Austin Journal of Pharmacology and Therapeutics

Open Access

Austin Publishing Group

Research Article

Formulation and Optimization of Herbal Sublingual Films for Migraine Management

Raul S[1], Bhalekar T[1], Hyalij C[1], Jadhav I[1], Choudhary S[1] and Shikalgar S[2]

[1]Department of Pharmaceutics, Alard College of Pharmacy, Pune – 411057, India

[2]Assitant Professor, Department of Pharmaceutics, Alard College of Pharmacy, Pune, India

***Corresponding author:** Suyash Raul, Department of Pharmaceutics, Alard College of Pharmacy, Pune – 411057, India

Tel: +919158545389;

Email: raulsuyash8@gmail.com

Received: March 31, 2025

Accepted: April 16, 2025

Published: April 21, 2025

Abstract

Migraine, a neurological disorder, requires immediate and effective relief. This research aims to formulate and optimize an herbal sublingual film for migraine management, combining Butterbur (5 mg) and Feverfew (15 mg) in a 1:3 ratio. The aim is to offer rapid relief from symptoms and incorporate preventive properties to minimize migraine recurrence.

Sublingual films were developed using a solvent casting method and optimized through a 3^2 full factorial design with HPMC E5 as the film-forming polymeric agent and PEG 400 as the plasticizer. The optimized formulation shows a disintegration time (DT) of 58 seconds, allowing for rapid absorption of the drug through the sublingual route. In vitro dissolution testing results show that 89% of the drug was released in 10 minutes, which was significantly better than that of conventional oral dosage forms. The films were also found to have excellent physicochemical stability with 85-fold endurance, 98.5% uniform drug content, and a neutral surface pH of ~6.8 to avoid mucosal irritation.

The findings indicate that these sublingual films provide an efficient and patient-friendly solution for migraine management, particularly beneficial for patients experiencing nausea and vomiting, where swallowing traditional tablets may be challenging. The rapid onset of action, combined with the natural medicinal benefits of Butterbur and Feverfew, enhances their therapeutic potential. However, certain limitations of this novel sublingual drug delivery system need to be further explored. Despite its effectiveness and patient convenience, comprehensive studies are required to evaluate its long-term safety, stability, and clinical efficacy.

Keywords: Migraease; Migraine care; Sublingual film; Butterbur; Feverfew; Rapid drug delivery

Introduction

Introduction to Migraine

Migraine is a prevalent neurological disease affecting around 12–15% of people globally, with a higher occurrence in women due to hormonal factors. It is known for recurrent headaches generally accompanied by vomiting, nausea, and sensitivity to sound and light. The underlying mechanisms of migraine are complex, involving neurovascular processes, cortical depression, and dysregulation of neurotransmitters like serotonin (5HT) and calcitonin gene-related peptide (CGRP) [11].

Migraines are primarily classified into two types: those with aura, which includes sensory disturbances such as visual changes, numbness, or speech difficulties, and those without aura. Triggers for migraines can vary widely among individuals and may encompass stress, hormonal changes, dietary influences, sleep issues, and environmental factors.

Treatment options for migraines include both pharmacological and non-pharmacological methods. For acute relief, analgesics, triptans, and CGRP inhibitors are commonly used, while preventive treatments may involve beta-blockers, antidepressants, antiepileptics, and herbal remedies like Butterbur and Feverfew. However, challenges remain in managing migraines, such as delayed medication effectiveness, side effects, and difficulties in patient adherence [7].

In response to these challenges, there is an increasing interest in innovative drug delivery systems to improve treatment outcomes. One promising development is the use of sublingual oral films, which facilitate faster drug absorption and enhance patient compliance. Current research is focused on the formulate and evaluation of these sublingual films for migraine relief, seeking to achieve quicker onset and better bioavailability than traditional oral medications.

Introduction of Drug Delivery System

Introduction to Sublingual Drug Delivery: Sublingual films are becoming an innovation in pharmaceutical and nutraceutical products. The concept of sublingual films emerged to solve the problems related to traditional oral dose forms and enhance absorption by maximizing treatment [26]. Sublingual administration is an alternative systemic drug delivery system with various advantages. Since the mucosa of the mouth (sublingual) is very vascular, drugs enter the systemic circulation directly from the sublingual administration of drugs without going through the gastrointestinal tract and the hepatic first-pass effect in the liver [4]. Sublingual films enhance active pharmaceutical ingredient [API] dissolution effectiveness in the short-term oral cavity after they meet less saliva than dissolving tablets. The drug is absorbed 3 to 10 times more quickly through

Citation: Raul S, Bhalekar T, Hyalij C, Jadhav I, Choudhary S, et al. Formulation and Optimization of Herbal Sublingual Films for Migraine Management. Austin J Pharmacol Ther. 2025; 12(3): 1194.

the sublingual pathway than through the oral pathway, and only hypodermic injection is more efficient [6]. Permeability-wise, the sublingual region of the oral cavity is more permeable than the buccal, which is more permeable than the palatal region. Permeability discrepancies are typically determined by the membranes' relative thickness, degree of keratinization and blood supply. In addition to changes in mucous membrane permeability, the degree of medication transport is influenced by the drug's physicochemical qualities [29].

Sublingual oral films will disintegrate in the mouth faster than pills, enhancing their bioavailability. To render sublingual films much more acceptable to young patients, flavour maskers and sweeteners have been added. Sublingual films offer steady dosages and are extremely stable. Rather than relying on the customer to measure it themselves, the manufacturers pre-formed the films for dose accuracy.

Sublingual Glands

Salivary glands are located underneath the tongue on the floor of the mouth. They are commonly referred to as sublingual glands (Figure 1).

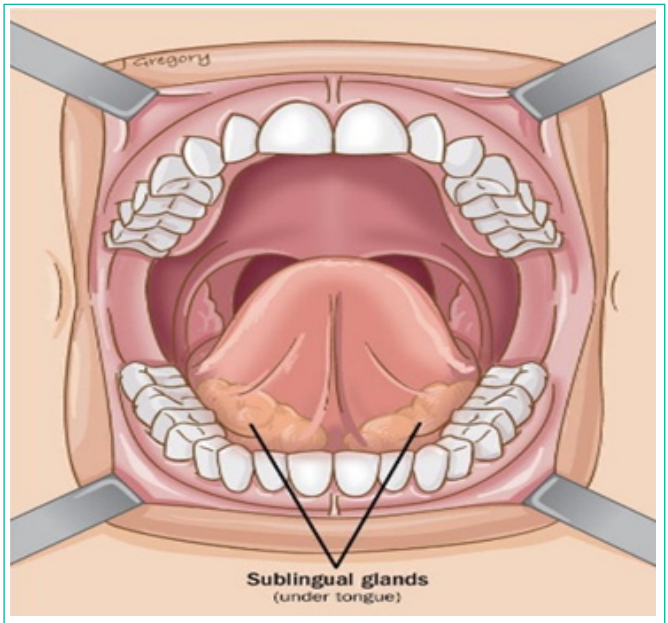


Figure 1: Sublingual glands.

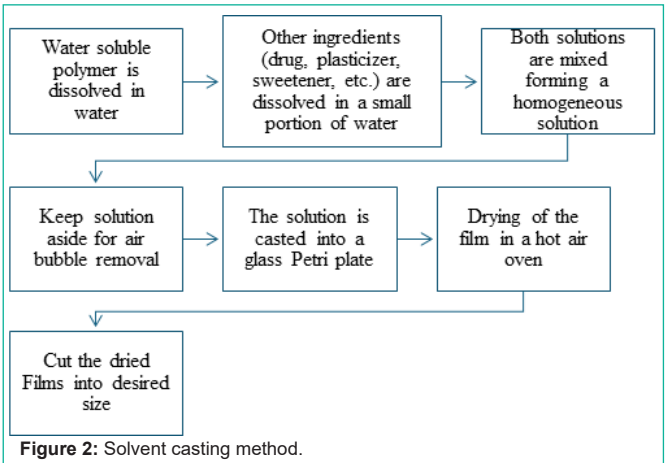


Figure 2: Solvent casting method.

The saliva is secreted by glands, which lubricates the inside of the mouth and is vital for mastication and swallowing food.

Absorption is the process of the drug's movement from the place where it was administered to the systemic circulation of the body, meaning that the absorption depends on the thickness of the tissue layers. The rate of drug absorption is as follows: Palatal<Gingival<Buccal<Sublingual. Owing to its rich blood supply and high permeability, the sublingual route provides a rapid onset of action. The medication is mixed with saliva, and subsequently, it is absorbed throughout the mouth [18].

- 2.3. Drug Properties for Sublingual Films [19]It must possess good stability and good solubility in water and saliva.
- The drug must be pleasant in taste
- Effectively penetrates oral mucosal tissues.
- It should possess small to moderate molecular weight.
- The incorporated drug must be below 40 mg
- ADVANTAGESConvenient dosing.
- Water is not required
- Easy handling & transport.
- Prevent choking.
- Avoids first-pass liver metabolism
- Rapid onset of action.

DISADVANTAGES

- Sublingual drug administration can disrupt eating and drinking.
- When taking sublingual medication, patients should stop smoking because it constricts blood vessels, which subsides the medication's absorption.
- Administration of high doses is unattainable
- When the patient is unconscious or uncooperative, it cannot be used.
- For medications that degrade in the oral cavity, it is unsuitable.

Mechanism of Sublingual Absorption

Sublingual formulations bypass hepatic first-pass metabolism by dissolving drugs in saliva. The sublingual mucosa, which consists of non-keratinized squamous epithelium, allows for drug absorption by transcellular and paracellular transport. After absorption, drugs penetrate capillaries that drain directly into the superior vein, providing fast action [7].

Factors Affecting the Sublingual Absorption [7]

- Drugs are absorbed more quickly sublingually because the sublingual epithelium is thinner (100–200 μm) than the buccal epithelium.

The saliva has a pH of 6.0, promoting drug absorption in

unionized. The oral mucosa absorbs drugs more efficiently when their pKa is less than 10 for bases and larger than 2 for acids [6].

The oil-water partition coefficient influences drug absorption from oral mucosa.

- The oil-water partition coefficient influences drug absorption through mucosa, which is best between 40 and 2000 for sublingual absorption.
- Drugs must dissolve in lipid and aqueous buccal secretions for optimal absorption.

Formulation of Sublingual Films [1]

Mouth-dissolving films, also referred to as sublingual films, are thin sheets with an area of 5 to 20 cm^2 that incorporate an active ingredient. These films dissolve rapidly in water or saliva by a specialized matrix composed of water-soluble polymers (Table 1). A Standard formulation consists of the following components:

Introduction of Drug

Butterbur [14,15]: Table 2.

Drug Characterization: Petasin.

Feverfew [11,12,15]: Table 3.

Drug Characterization (Feverfew Extract).

Material and Method

Material

The ingredients used in the preparation are Feverfew and Butterbur, which have been used as the Active Pharmaceutical Ingredients (APIs) and are obtained from Kshipra Biotech, Indore. Polyethylene Glycol 400, received from Analab Fine Chemical, Mumbai, is used as a plasticizer, whereas HPMC E5, also received from Analab Fine Chemical, is used as a polymer. Stevia, utilized as a sweetener, is obtained from Organic India, New Delhi. Citric Acid, a saliva-stimulating agent, is obtained from Analab Fine Chemical, Mumbai. Peppermint, a flavoring agent, is also obtained from Icon Aromatic, Mumbai.

Calculation of the dose of Butterbur & Feverfew [20]

Dose of drug = 20 mg,

Drug ratio (Butterbur: Feverfew) = 1:3,

Diameter of Petri dish = 9.1 cm,

Radius = Diameter /2

= 9/2 = 4.55 cm

Area of Petri dish = $\pi r2$ = 3.14 X 4.55 X 4.55,

Area of petri dish = 65.001 cm^2,

Now, the Dose is 20 mg, and the area of the film is 2 cm^2,

2 cm^2 contains 20 mg drug,

So, 65.001 Cm^2 contains approximately 650mg.

Table 1: Composition of sublingual film [19].

Sr.No	Composition	Quantity
1	Active Pharmaceutical Agent [API]	1%-25%
2	Film-forming Polymer	40%-50%
3	Plasticizer	0-20%
4	Sweetening agent	3%-6%
5	Saliva Stimulating Agent	2%-6%
6	Flavouring Enhancer	10%
7	Water	Q.S

Preparation of Sublingual Films

Method of Preparation: ***Solvent casting method (Figure 2).***

Formulation of Trial Batches of Sublingual Films:

Trail batches of herbal anti-migraine sublingual films were prepared to employ hydroxypropyl methylcellulose (HPMC) polymers of varying grades of viscosity. HPMC E5 and HPMC E50 were chosen as they have already established efficacy in quick drug-release formulations [3]. Polyethylene glycol 400 (PEG 400) was added as plasticizer to increase the flexibility of film, whereas citric acid was added as a saliva stimulant to enable quick disintegration. Stevia was added as a natural sweetener to enhance palatability. As water was not part of the final product, about 30.0 mL was used during the process of film casting in all formulations to maintain uniformity and consistency [3] (Table 4).

Application of Factorial Design:

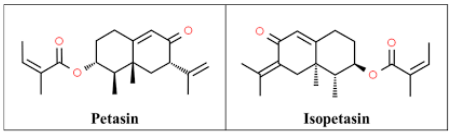
Rephrasing this, factorial design, an experimental method that hugely minimised the quantity of time, funds, and man-hours spent on the procedure, was utilized to develop an extremely successful medication formula. Alternatively, classical methods that involve "one factor at a time" are time-consuming, more likely to lead to extensive experimentation, and yield very limited information about interactions between variables. To rephrase, we employed Design Expert software, a high-capacity factorial design application that enables in-depth analysis of independent variables and their interactions, to get around these limitations. To rephrase, we improved the development process by using the software to create experiments that systematically examined the effects and interactions of several variables at once.

Rephrasing this, the Yi response variable was rigorously examined through a polynomial equation, which included main effects, interaction terms, and their statistical significance. Alternatively, by obtaining a high correlation coefficient from the model, we ensured the strength of the fit, ensuring the predicted responses were precise and had minimal variance. To rephrase, this statistically robust method not only streamlined the formulation development process but also gave a data-driven model that enabled researchers to make informed decisions based on a solid analysis. In other words, by applying factorial design and sophisticated software tools, we could curtail the formulation process considerably while making the results more reliable.

3^2 Full Factorial Designs [19]: Table 5.

All 9 factorial batches were assessed for disintegration time (Dt), folding endurance, and 10 min % release (Y1, Y2, and Y3) to determine how both parameters (X1, X2) impacted the film.

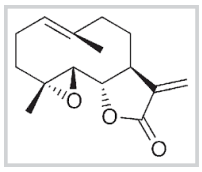
Table 2: Introduction to Butterbur.

General Properties:		
Scientific name	Petasites hybridus.	
Family	Asteraceae	
Appearance	Brownish Powder	
Parts used	Flower, Stem & Leaves	
Taste	Characteristic	
Chemical Constituents	Petasins – Isopetasin , Neopetasin , PA (0%),Sesquiterpines	
Structure	 Petasin Isopetasin	
Category	Anti-inflammatory	
Description	Petasin is an enoate ester that is produced by the formal condensation of the carboxy group from angelic acid. It functions as a plant metabolite, acts as a vasodilator, and serves as an anti-allergic agent.	
MW	316.44 g/mol	
Chemical Formula	$C_{20}H_{28}O_3$	
IUPAC Name	[(1R,2R,7S,8aR)-1,8a-dimethyl-6-oxo-7-prop-1-en-2-yl-1,2,3,4,7,8-hexahydronaphthalen-2-yl] (Z)-2-methylbut-2-enoate	
XLogP3-AA	4.6	
Identification	NMR spectra, GC Mass Spectroscopy	
Dose	For Adults - 4 g / day	
Pharmacokinetic Properties:		
Absorption	Higher Absorption was found in the Duodenum, followed by the ileum and jejunum from the Intestinal ligations of the rat.	
Metabolism	hepatic metabolism, cytochrome P450 enzyme system	
Half-life	Not well documented	
Excretion	Renal & Fecal excretion: since the drug is lipophilic, it may undergo enterohepatic recirculation before complete elimination.	
Pharmacological Properties:		
Indication	Commonly indicated for migraine prevention, Allergic rhinitis, Asthma, IBS, & inflammation.	
Contraindication	Contraindicated for patients who are currently taking Anticholinergic drugs	
Mechanism of Action	Inhibit action of cGRP & Inhibit biosynthesis of PGs & Leukotrienes.	
Analyses	**Drug Characterization: Petasin**	
	Specification	Results
Composition Specification		
Assay Petasin	NLT 15 %	15.34 %
Pyrrolizidine Alkaloid(PA)	Absent	Absent
Loss on drying (at 105 C)	Max 7%	3.6 %
pH (1% sol)	3-6	3.65
Water solubility	Min 70%	75.58%
Alcohol Solubility (water 50 %, Alcohol 50%)	Min 70%	73%
Chemical Properties		
Heavy Metals	< 10 PPM	4.5 PPM
Microbiological Test		
Total Plate Count	< 10000 CFU/G	290 CFU/G
Yeast & Mold	<100 CFU/G	10 CFU/G
E.coli Salmonella Coliforms	Absent	Absent

Independent variables	Dependent variables
• X1-Amount of • X2-Amount of PEG 400	• Y1- Disintegration time • Y2- Folding Endurance • Y3- 10 min % Drug Release

Formulation development of Antimigraine sublingual films: Table 6.

Table 3: Introduction to feverfew.

Scientific Name	Tanectum parthenium	
Family	Asteraceae	
Appearance	Brown	
Taste	Bitter	
Chemical Constituents	Sesquiterpene lactones [parthenolides (primary active compound),costunolide] Flavonoids (Quercetin, Apigenin), Volatile oil (camphor,α pinene)	
Structure	 Parthenolide	
Category	Anti-inflammatory, Anticancer	
Chemical formula	$C_{15}H_{20}O_3$	
Molecular weight	248.32g/mol	
IUPAC name	(1S,2R,4R,7E,11S)-4,8-dimethyl-12-methylidene-3,14-dioxatricyclo[9.3.0.0^{2,4}]tetradec-7-en-13-one	
Identification	TLC, HPLC	
Dose	50-150 mg / daily	
Pharmacokinetic Properties:		
Absorption	It binds with the mucosal membrane owing to its Lipophilicity.	
Bioavailability	Limited Data available	
Metabolism	Hepatic Metabolism (Phase 1 reactions)	
Half-life	1.5 (Orally Administered)	
Excretion	Urinary Excretion (Phase 2 reaction) Fecal Excretion (Binds with Bile)	
Pharmacological Properties:		
Indication	Migraine prevention, Menstrual cramps, Anti-inflammatory.	
Contraindication	Pregnancy (May cause miscarriage), Bleeding Disorders.	
Mechanism of Action	Vasodilation, COX 2 inhibition, & inhibition of NF-κB (inflammatory cytokines)	
	Drug Characterization (Feverfew Extract)	
Analysis	Specification	Result
Moisture Content	< 5.0%	3.65%
Heavy Metals	<10 ppm	Confirm
Pb	< 3 ppm	< 1 ppm
As	< 2 ppm	< 1 ppm
Cd	< 1 ppm	< 1 ppm
Hg	< 0.5 ppm	0.5 ppm
Lactone – Parthenolide	NLT 0.7%	0.79%
Total Plate Count	< 10000 CFU/G	600 CFU/G
Yeast & Mold	<1000CFU/G	80 CFU/G
E.coli Salmonella Coliforms	Absent / 10 G Negative < 100 CFU/G	Absent Negative 10 CFU/G
Image		

Evaluation Studies [18,19]

Thickness

The thickness was determined using a digital vernier caliper of 3 films.

Surface pH

The surface pH indicates the potential for side effects. An acidic or basic pH can irritate the oral mucosa, so it is kept near neutral. The pH was measured with a pH meter over three experiments, and the average with standard deviation was reported [20].

Drug Content

The film was kept in the 100 ml stimulated salivary fluid. The solution was diluted and filtered and was determined by UV spectrophotometer.

Swelling Index

The stimulated saliva was utilized to determine the swelling index

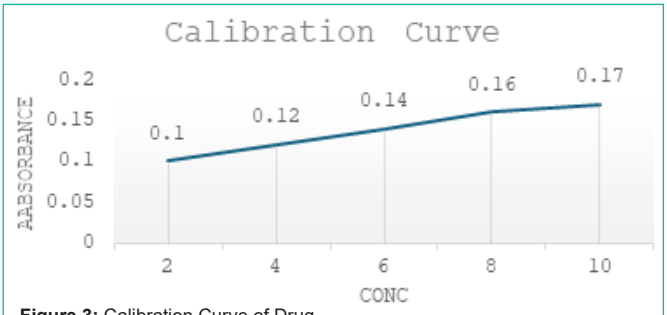


Figure 3: Calibration Curve of Drug.

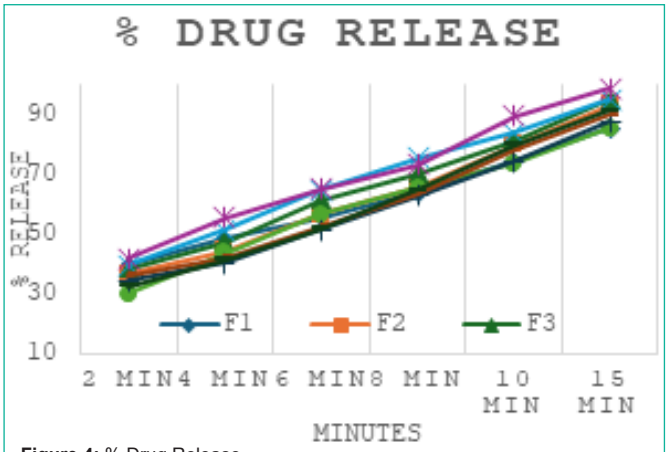


Figure 4: % Drug Release.

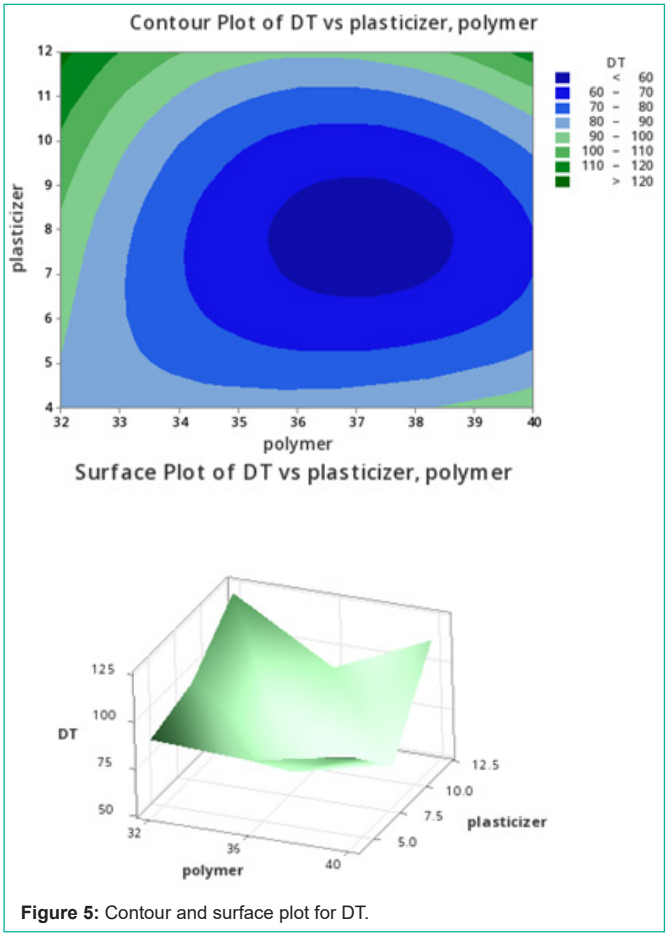


Figure 5: Contour and surface plot for DT.

of films. Initially the film was weighted and kept aside in the Petri plate with 10 ml saliva. The increase in the weight of the film was recorded until there was no change in weight.

Drug Content

The 3 films of size 2 cm× 1cm were kept in 100 ml of phosphate buffer. After complete dissolution, the solution was diluted and estimated by the UV method. Drug content was calculated from the calibration curve.

In Vitro Dissolution Study

A dissolution analysis of sublingual films was performed with USP type II (Paddle apparatus) under 500 ml phosphate buffer (pH 6.8) as a medium kept at 37 °C. The medium was stirred at 50 rpm. Samples were collected every 2 minutes, with an equal volume of fresh medium added. Drug concentration in the samples was analysed using a UV spectrophotometer, and a graph of drug release percentage over time was created [18].

Measurement of Mechanical Properties

The mechanical property of the film provides insight into the degree to which the film can sustain the stress or force throughout processing, packaging, and transport [28].

Tensile Strength: Tensile strength is the maximum stress on a point at which the film ruptures. The tensile strength (TS) is obtained by dividing the maximum stress required by the initial cross-sectional area of the specimen and is measured in force per unit area (N/mm^2) [19].

Percent Elongation at break (%E): When stress is applied, a film is elongated, and the stress is known as strain. Strain is simply the deformation of the film from the initial specification of the sample. As plasticizer concentration is increased, elongation of the film increases.

Folding Endurance: Folding endurance was determined by folding the film at the same point repeatedly until it ruptured. The number of folds the film can be made at the same point before breaking gives the value of folding endurance.

Results and Discussion

Calibration Curve of Drug

A calibration curve for the drug was obtained using a 6.8 pH phosphate buffer solution. The graph shows concentration on the X-axis and absorbance on the Y-axis, allowing for the relationship between the two to be analyzed ***(*Figure 3*)***.

Concentration (ppm)	2	4	6	8	10
Absorbance	0.1	0.12	0.14	0.16	0.17

Evaluation of Trial Batches

To finalize the selection of this polymer, the prepared film trial samples were evaluated based on fundamental assessment parameters. The outcomes were systematically recorded in the table below [19] (Table 7).

Both polymers showed, which is indeed an important consideration, good film-forming abilities. Further evaluations were conducted based on physical and, as noted in various studies,

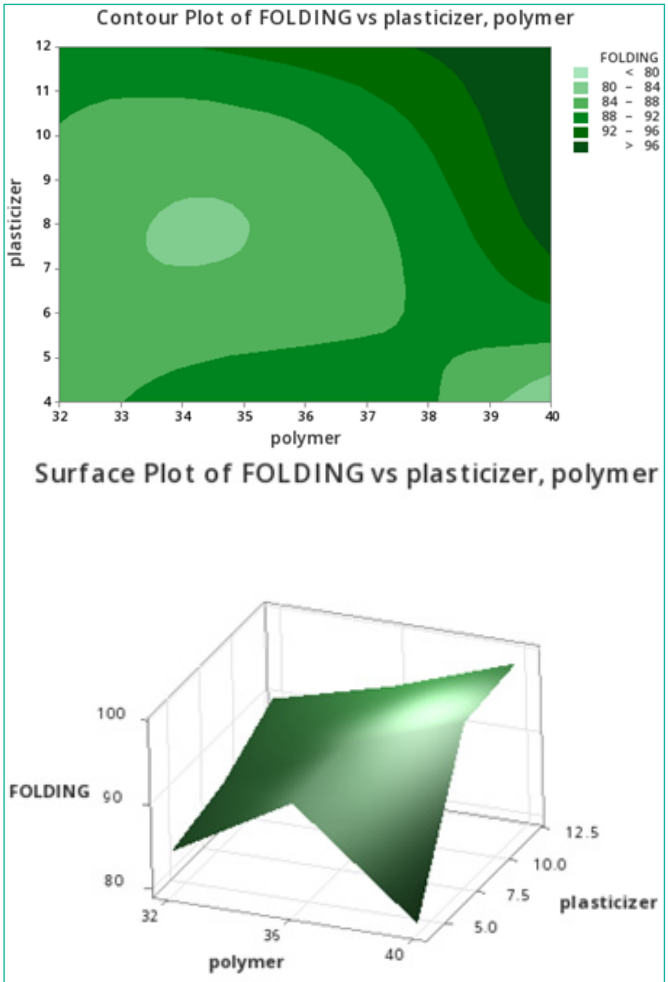


Figure 6: Contour and Surface plot for folding endurance.

Table 4: Formulation of trial batches.

Ingredients	*T1*	*T2*	*T3*	*T4*
Drug	*20*	*20*	*20*	*20*
HPMC E50	*36*	*40*	*-*	*-*
HPMC E5	*-*	*-*	*36*	*40*
PEG 400	*8*	*8*	*8*	*8*
Citric acid	*3.2*	*3.2*	*3.2*	*3.2*
Stevia	*4.8*	*4.8*	*4.8*	*4.8*
Peppermint	*8*	*8*	*8*	*8*
Water	*Q.S*	*Q.S*	*Q.S*	*Q.S*

Table 5: Full Factorial Design.

Batch No.	X1 (HPMC E5)	X2 (PEG 400)
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Translation of coded level in actual limit

Independent variables	Actual Value		
	Low(-1)	Medium(0)	High(+1)
Amount of polymer (X1)	32	36	40
Amount of PEG 400(X2)	4	8	12

Table 6: Factorial Design.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	20	20	20	20	20	20	20	20	20
Polymer	32	32	32	36	36	36	40	40	40
PEG 400	4	8	12	4	8	12	4	8	12
Citric acid	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2
Peppermint oil	8	8	8	8	8	8	8	8	8
Stevia	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
Water	QS	QS	QS	QS	QS	QS	QS	QS	QS

Table 7: Evaluation of trial batches.

Formulation code	*Stickiness*	*Film clarity*	*Surface appearance*	*Quality*
T1	*Sticky*	*Clear*	*Non-uniform*	*Poor*
T2	*Non-Sticky*	*Clear*	*Uniform*	*Good*
T3	*Non-Sticky*	*Clear*	*Uniform*	*Good*
T4	*Non-Sticky*	*clear*	*Uniform*	*Good*

Table 8: Evaluation of trial batches.

Formulation code	*Weight variation(mg)*	*Thickness (mm)*	*Disintegration time (sec)*	*Folding Endurance*
T1	*103*	*0.9*	*135*	*94*
T2	*156*	*0.12*	*170*	*102*
T3	*86*	*0.11*	*68*	*95*
T4	*90*	*0.10*	*75*	*91*

chemical parameters to finalize the selection of the polymer. In other words, the weight variation was within the acceptable limits, and the folding endurance was found to be affected by the amounts of polymer and plasticizer used. Additionally, the films displayed a uniform, specifically in terms of effectiveness, thickness, ensuring consistency in the formulation (Table 8).

Hydroxypropyl Methylcellulose (HPMC) E50 and HPMC E5 were used as polymeric bases in the formulation of the sublingual films. Both polymers had the ability to form films.

However, due to its viscosity, HPMC E50 was found to have a longer disintegration time in the evaluation. In contrast, HPMC E5 demonstrated a reduced disintegration time while still fulfilling all required parameters.

Because of its enhanced performance, HPMC E5 was chosen as the best polymer for formulation based on these results.

Evaluation of Factorial Batches

The evaluation of factorial batches F1 to F9 focused on various parameters to assess their quality and performance. Key metrics examined included weight variation, drug release, surface pH, drug content, disintegration time, folding endurance, thickness, swelling index, elongation percentage, and tensile strength. These parameters were systematically analyzed, and the findings are detailed in the accompanying table (Table 9,10,11).

Table 9: Evaluation of Factorial batches.

Formulation	*Stickiness*	*Film clarity*	*Surface Appearance*	*Quality*
F1	*Non-sticky*	*Clear*	*Uniform*	*Good*
F2	*Non-sticky*	*Clear*	*Uniform*	*Good*
F3	*Non-sticky*	*Clear*	*Uniform*	*Good*
F4	*Non-sticky*	*Clear*	*Uniform*	*Good*
F5	*Non-sticky*	*Clear*	*Uniform*	*Good*
F6	*Non-sticky*	*Clear*	*Uniform*	*Good*
F7	*Non-sticky*	*Clear*	*Uniform*	*Good*
F8	*Non-sticky*	*Clear*	*Uniform*	*Good*
F9	*Non-sticky*	*Clear*	*Uniform*	*Good*

Table 10: Evaluation of Factorial batches.

Formulation	Weight variation(mg)	Thickness (mm)	Surface pH	Swelling index	Disintegration time(sec)
F1	120±3.0	0.48	6.9	10.41	135
F2	110±2.75	0.67	6.7	14.5	104
F3	80±1.76	0.45	6.5	18.22	62
F4	85±2.125	0.74	6.8	15.33	86
F5	90±2.25	0.72	7.1	12.4	58
F6	90±2.25	0.16	6.9	16.2	92
F7	163±3.5	0.12	6.8	24.2	160
F8	110±2.42	0.51	7.0	12.5	70
F9	70±1.54	0.39	6.8	17.2	115

Table 11: Evaluation of Factorial batches.

Formulation	Folding endurance	% Elongation	Tensile strength(N/mm²)	Drug content (%)
F1	84	20.12	2.65	99.1
F2	86	24.5	3.10	97.1
F3	78	18.2	2.91	94.2
F4	94	22.63	2.96	98.4
F5	85	17.2	2.41	98.5
F6	81	14.6	2.15	98.3
F7	80	12.52	2.01	95
F8	98	24.5	3.45	95
F9	92	26.5	3.50	98.2

Factorial batch evaluations showed that all formulations had acceptable weight variation, surface pH, and drug content (94.2% to 99.1%), with F5 demonstrating the fastest disintegration time (58 sec) and the highest drug release (98.45% at 15 minutes). The optimized formulation, F5, provided the best balance of mechanical strength, efficient drug release, and rapid disintegration, making it suitable for effective sublingual drug delivery (Figure 4).

During the initial stages of this project, careful consideration was given to selecting the appropriate concentrations of the film-forming polymer. This was a vital step in achieving the optimum balance between flexibility, durability, and mechanical strength, of sublingual films. The study aimed to formulate films that are resistant to various stresses without compromising their structural integrity or activity. To rephrase, hydroxypropyl methylcellulose (HPMC) E5 was used as the major film-forming polymer, and Polyethylene glycol (PEG) 400 was employed as a plasticizer to impart flexibility and texture to the films [27]. The combination of HPMC E5 and PEG 400 resulted in films that were flexible and, hence, applicable for sublingual delivery. Concentrations of the key ingredients were optimized by using Design Expert (version 13) software.

3^2 full factorial design was employed in sublingual film design as well as for the investigation of the relationship between independent and dependent variables. In vitro drug release analysis revealed 98.45% at 15 minutes, i.e., the films disintegrate totally within the time, and drug release is not influenced by excipients. The optimised batch demonstrated a drug content of 98.5%. Different mathematical models and regression analysis were applied by utilizing Minitab 16 software to optimize the formulation further.

Statistical Analysis of Factorial Design

After analyzing the data using Minitab 16, both experimental and regression analyses were conducted. The results of these analyses are presented below (Table 13).

Analysis of Variance for Disintegration Time (sec)

ANOVA for DT shows that polymer and plasticizer significantly affect DT, and their interaction further modifies the disintegration characteristics of the film (Table 14, Figure 5).

The surface plots and contour plots illustrate the interaction between plasticizer and polymer content in relation to disintegration time (DT) with increasing polymer concentration, DT tends to increase.

Analysis of Variance for Folding Endurance

Both polymer and plasticizer have a notable effect on folding endurance ($P < 0.05$), with their interaction further influencing film flexibility. Optimizing their concentration is crucial for enhancing film strength and durability.

The plots show that folding endurance improves with higher polymer and plasticizer concentrations, indicating better film flexibility and strength (Table 15, Figure 6).

Table 12: % Drug Release.

Batches	% Release					
	2 min	4 min	6 min	8 min	10 min	15 min
F1	39.2	48.24	55.1	63.7	74.1	85.15
F2	36.6	44.31	56.25	65.75	79.75	92.85
F3	38.45	47.25	61.3	70.1	81.25	94.75
F4	39.55	51.20	64.35	75.2	83.85	96.63
F5	41.75	55.25	64.85	72.85	89.4	98.45
F6	29.85	43.45	56.5	65.2	73.25	85.35
F7	34.2	40.2	51.02	62.54	74.2	87.5
F8	36.1	41.8	52.2	63.25	78.2	89.65
F9	32.25	41.2	51.6	64.37	79.8	91.15

Table 13: Statistical analysis of drug [19].

Batch	Coded Factors		Actual factors		Response		
	X1	X2	X1	X2	Y1 (DT)	Y2 (Folding Endurance)	Y3 (% drug release)
A1	-1	-1	32	4	135	84	74.1
A2	-1	0	32	8	143	86	79.7
A3	-1	1	32	12	62	90	81.2
A4	0	-1	36	4	86	92	83.8
A5	0	0	36	8	58	85	89.4
A6	0	1	36	12	92	94	73.25
A7	1	-1	40	4	160	80	74.2
A8	1	0	40	8	70	98	78.2
A9	1	1	40	12	115	99	79.8

3^2 Full Factorial Design levels

Independent Factors	Levels		
	Low (-1)	Medium (0)	High (1)
X1= Amount of HPMC E5 (mg)	32	36	40
X2= Amount of PEG 400 (ml)	4	8	12

Table 14: ANOVA of DT.

Source	DF	Adjusted. SS	Adjusted. MS	F Value	P Value	Remark
Model	8	9398	1174.7	117475.0	0.0023	Significant
Linear	4	3759	939.7	93975.0	0.0024	Significant
Polymer	2	2005	1002.3	100250.0	0.0022	Significant
Plasticizer	2	1754	877.0	87700.0	0.0024	Significant
2-Way Interactions	4	5639	1409.8	140975.0	0.0020	Significant
Polymer * Plasticizer	4	5639	1409.8	140975.0	0.0020	Significant
Error	1	0.01	0.01	-	-	-
Total	8	9398	-	-	-	-

Table 15: ANOVA for Folding Endurance.

Source	DF	Adjusted. SS	Adjusted. MS	F Value	P Value	Remark
Model	8	372.22	46.53	4653.0	0.0023	Significant
Linear	4	135.78	33.94	3394.0	0.0025	Significant
Polymer	2	80.89	40.44	4044.0	0.0022	Significant
Plasticizer	2	54.89	27.44	2744.0	0.0024	Significant
2-Way Interactions	4	236.44	59.11	5911.0	0.0020	Significant
Polymer * Plasticizer	4	236.44	59.11	5911.0	0.0020	Significant
Error	1	0.01	0.01	-	-	-
Total	8	372.22	-	-	-	-

Table 16: ANOVA for % Drug release 10 min.

Source	DF	Adjusted. SS	Adjusted. MS	F Value	P Value	Remark
Model	8	115.67	14.46	1446.0	0.0023	Significant
Linear	4	63.30	15.82	1582.0	0.0025	Significant
Polymer	2	24.50	12.25	1225.0	0.0022	Significant
Plasticizer	2	38.80	19.40	1940.0	0.0024	Significant
2-Way Interactions	4	52.37	13.09	1309.0	0.0020	Significant
Polymer * Plasticizer	4	52.37	13.09	1309.0	0.0020	Significant
Error	1	0.01	0.01	-	-	-
Total	8	115.67	-	-	-	-

Analysis of Variance (ANOVA) for % Drug Release at 10 Minutes

Both polymer and plasticizer have a significant impact on drug release at 10 minutes ($P < 0.05$), with their interaction further influencing the release profile. Optimizing their concentrations is essential for achieving the desired dissolution rate and formulation performance (Table 16).

The plots show that drug release improves with balanced polymer and plasticizer concentrations, indicating an optimal range for effective release (Figure 7).

Discussion

The development of a sublingual oral film for migraine management with the use of Butterbur (5 mg) and Feverfew (15 mg) is proposed to improve the delivery of medication with rapid absorption, increased bioavailability, and patient compliance. Butterbur alleviates inflammation and widens blood vessels, whereas Feverfew regulates serotonin and inhibits inflammation caused by nerve stimulation. Bypassing the liver, sublingual delivery provides faster relief compared to pills or capsules. The films had a uniform distribution of drugs, adequate thickness, and strength for easy handling and dosing. Rapid dissolution provides rapid relief in migraine, which was established to be safe and stable under various conditions. Such an approach makes nausea and vomiting patients easier because it does not involve any pill-swallowing action [6]. Optimization and design of the sublingual film for migraine drug delivery were conducted through a 3^2 full factorial design to quantify impact of polymer concentration (HPMC E5) and plasticizer (PEG 400) on some of the formulation's key characteristics. Dependent variables were the disintegration time (Dt), folding endurance, and % drug release. The design allowed for the identification of optimal formulation parameters, showing an equilibrium balance of fast disintegration, sufficient drug release, and mechanical stability. A sublingual oral film for migraine control was developed through a 3^2 full factorial design for polymer concentration (HPMC E5) and plasticizer (PEG 400). F5 batch having 58 seconds disintegration time, 89% release of drug in 10 minutes, and adequate mechanical strength was the optimal formulation. Butterbur (5 mg) and Feverfew (15 mg) were chosen because of their anti-inflammatory, vasodilatory, and serotonin-modulating actions. Sublingual delivery offers quick absorption and increased bioavailability. Physicochemical evaluations ensured that the dosage form met all the critical quality attributes (CQAs) like drug content uniformity, tensile strength, and folding endurance, and therefore, it is a potential alternative for conventional oral migraine therapy. Nevertheless, certain limitations need to be further explored:

Stability Studies: The long-term stability test shall be conducted to define the long-term stability of the formulation.

Clinical Assessment: Clinical trials and in vivo pharmacokinetics must be conducted to ascertain actual-world safety and efficacy.

Conclusion

In this research, a fast-dissolving herbal sublingual film for migraine relief was successfully developed and optimized. As a patient-friendly substitute for conventional oral dosage forms, the film formulation contains Butterbur (5 mg) and Feverfew (15 mg), offering immediate relief from symptoms as well as migraine prevention. The

optimized film was found to have an incredibly low disintegration time of 58 seconds with 89% drug release at 10 minutes, making it faster to absorb and better in bioavailability than conventional dosage forms.

The application of HPMC E5 and PEG 400 yielded excellent mechanical strength, flexibility, and stability of the film. Additionally, its surface pH (near 6.8), being neutral, leads to minimal irritation, which makes the patient more comfortable. In contrast to tablets or capsules, these ultra-thin films do not need water and are perfect for patients who undergo nausea or dysphagia during a migraine attack. With its rapid onset of action, endogenous therapeutic modality, and high patient compliance, this formulation can transform the treatment for migraine. Further clinical trials will have to establish its effectiveness in the clinical setting and for long-term stability. If effective in human trials, the sublingual films can be delivered as an immediate first-line therapy for migraine patients, providing relief in a more efficient and user-friendly delivery system. By bridging the gap between natural and modern technology, this ground-breaking delivery system is a huge leap forward in migraine treatment, putting patients closer to quicker and more consistent relief.

Acknowledgement

We sincerely thank Dr. Sonia Singh, Dean of Alard College of Pharmacy, for her continuous support and encouragement. We are immensely grateful to Mr. Sakib Shikalgar for his valuable guidance during this research. Additionally, we extend our heartfelt appreciation to Poonam Ma'am and Reshma Ma'am from the laboratory staff for their assistance and cooperation during the experimental work.

Authors Contribution

Suyash Raul led the research work and designed the experiment. Tanvi Bhalekar performed the experimental study. Ishita prepared the initial draft of the manuscript. Chetan Hyalij and Suresh reviewed and corrected the manuscript.

References

1. Prabhu Shruti & Parsekar Sarvesh & Shetty, Amitha & Monteiro, Samuel & Azharuddin, Mohd & Shabaraya, A. A Review On Fast Dissolving Sublingual Films For Systemic Drug Delivery. 2018.
2. Mishra Soumya & Bais Nidhi & Jain Sachin. Formulation And Evaluation Of Mouth-Dissolving Film Of Imipramine Hcl. Journal Of Biomedical And Pharmaceutical Research. 2023; 12: 22-29.
3. Raul S, Bhalekar T, Hyalij C & Shikalgar S. Polymer Paradigm: Revolutionizing Drug Delivery. Bohr Journal Of Pharmaceutical Studies. 2024; 2: 5–12.
4. Palepu S, Sathyanarayana T, Ravali M, Dakshyani P, Sirisha U, Divya Sri P, Srinu M, Formulation And Evaluation Of Fast Dissolving Sublingual Film Of Lisinopril, Journal Of Drug Delivery And Therapeutics. 2019; 9:101-106.
5. Chenna M Shalini, Asireddy Sathvika Reddy, Vallarapu Nanda Krishna Veni, Madeira Jaya Prakash, Rama Rao T. Fast Dissolving Oral Thin Films: A Review. Research & Reviews: A Journal Of Drug Design & Discovery. 2024; 11: 24-31.
6. Naimish Sarkhejiya & Patel Vipul & Devang Pandya. Sublingual Delivery: A Promising Approach To Improve Bioavailability. 2013.
7. Saha Puja & Verma Sushma & Das Pratik. Sublingual Drug Delivery: An Indication Of A Potential Alternative Route. International Journal Of Current Pharmaceutical Research. 2017; 9: 5.
8. Prachi P, et al. Fast Dissolving Sublingual Film Of Zolmitriptan, Indian Journal Of Pharmaceutical Education And Research. 2014; 48.
9. Oelkers-Ax R, Leins A, Parzer P, Hillecke T, Bolay Hv, Fischer J, et al. Butterbur Root Extract And Music Therapy In The Prevention Of Childhood Migraine: An Explorative Study. Eur J Pain. 2008; 12: 301-313.
10. Drugs And Lactation Database (Lactmed®) [Internet]. Bethesda (Md): National Institute Of Child Health And Human Development; 2006–. Feverfew. 2022.
11. Tepper Sj, Tepper K. Nutraceuticals And Headache 2024: Riboflavin, Coenzyme Q10, Feverfew, Magnesium, Melatonin, And Butterbur. Curr Pain Headache Rep. 2025; 29: 33.
12. Saranitzky E, White Cm, Baker El, Baker Wl, Coleman Ci. Feverfew For Migraine Prophylaxis: A Systematic Review. J Diet Suppl. 2009; 6: 91-103.
13. Johnson Es, Kadam Np, Hylands Dm, Hylands Pj. Efficacy Of Feverfew As Prophylactic Treatment Of Migraine. Br Med J (Clin Res Ed). 1985; 291: 569-573.
14. Rajapakse T, Davenport Wj. Phytomedicines In The Treatment Of Migraine. Cns Drugs. 2019; 33: 399-415.
15. Benemei S, De Logu F, Li Puma S, Marone Im, Coppi E, Ugolini F, et al. The Anti-Migraine Component Of Butterbur Extracts, Isopetasin, Desensitizes Peptidergic Nociceptors By Acting On The Trpa1 Cation Channel. Br J Pharmacol. 2017; 174: 2897-2911.
16. Fuakye E, Hailemeskel B & Fullas F. Migraine Management Using Feverfew, Butterbur, Peppermint, And Ginger: Perspectives Of Pharmacy Students. European Journal Of Theoretical And Applied Sciences. 2024; 2: 412-419.
17. Lipton Rb, Göbel H, Einhäupl Km, et al. Petasites Hybridus Root (Butterbur) Is An Effective Preventive Treatment For Migraine. Neurology. 2004; 63: 2240-2244.
18. Mayreddy Mr, Gumudevelli S, Vankayala R, Vankayala P And Gumudevelli S. Formulation, Optimization And Characterization Of Fast-Dissolving Sublingual Film Containing Clove Oil. Int J Pharm Sci & Res. 2023; 14: 3516-3521.
19. Jyothi B, et al. A Review on Fast Dissolving Sublingual Films. IJPPR Human. 2023; 26: 378-393.
20. Joshi Arjun & Raval Anil. Formulation And Evaluation Of Sublingual Films Of Apixaban. International Journal Of Pharmaceutical And Biological Science Archive. 2019; 7.
21. Rita N Wadetwar, Farheen Ali & Pranita Kanojiya. Formulation And Evaluation Of Fast-Dissolving Sublingual Film Of Paroxetine Hydrochloride For Treatment Of Depression. Asian Journal Of Pharmaceutical And Clinical Research. 2019; 12: 126–132.
22. Arya Arun & Chandra Amrish & Sharma Vijay & Pathak Kamla. Fast Dissolving Oral Films: An Innovative Drug Delivery System And Dosage Form. International Journal Of Chemtech Research. 2010; 2: 576-583.
23. Nagar P & Chauhan Iti & Yasir Mohd. Insights Into Polymers: Film Formers In Mouth Dissolving Films. Drug Invention Today. 2011; 3: 280-289.
24. Rajagopalan S, Rajendhiran D, Mohamed IA, Sherbudeen SB. Fast dissolving oral thin films: an innovative herbal drug delivery system. Int J Res Med Sci. 2024; 12: 3085-3090.
25. Tomar A, Sharma K, ChauhanNS, MittalA, Bajaj U. Formulation and Evaluation of Fast Dissolving Oral Film of Dicyclomine as potential route of Buccal Delivery. International Journal of Drug Development & Research. 2012; 4: 408-441.
26. Panchal MS, Patel H, Bagada A, Vadalia KR. Formulation and Evaluation of Mouth Dissolving Film of Ropinirole Hydrochloride by Using Pullulan Polymers. International Journal of Pharmaceutical Research & Allied Sciences. 2012; 1: 60-72.
27. N Ajay Kumar S. Rajiv Gandhi University of Health Sciences (India) ProQuest Dissertations & Theses. 2017; 30275590.
28. Vinita Patole, Rajnigandha Gaikwad and Kishanchandra Khandelwal. "THYME OIL LOADED CASSAVA STARCH TRANSDERMAL FILM FOR WOUND HEALING." IDMA. 2021.
29. Rathore R, Gupta AK, Parashar AK. Formulation and Evaluation of fast dissolving films of Granisetron Hydrochloride. J. Drug Delivery Ther. [Internet]. 2019; 9: 36-38.
30. Lavith Kumar H, Bhavya Shree T and Krishnananda Kamath K. "REVIEW ON FAST DISSOLVING SUBLINGUAL FILMS." European Journal of Biomedical and Pharmaceutical Sciences (EJBPS). 2024.