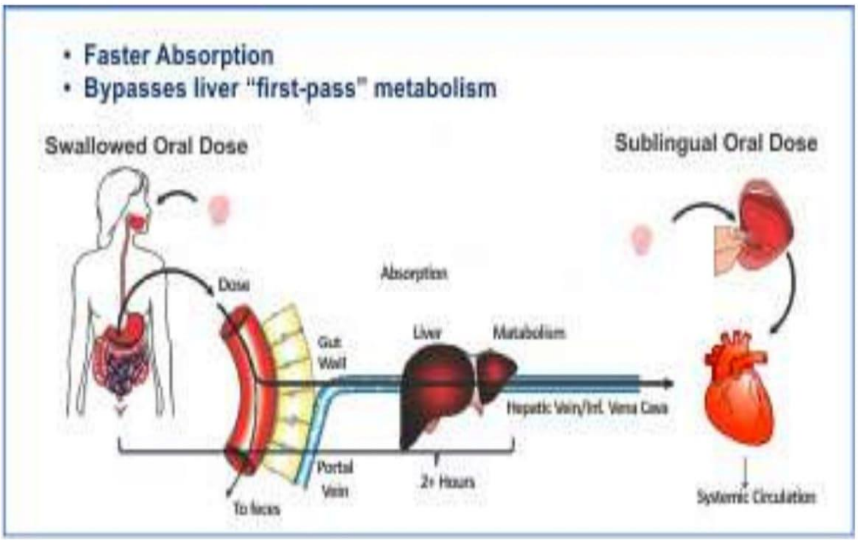
The sublingual artery supplies blood to the sublingual gland, surrounding muscles, and the mucous membranes of the tongue, gums, and mouth. Two symmetrical branches of this artery connect behind the jawbone and under the tongue, meeting at the tip. Another branch forms an anastomosis with the submental branches of the facial artery. The lingual artery, a branch of the external carotid artery, provides the primary blood supply to the tongue and the floor of the mouth. Notably, the internal carotid artery, which supplies most of the cerebral hemisphere, is easily accessible due to its proximity.

Osmosis

For a nutrient to be absorbed sublingually, it must pass through the buccal mucosa membranes. This process is facilitated by diffusion, specifically osmosis, which governs all forms of absorption in the body, including both intestinal and sublingual absorption. The movement of water across cell membranes is influenced by the osmotic gradient between the intracellular and extracellular fluids in the blood. The outward hydrostatic pressure and the in-vivo osmotic pressure of the plasma collectively regulate water distribution across blood vessel walls.

Unlike cell membranes, capillary walls allow small molecules to pass through rapidly and freely. The molecular weight of a particle determines its ability to diffuse through a water-permeable membrane. Small particles dissolve easily in water, enabling their smooth transit between biological tissues. Once substances actively translocate into cells, they are rapidly metabolized.

Cellular metabolism depends on molecules like glucose (or fructose) and amino acids, which require specific mechanisms for efficient diffusion across cell membranes. These processes are vital for maintaining cellular function and energy production.



Pharmacokinetics of sublingual Film

1. Absorption

Rapid Onset: Drugs delivered via sublingual films are absorbed directly into the bloodstream through the mucosa under the tongue. This bypasses the gastrointestinal (GI) tract and avoids first-pass metabolism in the liver.

High Bioavailability: Sublingual delivery generally results in higher bioavailability compared to oral tablets or capsules, as the drug avoids degradation by stomach acids or hepatic enzymes.

Factors Influencing Absorption

a. Film dissolution rate.
b. Drug solubility and permeability.
c. Mucosal blood flow.
d. pH of saliva and film composition.

2. Distribution

After absorption into the sublingual veins, the drug enters systemic circulation.

Distribution depends on the drug's lipophilicity, protein-binding properties, and molecular weight.

Drugs absorbed sublingually rapidly reach target tissues, making this route suitable for emergencies (e.g., angina or pain relief).

3. Metabolism

Reduced First-Pass Metabolism: Sublingual administration largely avoids the liver's first-pass effect, preserving the active drug's concentration.

Some drugs might undergo minimal metabolism in the systemic circulation or tissues, depending on their chemical properties.

4. Excretion

Excretion pathways for sublingually delivered drugs depend on their metabolism
Unchanged Drug: Some drugs are excreted via the kidneys without significant metabolism.

Metabolized Drug: Metabolites may be excreted via urine (renal clearance) or bile (fecal excretion).

The excretion half-life varies by drug.

Design and formulation aspects

Ingredients use in the formulation

1) Drug
2) Polymer
3) Plasticizer
4) Saliva Stimulating Agent
5) Sweetening Agent
6) Flavoring Agent

1) Drug: The active pharmaceutical ingredient (API) is the primary component that delivers the intended therapeutic effect. Sublingual films allow rapid dissolution and absorption of the drug through the sublingual mucosa, bypassing the gastrointestinal tract and first-pass metabolism for quicker onset of action.

2) Polymer: Polymers are used to form the structural matrix of the film. They provide

a. Mechanical strength and flexibility.
b. Controlled disintegration and dissolution rate.
c. Uniformity for drug dispersion.

E.g. hydroxypropyl methylcellulose (HPMC) or pullulan

3) Plasticizer: Plasticizers are added to improve the elasticity and flexibility of the film. They reduce brittleness and make the film easy to handle and comfortable for the patient to use.

E.g., glycerin, propylene glycol.

4) Saliva Stimulating Agent: These agents increase saliva production, promoting faster disintegration of the film and enhancing drug release. This is especially important for rapid drug delivery.

E.g., citric acid, tartaric acid.

5) Sweetening Agent: Sweetening agents improve the palatability of the film, especially for drugs with a bitter taste. This ensures better patient compliance, particularly in pediatric or geriatric populations.
E.g., sucralose, aspartame.

6) Flavoring Agent: Flavoring agents mask the taste of the drug and make the product more appealing. These are essential for patient acceptability, ensuring the film is pleasant to use.
E.g., peppermint oil, orange flavour.

Impact of formulation on Pharmacokinetics
The formulation of a sublingual film significantly impacts the pharmacokinetics (PK) of the drug, influencing its absorption, distribution, metabolism, and excretion. Here’s how:

1. Absorption
Rapid Onset of Action: Sublingual films dissolve quickly in saliva, allowing the drug to be absorbed directly through the sublingual mucosa. This provides faster absorption compared to oral tablets or capsules.

Avoidance of First-Pass Metabolism
Drugs absorbed through the sublingual route bypass the liver's first-pass metabolism, increasing bioavailability. For drugs like Metoprolol, this can lead to more consistent and predictable plasma levels.

1) Improved Solubility
Polymers and saliva-stimulating agents can enhance the solubility of poorly water-soluble drugs, improving absorption rates.

2. Distribution
Systemic Circulation: Once absorbed, the drug enters the systemic circulation directly, allowing rapid distribution to target tissues.

Reduced Variability: The sublingual route minimizes inter-patient variability caused by gastrointestinal factors like pH, enzymes, and motility.

3. Metabolism

Reduced First-Pass Effect: By bypassing the gastrointestinal tract and liver, sublingual films reduce the enzymatic degradation of the drug, leading to higher systemic availability and prolonged therapeutic effects.

Enzymatic Stability: Certain formulations protect the drug from salivary enzymes, maintaining its integrity until absorption.

4. Excretion

The faster absorption and bypass of the liver can alter the drug's elimination half-life. This may result in shorter or longer durations of action, depending on the drug’s pharmacokinetics.

Applications of Sublingual Films

1. Rapid Drug Delivery: Sublingual films bypass the digestive system, allowing faster drug absorption directly into the bloodstream through the mucous membranes under the tongue.

2. Improved Bioavailability: These films avoid first-pass metabolism in the liver, enhancing the bioavailability of the drug.

3) Ease of Use: They are suitable for patients who have difficulty swallowing, such as children, elderly individuals, or bedridden patients.

4) Portable and Discreet: Lightweight and easy to carry, sublingual films can be used discreetly without requiring water.

5) Controlled Dosing: Provide accurate dosing, reducing the risk of under- or overmedication.

6) Patient Compliance: Ideal for patients who find it challenging to take traditional tablets or capsules.

Examples of Drugs Delivered via Sublingual Films

1. Nitroglycerin: Used to treat acute angina pectoris (chest pain), offering rapid relief by dilating blood vessels.

2) Buprenorphine and Naloxone (Suboxone): Used for opioid dependence treatment, preventing withdrawal symptoms and reducing cravings.

3) Ondansetron: Prevents nausea and vomiting caused by chemotherapy, radiation, or surgery.

4) Zolpidem: Treats insomnia with a fast onset of action for sleep induction.

5) Edaravone: Provides antioxidant treatment for ALS (Amyotrophic Lateral Sclerosis), delivering rapid therapeutic effects.
6) Vitamin D or B12: Used for nutritional supplementation in individuals with deficiencies.
7) Loratadine: Antihistamine that provides fast-acting relief from.

Challenge and limitations

1. Stability Issues

Sublingual films are highly sensitive to environmental factors such as moisture, temperature, and light, which can lead to degradation of the drug or the polymer matrix. Ensuring the stability of Metoprolol requires specialized storage conditions and robust packaging to protect the formulation from these external influences.

2) Taste Masking

The bitter taste of Metoprolol poses a significant challenge to patient compliance. Effective taste-masking strategies, such as incorporating sweeteners, flavoring agents, or advanced technologies, must be employed. These additions should not compromise the drug's dissolution and release profile.

3) Manufacturing Challenges

Maintaining uniformity in film thickness, weight, and drug distribution is critical but challenging, especially during large-scale production. Additionally, ensuring the mechanical properties of the films—such as flexibility and tensile strength—is essential to prevent issues like breaking or sticking during handling.

4) Drug Solubility and Permeability

Metoprolol's solubility in saliva and its permeability across the sublingual mucosa are key factors influencing its absorption and bioavailability. Formulation optimization to enhance these properties involves overcoming complex technical and scientific barriers.

5) Rapid Disintegration and Dissolution

Sublingual films need to disintegrate rapidly under the tongue while maintaining their structural integrity during production, storage, and handling. Balancing these attributes can be a significant formulation challenge.

6) Patient Factors

Individual variations in saliva production, pH levels, and mucosal thickness can influence the absorption and efficacy of the drug. Moreover, patient acceptability, including ease of use, comfort, and taste, plays a crucial role in ensuring the success of the dosage form.

7) Regulatory and Compliance Requirements

Meeting stringent regulatory standards for quality, safety, and efficacy is essential for sublingual films. This involves comprehensive testing, detailed documentation, and ensuring consistency across production batches—an area that can be particularly demanding for novel dosage forms. allergy symptoms like sneezing and itching.

Future Prospects

The sublingual route offers immense potential for delivering drugs with low bioavailability, such as proteins and peptides, which are traditionally administered through injections. With advancements in formulations like orally disintegrating thin strips (ODTS), sublingual delivery can overcome challenges like enzymatic degradation and first-pass metabolism, ensuring higher bioavailability. These innovations provide a patient-friendly, non-invasive alternative to injections, particularly for high-molecular-weight biomolecules. Future developments are likely to focus on enhancing stability, absorption, and therapeutic efficacy, making sublingual systems a promising tool for modern drug delivery.

CONCLUSION

This study highlights that sublingual films significantly enhance patient compliance and improve drug delivery, especially for pediatric and geriatric patients. Sublingual films are particularly beneficial for fast-acting medications, offering a convenient alternative to traditional oral tablets by eliminating the need for water. These films dissolve under the tongue, allowing the medication to be absorbed directly into the bloodstream through the sublingual glands, leading to rapid peak blood levels within 10-15 minutes, much faster than oral tablets. Sublingual absorption is more efficient and quicker compared to conventional oral dosage forms like tablets and capsules. With the availability of various sublingual film formulations in the market, this delivery system presents a promising solution for rapid onset and improved therapeutic outcomes.

REFERENCE

1. Puja S., Sushma V., Pratik S.D.Sublingual drug delivery: an indication of potential Alternative route. International journal of current pharmaceutics resesrch, 13 Oct, 2017; 9(6): 5.
2. Patidar v, Gupta A, Sharma P.K., Sharma R., Koka S., Darwhekar G.N. Sublingual drug delivery system. International journal of biology, pharmacy and allied sciences, 1 Aug 2022; 3523-32.
3. Sattar M, Sayed OM, Lane ME. Oral transmucosal drug delivery–current status and future prospects. International journal of pharmaceutics, Aug. 25, 2014; 471(1-2): 498- 506.
4. Davies A, Mundin G, Vriens J, Webber K, Buchanan A, Waghorn M. The influence of low salivary flow rates on the absorption of a sublingual fentanyl citrate formulation for breakthrough cancer pain. Journal of Pain and Symptom Management, 2016; 51(3): 538-45.
5. Ashok K.S., Dr. Pushpendra S.N., Shankar S., Mohit K., Aman S., Mehul. Sublingual tablet – advancement in tablet dosage. International journal of current pharmaceutical review and research, 23 May, 2019; 11(2): 01-05.
6. Nehal Siddiqui MD, Garg G and Sharma PK. A short review on-A novel approach in oral fast dissolving drug delivery system and their patents. Advances Bio Res., 2011; 5(6): 291-303.
7. Patel P, Patel J, Patel K, Nihar S, Shah S, A Review on Fast Dissolving Sublingual Film, JPSBR, 2015; 5(3): 279-285.
8. Sarkhejiya NA, Patel VP and Pandya DJ. Sublingual delivery: A promising approach to improve bioavailability. Pharm Sci Monitor, 2013; 4(2): 3870-89.
9. Tarun G., Bhaskara J., Xiaoling Li. Critical reviews in therapeutic drug carrier system, 2008; 25(5): 449-484.
10. Bhakti K.P., Dr. Pravin B.C. Review on sublingual dosage form. International journal of pharmaceutical research and application, 23 Dec 2022; 1636-43.
11. Ashok T., Nawaz M., Madhavi C., Nandini K., Sirisha S., Sapandana D. Sublingual tablet – an updated review. Asian Journal of pharmaceutical research, June 2019; 9(2): 97-103.
12. Steiner SS, Feldstein R, Pohl R, Rhodes D, Steiner E, inventors; Biodel Inc., assignee. Method and device for sublingual drug delivery using iontophoresis. United States patent US 20070191757, Aug 16, 2007.

13. Mathur P, Rana A, Saroha K, Mathur K, Sublingual Route: An Approach to Administered Drugs in Systemic Circulation, International Journal of Pharmaceutical Research Health Science, 2019; 7(1): 2869-73.
14. Narang N and Sharma J, Sublingual mucosa as a route for systemic drug delivery, International Journal of Pharmacy and Pharmaceutical Sciences, 2011; 3: 18-22.
15. McElnay JC, Al-Furaih TA, Hughes CM, Scott MG, Elborn JS, Nicholls DP. The effect of pH on the buccal and sublingual absorption of captopril. Eur J Clin Pharmacol, 1995; 48(5): 73-379.
16. John DN, Fort S, Lewis MJ, Luscombe DK. Pharmacokinetics and Pharmacodynamics of Verapamil following sublingual and oral ad-ministration to healthy volunteers. Br J Clin Pham., 1992; 33: 623-627.
17. Lea L. Sublingual Administration. Colon Health, 1996; 13.
18. Boer D et. al. Drug absorption by sublingual and rectal routes. British J Anaesthesia, 1984; 56(1): 69-82.
19. Datkhile S.V., Jadhav S.L., Gadhave M.V., Gaikwad D.D. Sublingual route for systemic drug delivery: a review. International journal of pharmaceutical excellence, 15 April 2014; 76-90.
20. Poonam P., Hemant S.G., Bhavana A.K. Sublingual route for systemic drug delivery. Journal of drug delivery and therapeutics, 15 Dec., 2018; 8(6-s): 340-343.
21. Kavitha K, Subramaniam K, Hui BJ, et al, Potential drug candidate for fast dissolving drug delivery: A pharmaceuitical review, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2013; 4(4): 1510-1526.
22. Vilayat AS, Mohammad A, Considerations in developing sublingual tablets: A pharmaceuitical review, PharmTech Advancing Development and Manufacturing, 2014; 38(11).
23. Nair varsa, S., Saudagar, R.B., Gondkar, S.B., A Review on fast dissolving sublingual films for systemic drug delivery, 2015; 4(3): 346.
24. Bhati R, Nagrajan RK. A detailed review on oral mucosal drug delivery system. International Journal of Pharmaceutical Sciences and Research, 2012; 3(3): 659.
25. Saheb R, Dhangar R, Patil ST, Pawar SP, Sublingual: A Route for Systemic Drug Delivery System, International Journal of Pharma and Chemical Research, 2017; 3(2): 301-306.
26. Hua S. Advances in nanoparticulate drug delivery approaches for sublingual and buccal administration. Frontiers in pharmacology, 2019; 10: 1328.

27. Pawar P, Ghorpade H, Kokane B, Sublingual route for systemic drug delivery. Journal of Drug Delivery & Therapeutics, 2018; 8(6): 340-343.
28. Patel P, Makwana S and et al. Sublingual route for the systemic delivery of Ondansetron. Int J of Drug Development & Research, 2011; 3(4): 36-44.
29. Soni A, Kumar A, Jamwal S, Kumar A, and Dr. Chaudhary A, Oral dosages form: tablet in sublingual formulations, World Journal of Pharmaceutical and Life Sciences, 2019; 5(9): 133-137.
30. Sah S, Badola A, Kothiyal P, Sublingual tablets: an overview. Indian J. Pharm. Biol. Res., 2016; 4(2): 20-26.
31. Fu Y, Yang S, Jeong SH, Kimura S, Park K. Orally fast disintegrating tablets: developments, technologies, tastemaking and clinical studies. Crit Rev Ther Drug Carrier Syst, 2014; 21: 433-76.
32. Harshita G., Ashish G., Priya M., Ravi S., Gajanan D. Sublingual drug delivery system: a promising route for system drug delivery. International journal of creative research thoughts, 3 March 2024; 89-95.
33. Patel P, Makwana S, Jobanputra U, Ravat M, Ajmera A, Patel M. Sublingual route for the systemic delivery of Ondansetron. Int J Drug Dev Res., 2011; 3: 36-44.
34. Shankar B.N., Shubham S., Manaswini P., Subhasmita B. Sublingual drug delivery system: a novel approach. International journal of pharmaceutics and drug analysis, 2017; 399-405.
35. Tuman P.R., Anup P., Dipayan P., Madhvi G., Shiv G. Sublingual route for the systemic delivery of drugs. World journal of pharmaceutical sciences, 2019; 7(1): 38- 45.
36. Koushik, S. S., Schwartz, R. H., Cherkalin, D., Sankar, V., Shaparin, N., & Viswanath, O. A Review of Sublingual Sufentanil Tablet (SST) and its Utility as an Analgesic Agent for Pain Procedures. Current pain and headache reports, 2022; 26(2): 145-149.
37. Patel KN, Pancholi SS, Sublingual route for systemic drug delivery: A pharmaceuitical review, International Journal of Research in Pharmaceutical and biomedical Sciences, 2012; 3(2): 913-923.
38. Khan AB, Kingsley T, Caroline P. Sublingual tablets and the benefits of the sublingual route of administration. Journal of Pharmaceutical Research, 2017; 16(3): 257-67.
39. Macedo, A. S., Castro, P. M., Roque, L., Thomé, N. G., Reis, C. P., Pintado, M. E., & Fonte, P. Novel and revisited approaches in nanoparticle systems for buccal drug delivery. Journal of Controlled Release, 2020; 320: 125-141.

40. Rameshwari S, Anandi J. formulation and evaluation of nifedipine sublingual tablets. Asian journal of pharmacy and clinical research, 2009; 2(3): 41-48.
41. Nagashree, K., Research and Reviews: Journal of Pharmaceutical Analysis Solid dosage forms: Tablets, 2015; 4(2): 62-63.
42. Di Costanzo MF. T-Mask Technologies. In: Proceedings of the 7th International Glatt Symposium, USA, 1997; 1-9.
43. Dobetti L. Fast-melting tablets: Developments and technologies. Phar Tech., 2001; 25(9): 44-50.
44. Dipti G. Phadtare, Amol R. Pawar, R.B. Saudagar, Govind K.Patil. Formulation and Evaluation of Stable Montelukast Sodium Sublingual Tablet by using Lyophilization Technique. Res. J. Pharm. Dosage Form. & Tech., 2017; 9(1): 06-14.