Development of Fast-Acting Sublingual Tablets of Levetiracetam: Formulation and Characterization

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ABSTRACT

The objective of the present study was to formulate and evaluate Levetiracetam 500 mg sublingual tablets to achieve rapid disintegration and enhanced bioavailability through the sublingual route. Four formulations (F1–F4) were developed by varying the concentrations of microcrystalline cellulose, crospovidone, PVP K-30, and mannitol, with a fixed amount of Levetiracetam and citric acid. Microcrystalline cellulose and mannitol were selected as diluents to promote mouthfeel and mechanical strength, while crospovidone was incorporated as a superdisintegrant to ensure rapid disintegration. PVP K-30 was employed as a binder to enhance tablet cohesion without delaying disintegration. Citric acid was included to aid in salivary stimulation and improve taste masking. The formulations were evaluated for pre-compression properties (angle of repose, bulk density, compressibility index) and post-compression characteristics (hardness, friability, disintegration time, wetting time, drug content, and in vitro dissolution). The optimized formulation exhibited rapid disintegration within seconds, satisfactory mechanical strength, and complete drug release, making it suitable for sublingual administration. This approach offers the potential for faster therapeutic onset and improved patient compliance, particularly in the management of epileptic seizures.

Keyword **-** Levetiracetam, Sublingual tablet, Rapid disintegration, Superdisintegrant, Epilepsy management

1.Introduction

A propensity to have epileptic seizures is the hallmark of epilepsy, a chronic neurological illness that has serious neurobiological, cognitive, psychosocial, and social repercussions. The World Health Organization (WHO) estimates that epilepsy is one of the most prevalent neurological conditions, affecting around 50 million individuals worldwide [1]. The long-term use of antiepileptic medications (AEDs) to reduce seizures and enhance quality of life is the mainstay of epilepsy treatment. AEDs are widely available, however there are still issues with their delayed onset of action, side effects, low patient compliance, and limitations compared to conventional drug delivery techniques.

A second-generation AED, levetiracetam has become widely accepted in clinical practice because of its unique mode of action, good safety record, low risk of drug interactions, and effectiveness in treating a variety of seizure types, such as partial-onset, myoclonic, and generalized tonic-clonic seizures [2]. Levetiracetam's chemical characterization is (S)-a-ethyl-2-oxo-1-pyrrolidine acetamide. By attaching itself to the synaptic vesicle protein SV2A, it modulates the release of neurotransmitters, which lowers neuronal excitability [3]. Levetiracetam has negligible hepatic metabolism, low plasma protein binding, and nearly 100% oral bioavailability. Nevertheless, the traditional oral method of administration has drawbacks such delayed absorption, gastrointestinal degradation, and the requirement for water intake, which can be troublesome during an acute seizure episode [4], even if it has a high oral bioavailability..

Rapid beginning of medication action is essential for efficient therapy in emergency settings, such as acute repeated seizures or status epilepticus. Because of their slower systemic drug availability, traditional oral tablets might not be the best option in these situations. Although other techniques, such intravenous (IV) administration, offer quick therapeutic levels, they are intrusive, need skilled medical personnel, and are not appropriate for self-administered [5]. Therefore, a fast-acting, non-invasive, and patient-friendly dosing form is preferred.

Sublingual drug delivery presents a promising alternative by allowing direct absorption of the drug into the systemic circulation via the highly vascularized sublingual mucosa, bypassing hepatic first-pass metabolism [6]. The sublingual route offers several advantages including: Rapid onset of action, critical in managing emergencies such as seizure episodes. Improved bioavailability due to avoidance of first-pass hepatic metabolism. Enhanced patient compliance, especially in populations with swallowing difficulties (e.g., pediatric,

geriatric, or debilitated patients). Convenience and ease of administration without the need for water. Potential for dose sparing and reduced variability in plasma concentrations [7].

Sublingual tablets are small, fast-dissolving units designed to release the drug quickly into the sublingual cavity, followed by rapid absorption into systemic circulation. The critical attributes of an effective sublingual tablet include rapid disintegration (preferably within 1-2 minutes), pleasant mouthfeel, acceptable mechanical strength to withstand handling, and an adequate drug loading capacity [8]. These performance characteristics are strongly influenced by the choice of formulation excipients, manufacturing methods, and the physicochemical properties of the drug.

Formulating Levetiracetam as a sublingual tablet poses specific challenges due to its bitter taste, requirement for high dose loading, and the need for ultra-rapid disintegration. To address these, formulation strategies such as the incorporation of suitable superdisintegrants (e.g., Croscarmellose sodium, Sodium starch glycolate), sweetening agents (e.g., Aspartame, Mannitol), flavoring agents (e.g., Peppermint, Orange), and optimization of compression parameters are critical [9]. Furthermore, direct compression emerges as a preferred method for manufacturing sublingual tablets because it is simple, cost-effective, and eliminates the need for complex steps like granulation, thus maintaining the stability of the moisture-serive drugs [10].

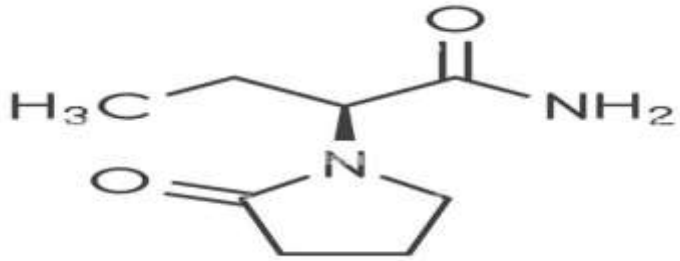
Numerous studies have demonstrated the success of sublingual delivery systems for other emergency-use medications such as Nitroglycerin and Fentanyl, highlighting the feasibility and clinical relevance of this approach [11]. Hence, developing sublingual Levetiracetam tablets could significantly benefit patients requiring immediate seizure control without depending on IV interventions or experiencing delayed onset associated with conventional oral tablets.

Thus, the present research work is designed with the primary objective to formulate and evaluate sublingual tablets of Levetiracetam using the direct compression method, employing various excipients aimed at ensuring rapid disintegration, acceptable mechanical strength, enhanced palatability, and immediate drug release. Pre-compression and post-compression studies were carried out to assess flow properties, tablet hardness, friability, disintegration time, drug content uniformity, and in vitro drug release, ensuring that the developed formulation meets the desirable criteria for effective sublingual delivery.

Drug profile

Levetiracetam

Structure



Chemical Name : (S)-a-ethyl-2-oxo-1-pyrrolidine acetamide

Molecular formula: C8H14N202

Molecular weight: 170.21 g/mol

Category. : Antiepileptic

Side Effects. : Drowsiness, dizziness, mood changes, fatigue

2 Aim And Objective

2.1Aim

The primary aim of this research is to develop and systematically evaluate sublingual tablets of Levetiracetam with the goal of achieving rapid onset of therapeutic action, improved bioavailability, and enhanced patient compliance. Epilepsy and related

neurological disorders often require immediate intervention to prevent severe complications, and conventional oral formulations may delay therapeutic onset due to gastrointestinal transit and first-pass metabolism.

By formulating Levetiracetam into a sublingual tablet, the drug can be rapidly absorbed through the rich vascular network present under the tongue, bypassing hepatic first-pass metabolism and leading to quicker systemic availability. This approach is expected to provide a more immediate therapeutic effect, which is particularly crucial in emergency seizure management.

The formulation strategy involves optimizing the use of superdisintegrants, binders, fillers, and other excipients to achieve a tablet that exhibits rapid disintegration, efficient wetting, sufficient mechanical strength, and high dissolution rate. Comprehensive pre-compression studies will ensure the powder blend has acceptable flow and compressibility properties for tablet production.

Following tablet fabrication, post-compression evaluations—including mechanical strength, friability, disintegration time, wetting time, and dissolution behavior—will be performed to ensure the final product meets pharmaceutical quality standards. Compatibility studies between Levetiracetam and the chosen excipients will also be conducted to ensure chemical stability and to prevent potential interactions that could affect the efficacy or safety of the final product.

Ultimately, the study aims not only to optimize the sublingual formulation of Levetiracetam but also to establish a robust and reproducible method for its manufacture, providing a patient-friendly dosage form that ensures faster onset of action and potentially better therapeutic outcomes.

2.2Objective

To design and develop sublingual tablet formulations of Levetiracetam using different proportions of superdisintegrants and excipients.

To evaluate pre-compression parameters of the powder blends, such as angle of repose, bulk density, and compressibility index, to ensure suitability for direct compression.

To assess post-compression characteristics, including weight variation, thickness, hardness, friability, disintegration time, wetting time, water absorption ratio, and in vitro dissolution profile.

To perform drug-excipient compatibility studies using analytical techniques such as Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC).

To optimize the formulation based on critical evaluation parameters and select the best-performing batch.

To compare the dissolution behavior of the optimized sublingual tablet with conventional oral dosage forms if applicable.

To conduct stability studies of the optimized formulation according to ICH guidelines to determine its shelf life and storage conditions.

3.Material and Methods

3.1Material

Levetiracetam, the active pharmaceutical ingredient (API), was obtained as a gift sample from Yarrow Chem Products, Mumbai, Maharashtra, and was used as received without further purification. Crospovidone, used as a superdisintegrant in the formulation, was procured from Loba Chemie Pvt. Ltd., Mumbai, Maharashtra, in pharmaceutical grade. Sodium starch glycolate, another superdisintegrant, was purchased from SD Fine-Chem Ltd., Mumbai, Maharashtra, and was of IP grade. Croscarmellose sodium, known for its rapid swelling properties, was obtained from Ashland India Pvt. Ltd., Navi Mumbai, Maharashtra, in NF grade.

Mannitol, a diluent with a sweet and cooling taste, was sourced from Qualikems Fine Chem Pvt. Ltd., Vadodara, Gujarat, in spray-dried IP grade form. Microcrystalline cellulose (Avicel PH 102), serving as a binder and filler, was supplied by Signet Chemical Corporation Pvt. Ltd., Mumbai, Maharashtra, and conformed to USP standards. Aspartame, a non-nutritive sweetener, was procured from Loba Chemie Pvt. Ltd., Mumbai, and was used in food-grade form suitable for sublingual applications.

Magnesium stearate, a commonly used lubricant, was acquired from Research Lab Fine Chem Industries, Mumbai, Maharashtra, in USP grade. Talc, used as a glidant to improve powder flow, was purchased from Central Drug House (CDH), New Delhi, and was of purified IP grade. All chemicals used for preparation of phosphate buffer (pH 6.8) required for in vitro dissolution studies, including sodium phosphate dibasic and potassium dihydrogen phosphate, were procured from Merck Specialties Pvt. Ltd., Bengaluru, Karnataka, and were of analytical reagent (AR) grade. Distilled water used throughout the formulation and evaluation process was obtained from an in-house double-distillation unit.

Active Pharmaceutical Ingredients:

Levetiracetam

Fig 1. Levetiracetam API

Table 1. Formulation table

Sr.no	Ingredient	Role
1	Levetiracetam	Active pharmaceutical ingredient
2	Microcrystallinecellulose	Filler and binder
3	Crospovidone	Disintegrant
4	PVP K-30	Ensure table cohesiveness
5	Mannitol	Sweetner and Filler
6	Citric acid	Enhance dissolution and taste mask
7	Magnesium stearate	Lubricant

Table 2 . Different concentration of Levetiracetam

Sr no	Ingredient	F1	F2	F3	F4
1	Levetiracetam	500	500	500	500
2	Microcrystalline cellulose	30	40	45	35
3	Crospovidone	30	25	20	30
4	PVP K-30	15	25	30	20
5	Mannitol	55	40	30	45
6	Citric acid	6	6	6	6
7	Magnesium stearate	4	4	4	4

3.1.1Method of Preparation

The study was conducted to formulate and evaluate sublingual tablets of Levetiracetam using the direct compression method, which is widely preferred due to its simplicity, avoidance of heat and moisture (ideal for moisture-sensitive drugs), and ease of scale-up in industrial production. The objective of this study was to develop a fast-disintegrating sublingual tablet that offers rapid onset of action by bypassing the hepatic first-pass metabolism.

Selection of Method

The direct compression technique was selected based on the physicochemical properties of Levetiracetam, especially its good compressibility and acceptable flow behavior when blended with suitable excipients. Additionally, the technique eliminates the need for wet granulation, preserving the drug's stability.

Formulation Design

Various batches of tablets were designed (F1–F6) using three superdisintegrants:

Crospovidone

Sodium Starch Glycolate (SSG)

Croscarmellose Sodium

Each superdisintegrant was used in two concentrations (3% and 5%) to study their effect on disintegration time, dissolution rate, and overall tablet performance.

All excipients and the drug were accurately weighed and passed through sieve #60 to obtain uniform particle size and remove lumps.

The drug was mixed with mannitol, MCC PH 102, superdisintegrant, and aspartame using geometric dilution technique in a mortar and pestle for 10–15 minutes to ensure uniform drug distribution.

After homogeneous blending, magnesium stearate and talc were added and gently mixed for 3–5 minutes. This step was critical to avoid over-lubrication, which may affect tablet disintegration.

The final blend was compressed using a single-punch tablet machine with flat-faced punches (8 mm diameter). The compression force was optimized to produce tablets with sufficient hardness yet rapid disintegration.

Experimental work:

Organoleptic Evaluation

Color :White to off-white

Odor :Odorless or slightly characteristic

Taste: Initially bland or slightly bitter

Angle of Repose

In order to determine a powder blend's flowability, which is essential for consistent die filling in tablet production.The fixed funnel method involves letting the powder fall into a conical heap on a level surface via a funnel that is fixed at a specific height. Determine the heap's radius ® and height (h).

Angle of Repose(θ)= $\tan^{-1}$ (h/r)

Bulk Density

To calculate, without compaction, the mass of powder per unit volume, which will show how the powder will respond under gravity.

Record the volume after carefully adding a known mass of powder to a graduated cylinder without tapping.

Bulk Density= mass of powder (g) / bulk volume (ml)

Tapped Density

To determine the powder's mass per unit volume following compaction, which indicates how well it settles. Tap the powder-filled cylinder until the volume stays constant after determining the bulk density, then note the final volume.

Tapped Density= Mass of powder (g) / tapped volume (ml)

Carr's Index

To assess a powder's compressibility, which influences the strength and homogeneity of tablets.

Carr's Index = (Tapped Density – Bulk Density/Tapped Density)× 100

Hausner Ratio

To evaluate the flow characteristics of a powder, which show how easily it can be processed.

Hausner Ratio = Bulk Density / Tapped Density

Evaluation test:

Drug Content

To evaluate the uniform distribution of Levetiracetam (500 mg) within the tablets of each formulation (F1 to F4) using a drug content assay. This ensures that each unit delivers the intended dose, critical for therapeutic efficacy.

Formula:

Drug Content= Absorbance of Sample /Absorbance of Standard × Label Claim(mg)

Drug Content % = Drug Content / Label Claim (mg) × 100

Weight Variation

Weigh 10 tablets individually and calculate the average.

Limit (as per IP/BP/USP):

Weight Variation = Some of Table Weight/ Number of Tablet

Hardness (Crushing Strength)

Test: Measure with a hardness tester.

Purpose: Ensures tablets withstand handling and packaging.

Limit: Usually 3–6 kg/cm² (depends on formulation)

Thickness

Tool: Vernier caliper or digital thickness gauge.

Purpose: Assures consistency and uniformity.

Limit: ±5% variation acceptable.

FriabilityTest: Using a friabilator (usually 100 rotations at 25 rpm).

Purpose: To check resistance to chipping and abrasion.

Limit: <1% weight loss

Formula for Friability : = (W(initial) -W(final) / W (final)) x 100

In Vitro Disintegration Study

Test: Using a USP disintegration tester in simulated saliva fluid or pH 6.8 buffer.

Purpose: Ensures rapid breakdown in sublingual environment.

Limit: <3 minutes (ideally <1 minute)

In Vitro Dissolution Study

The dissolution study of Levetiracetam sublingual tablets was carried out using pH 6.8 phosphate buffer as the dissolution medium, employing the USP Type II (paddle) apparatus at 50 rpm and a temperature of 37 ± 0.5°C. The in vitro drug release profiles of four formulations (F1–F4) were compared with the pure drug over a 15-minute period. The pure Levetiracetam exhibited a significantly slower dissolution rate, with only 63.2% of the drug released at the end of 15 minutes. In contrast, all formulated sublingual tablets demonstrated a markedly enhanced dissolution profile. Among the formulations, F3 showed the fastest drug release, achieving nearly complete drug release (100%) within 10 minutes, likely due to the higher concentration of PVP K-30 (a hydrophilic polymer that

enhances wettability and solubility) and a lower amount of mannitol. F2 and F4 also exhibited rapid dissolution, with over 99% of the drug released by 15 minutes. F1 showed a relatively slower release among the formulations but still outperformed the pure drug, reaching 98.7% drug release at 15 minutes. These findings indicate that the sublingual tablet formulations significantly improved the dissolution rate of Levetiracetam, with F3 emerging as the most promising formulation for rapid onset of action.

4.RESULT AND DISCUSSION

Determination of wavelength of maximum

Absorbance (λmax value)

The determination of the wavelength of maximum absorbance (λmax) of Levetiracetam was carried out using a UV-Visible spectrophotometer. A standard stock solution of Levetiracetam was prepared by dissolving 10 mg of the pure drug in 10 mL of methanol to obtain a concentration of 1000 µg/mL. From this stock solution, 1 mL was diluted to 100 mL with methanol to obtain a working solution of 10 µg/mL. The prepared solution was scanned In the UV range of 200–400 nm using methanol as the blank. The λmax, or the wavelength at which maximum absorbance was observed, was found to be approximately 205 nm. This wavelength was used for further spectrophotometric analysis of Levetiracetam in the formulated sublingual tablets.

Table 3. Angle of Repose

Angle of repose decreased from F1 to F4, indicating progressively improved flow properties; F4 showed excellent flow with 28.5°

Formulation	Angle of Repose
F1	32.4°
F2	30.3°
F3	29.6°
F4	28.5°

Table 4. Bulk Density

Bulk density increased gradually from F1 to F4, suggesting improved packing efficiency and powder flow in optimized formulation F4.

Formulation	Bulk Density
F1	0.615
F2	0.667
F3	0.702
F4	0.645

Table 5. Tapped Density

Tapped density slightly increased from F1 to F4, indicating better particle packing and flow characteristics, with F4 showing highest value.

Formulation	Tapped Density
F1	0.741
F2	0.784
F3	0.833
F4	0.769

Table 6. Carr's Index

All formulations showed acceptable flow; F4 had optimal density and lowest Carr's index and Hausner ratio, indicating excellent compressibility.

Formulation	Carr's Index %
F1	17.0
F2	15.0
F3	15.7
F4	16.1

Table 7. Hausner **Ratio**

Formulation	Hausner Ratio
F1	1.20
F2	1.17
F3	1.19
F4	1.19

Tablet evaluation results:

Drug Content

Ten tablets from each formulation were randomly selected, crushed, and accurately weighed. An amount equivalent to 500 mg of Levetiracetam was transferred to a volumetric flask and diluted appropriately with a suitable solvent (e.g., methanol or phosphate buffer). The solution was filtered and analyzed spectrophotometrically at the λmax of Levetiracetam (~230 nm). The concentration was calculated using a pre-validated calibration curve.

Table 8. Drug Content

Formulation	Drug Content
F1	99.1
F2	97.5
F3	99.8
F4	99.1

Table 9. Weight variation

Weight variation of all batches was within the permissible limits (±5%).

Formulation	Weight (Mg)
F1	640 mg
F2	640 mg
F3	635 mg
F4	639.7 mg

Table 10. Hardness

Tablet hardness ranged between 3–5 kg/cm², providing sufficient mechanical strength without affecting disintegration.

Thickness of tablets showed minimal variation.

Formulation	Hardness (Kg/cm$^{2)}$
F1	4.14
F2	4.6
F3	3.92
F4	4.26

Table 11. Friability

Friability was found to be less than 1% for all formulations, indicating good durability.

Formulation	Friability %
F1	0.94
F2	0.625
F3	1.26
F4	0.78

Table 12. Disintegration Test

Disintegration test for the optimized batch was below 60 seconds, suitable for sublingual administration.

Formulation	Disintegration Test(Sec)
F1	80
F2	75
F3	95
F4	88

Table 13 . In Vitro Dissolution Studies of Different Batches

Pure Drug : Levetiracetam

Time (Min)	Pure Drug %	Formulation 1 %	Formulation 2 %	Formulation 3 %	Formulation 4 %
2	12.5	35.2	38.7	42.1	39.8
4	22.4	56.1	60.5	67.8	63.2
6	33.8	72.3	76.4	84.5	79.7
8	41.7	85.6	89.2	96.1	93.8
10	52.3	94.5	97.6	99.4	98.9
15	63.2	98.7	99.8	100.0	99.9

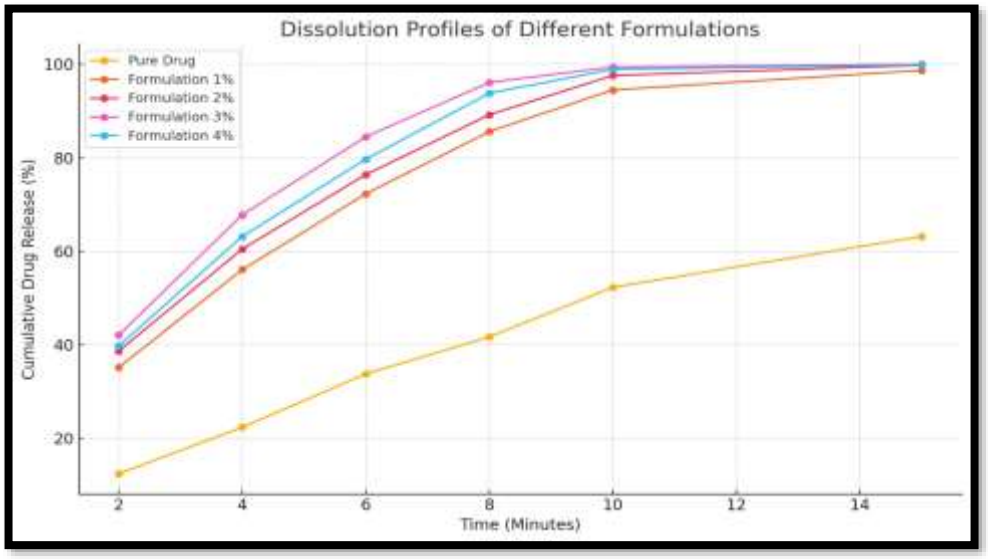


Fig 2. In Vitro Dissolution Studies of Different Batches

CONCLUSION

The present study successfully developed a sublingual tablet formulation of Levetiracetam with the objective of providing rapid onset of action, improved patient compliance, and effective management of seizures. Various formulations were prepared using different concentrations of superdisintegrants and evaluated for their pre-compression and post-compression parameters.

Among the developed formulations, the optimized batch exhibited acceptable physical properties, rapid disintegration time, and high drug release within 10 minutes, meeting all pharmacopeial specifications. In-process quality control tests ensured consistency and quality during manufacturing. The sublingual route effectively bypasses first-pass metabolism, making this formulation a promising alternative to conventional oral tablets, especially in emergency situations or for patients with swallowing difficulties.

Future studies can include in vivo evaluation and scale-up validation to further establish the clinical efficacy and commercial viability of the formulation.

Reference:

1) World Health Organization (WHO). "Epilepsy: A Public Health Imperative." WHO Report, 2019.
2) Patsalos PN. (2000). "Clinical pharmacokinetics of levetiracetam." Clinical Pharmacokinetics, 38(8): 559–572.
3) Lynch BA, Lambeng N, Nocka K, et al. (2004). "The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam." Proceedings of the National Academy of Sciences of the USA, 101(26): 9861–9866.
4) Abou-Khalil B. (2008). "Levetiracetam in the treatment of epilepsy." Neuropsychiatric Disease and Treatment, 4(3): 507–523.
5) Brodie MJ, Covanis A, Gil-Nagel A, et al. (2011). "Fast-acting treatments for acute seizures: a unmet clinical need." Epileptic Disorders, 13(3): 197–211.
6) Shojaei AH. (1998). "Buccal-sublingual drug delivery: A review." Journal of Pharmacy and Pharmaceutical Sciences, 1(1): 15–30.
7) Chinna Reddy P, Chaitanya KSC, Madhusudan Rao Y. (2012). "A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods." DARU Journal of Pharmaceutical Sciences, 20(1): 1–12.
8) Desai PM, Liew CV, Heng PWS. (2016). "Review of disintegrants and their use in orally disintegrating dosage forms." Asian Journal of Pharmaceutical Sciences, 11(2): 174–182.
9) Kuchekar BS, Badhan AC, Mahajan HS. (2003). "Mouth dissolving tablets: A novel drug delivery system." Pharma Times, 35(7): 7–9.
10) Lachman L, Lieberman HA, Kanig JL. (1991). "The Theory and Practice of Industrial Pharmacy." 3rd Ed., Varghese Publishing House, Bombay.
11) Joshi P, Yadav A, Pandey M. (2021). "Recent advances in sublingual drug delivery system: A review." Research Journal of Pharmacy and Technology, 14(2): 957–962.

BIOGRAPHIES

I Mayur S. Jadhav dedicated final-year Bachelor of Pharmacy student with a keen interest in Drug Development, novel drug delivery systems and pharmaceutical formulation development. With a strong continuous Foundation and hands-on experience in formulation science, he has undertaken research focused on enhancing the Therapeutic efficacy of antiviral drugs. My project on mucoadhesive Famciclovir tablets reflects his commitment to Improving bioavailability and patient compliance through innovative drug delivery strategies. I aspires to contribute To the pharmaceutical industry by developing patient-centric formulations. I am also passionate about continuous Learning and applying scientific principles to solve real-world healthcare challenges.