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Research Paper

Formulation Development and Evaluation of Thermo-Sensitive In-Situ Nasal Gel for Rapid Delivery of Antimigraine Drug Dihydroergotamine

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ABSTRACT

Migraine is a common and debilitating neurological disorder characterised by recurrent episodes of moderate to severe headache accompanied by nausea, vomiting, photophobia, and phonophobia. Although dihydroergotamine mesylate (DHE) is an effective antimigraine agent, its conventional dosage forms are associated with limitations such as poor oral bioavailability, extensive first-pass metabolism, variable nasal absorption, and rapid mucociliary clearance. The present study aimed to formulate and evaluate a thermo-sensitive in-situ nasal gel of DHE for rapid and sustained intranasal drug delivery. The formulation was prepared using the cold method with Poloxamer 407 as the primary thermosensitive polymer, Poloxamer 188 to optimize gelation temperature, and chitosan as a mucoadhesive and permeation-enhancing polymer. Preformulation studies, including solubility, melting point, partition coefficient, FTIR, and DSC analyses, confirmed the suitability and compatibility of the drug with the selected excipients. Three formulations (F1, F2, and F3) were prepared and evaluated for physicochemical properties, pH, viscosity, gelation temperature, gelation time, gel strength, drug content, mucoadhesive strength, spreadability, in-vitro drug release, ex-vivo nasal permeation, and stability. Among the formulations, F3 demonstrated optimum performance with a gelation temperature of 32.8°C, drug content of 99.1%, excellent mucoadhesive strength, sustained drug release of 93.8% over the study period, and ex-vivo permeation of 91.5%. Stability studies conducted for three months showed no significant changes in appearance, pH, drug content, viscosity, or gelation temperature. The findings indicate that the optimized thermo-sensitive in-situ nasal gel offers prolonged nasal residence time, enhanced drug permeation, sustained release, and improved bioavailability, making it a promising alternative for effective and patient-friendly management of acute migraine

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INTRODUCTION

1.1 Overview of Migraine

Headaches occurring frequently, with a moderate to strong intensity and with pulsating nature are typical symptoms of a migraine. Migraine has photophobia, phonophobia, nausea, and vomiting. It is estimated that migraines affect about 15% of the world's population, which makes migraine one of the leading causes of disabilities among young individuals. Migraine has serious implications on healthcare expenditures, work performance, and quality of life.

Migraines may occur with an aura or without it; however, regardless of the presence of the aura, migraines can persist for four to seventy-two hours. Due to hormones, females are twice as likely to experience migraines in comparison with males. According to recent research, migraine is a complex neurovascular disease.(Frimpong-Manson et al., 2024)

1.2 Pathophysiology of Migraine

All of these events, including trigeminovascular activation, spreading depression of cortex, neurogenic inflammation, and secretion of vasoactive neuropeptides such as calcitonin gene related peptide (CGRP), constitute the pathophysiology of migraines. Activation of trigeminal sensory nerves leads to dilation of blood vessels of the brain and pain sensation transmitted to the central nervous system.

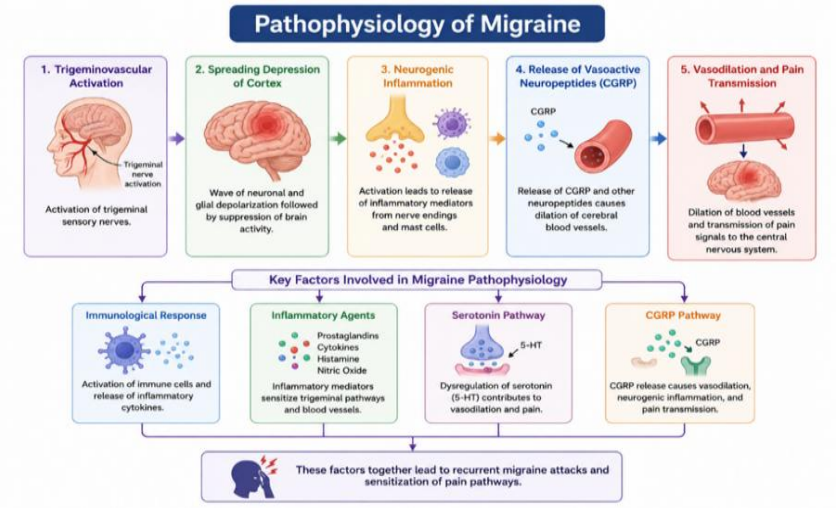

Figure: 1. Pathophysiology of Migraine

Immunological response, inflammatory agents, serotonin pathway, and CGRP pathway have recently emerged as important factors involved in the pathophysiology of migraines. They cause recurrent episodes of migraine attacks and sensitization of pain pathway.(Ha & Chu, 2024)

1.3 Chemical Structure

Dihydroergotamine is a hydrogenated ergot alkaloid obtained from ergotamine. The hydrogenation process reduces its vasoconstrictive effects while maintaining its antimigraine activity. The molecule contains an ergoline ring system responsible for its pharmacological action.

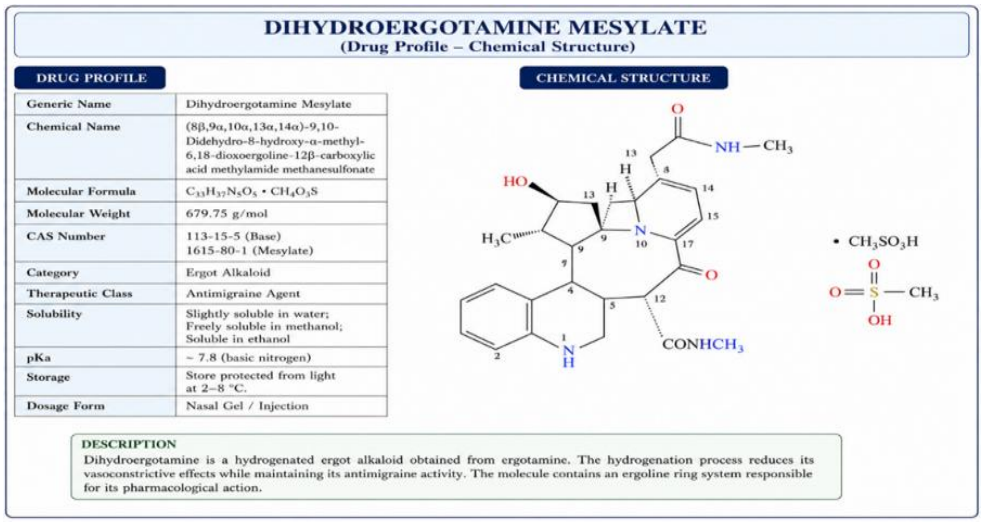

Figure No: 2. Chemical Structure

1.4 Current Treatment Approaches for Migraine

Acute care

NSAIDs, non-steroidal anti-inflammatory drugs (NSAIDs)

These drugs are often employed for the management of patients with mild to moderate attacks of migraines. NSAIDs reduce the production of prostaglandins through blocking the actions of COX enzymes, and prostaglandins are known to stimulate headaches and cause inflammation. Common NSAIDs include aspirin, ibuprofen, naproxen sodium, and diclofenac. NSAIDs help in alleviating pain during the early phase of a migraine attack.

Triptans

Triptans have the ability to activate selective serotonin (5-HT1B/1D) receptors and block pain receptors. Triptans reduce the dilation of cerebral blood vessels while preventing the release of neuropeptides such as CGRP. Examples of common triptans include sumatriptan, rizatriptan, zolmitriptan, and eletriptan.

DHE or Di-Hydro-Ergotamine

DHE or di-hydro-ergotamine is used in the treatment of acute migraines and migraines of prolonged duration known as status migrainosus. It is an ergot alkaloid and a semi-synthetic drug. DHE inhibits neuroinflammation and constricts cranial vessels using the mechanism of serotonin, adrenergic, and dopamine receptors. DHE is available in injectables and nasal sprays and has a reduced rate of recurrence compared to triptans.

Gepants

The gepants are one of the newer classes of drugs used for treating migraines. They work as antagonists to the CGRP receptors. The use of gepants in individuals with cardiac risks is preferred since unlike triptans, they do not cause any vasoconstriction. Examples include Zavegepant, rimegepant, and ubrogepant.

Antiemetics

Vomiting and nausea are frequent signs of migraine attacks. Adjunctive therapy frequently includes antiemetic drugs such metoclopramide, domperidone, chlorpromazine, and prochlorperazine. These treatments alleviate nausea and vomiting symptoms, improve stomach emptying, and increase oral medication absorption.

Preventive Treatment

When there is an issue of severe impairment or frequent episodes of migraine, prevention becomes necessary. The goal would be to lower the frequency, severity, and need for use of any acute medication.

Beta-Blockers

Among the commonly prescribed medicines used in preventing migraines, the beta blockers are a prominent one. This is because they help normalize the tone of the blood vessels, as well as decrease neural excitation. Some effective beta-blockers that can prevent migraine include timolol, atenolol, metoprolol, and propranolol. These are very effective for patients suffering from anxiety disorders or hypertension.

Anti-depressants

Some anti-depressants have been observed to help prevent migraine among people having anxiety disorders or depressions. Commonly used tricyclic anti-depressants include nortriptyline and amitriptyline.

Anti-Epileptic Drugs

Anti-epileptic drugs are helpful in preventing migraines because of their ability to stabilize neural membranes and reduce cortical hyper-excitability. Some examples of anti-epileptic drugs that are commonly used are topiramate, valproate, and gabapentin. Based on clinical studies, topiramate is among the best preventive treatments for migraines.

Monoclonal CGRP Antibodies

Monoclonal CGRP antibodies are a new approach to the prevention of migraines. Their efficacy results from their targeted interference with the action of calcitonin gene-related peptide or its receptor which plays an important role in the pathogenesis of migraines. Thereare several monoclonal CGRP antibodies such as erenumab, fremanezumab, galcanezumab, and eptinezumab.(Burch, 2024),

1. Dihydroergotamine as an Antimigraine Drug

A widely employed semisynthetic ergot alkaloid that is useful for the acute treatment of migraine attacks is dihydroergotamine (DHE). The drug works agonistically on dopaminergic, adrenergic, and serotonin (5-HT1B/1D) receptors to elicit its medicinal effects. DHE decreases neurogenic inflammation and leads to cranial vasoconstriction.

DHE has been found to exert a relatively prolonged duration of action, with a reduced frequency of recurrence as compared to triptans. The effectiveness and safety of DHE nasal sprays in the treatment of acute migraines have been confirmed by recent studies. (Tepper et al., 2024)

2. Nasal Drug Delivery System

One method of achieving systemic delivery without invasion is the use of nasal delivery. The large amount of surface area, extensive vascularization, and high permeability in the nasal cavity make rapid absorption into the bloodstream possible.

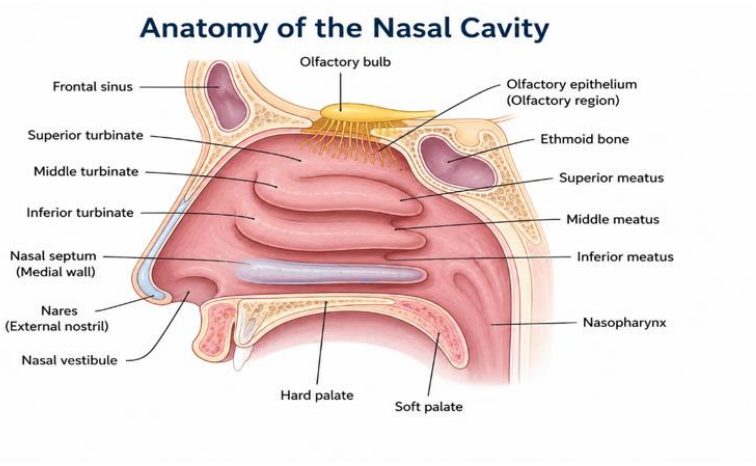

Figure: 2. Anatomy of the Nasal Cavity

The nasal method offers faster onset since first-pass effect through the liver and digestive system can be avoided, making it more beneficial to treat neurological diseases, such as migraines.

Advantages of Intranasal Drug Delivery

- Rapid onset of action
- Avoidance of first-pass metabolism
- Improved bioavailability
- Non-invasive administration
- Enhanced patient compliance
- Potential nose-to-brain delivery
- Suitable for emergency migraine treatment

3. In-Situ Gel Drug Delivery Systems

In-situ gels are the polymer formulations that experience transformation from sol to gel form on exposure to physiological conditions such as temperature, pH, or ionic strength. They transform into gels following their administration in liquid form.

The use of in-situ gels in nasal drug delivery enhances their effectiveness due to increased retention and decreased clearance rate.

4. Thermo-Sensitive Polymers

Temperature changes lead to the phase transition of thermosensitive polymers. Two types of thermoreversible polymers that are mostly used in nasal formulations include Poloxamer 407 and Poloxamer 188.

These polymers remain in a fluid state at room temperature but become gelled at nasal cavity temperature of 32°C to 34°C. This property makes them highly suitable for nasal in-situ gels.

Advantages of Thermo-Sensitive In-Situ Nasal Gels

- Fast liquid delivery
- Fast gel formation at nose temperature
- Long duration of presence in the nose
- Slow and prolonged drug release
- Reduced frequency of dosing
- Improved compliance
- Increased drug availability

Possibility for targeted delivery to the brain

In view of these advantages, thermo-sensitive gels in nasal application appear to be promising vehicles for antimigraines.

Rationale For Present Work

Even though DHE is effective against migraine, conventional forms have some limitations, such as mucociliary transport, short period of stay in the nose, and inconsistent drug absorption. These problems can be overcome by designing an in-situ nasal gel which is fast to act and better absorbed.(Dafer et al., 2024)

2. MATERIALS AND METHODS

Materials

Dihydroergotamine Mesylate was selected as the active pharmaceutical ingredient. Poloxamer 407 was used as the primary thermosensitive polymer, while Poloxamer 188 was incorporated to optimize the gelation temperature. Chitosan was used as a mucoadhesive and permeation-enhancing polymer. Benzalkonium chloride served as a preservative, acetic acid was used for dissolving chitosan and pH adjustment, and purified water was used as the vehicle.

Formulation Composition

Three formulations (F1–F3) of 10 mL were prepared with varying concentrations of Poloxamer 407, Poloxamer 188, and chitosan. Dihydroergotamine Mesylate (10 mg) and benzalkonium chloride (2 mg) were kept constant in all formulations.

Table 1: Formulation Composition of Dihydroergotamine Mesylate Thermo-Sensitive In-Situ Nasal Gel (10 mL)

Ingredients	F1	F2	F3
Dihydroergotamine Mesylate	10 mg	10 mg	10 mg
Poloxamer 407	1.8 g (18%)	2.1 g (21%)	2.4 g (24%)
Poloxamer 188	0.8 g (8%)	0.6 g (6%)	0.4 g (4%)
Chitosan	50 mg (0.5%)	100 mg (1.0%)	150 mg (1.5%)
Benzalkonium Chloride	2 mg	2 mg	2 mg
Acetic Acid	q.s.	q.s.	q.s.
Purified Water	Up to 10 mL	Up to 10 mL	Up to 10 mL

Method of Preparation

The thermo-sensitive in-situ nasal gel was prepared by the cold method. Accurately weighed Poloxamer 407 and Poloxamer 188 were slowly dispersed in chilled purified water at approximately 4°C with continuous magnetic stirring. The polymeric solution was refrigerated overnight to ensure complete hydration and formation of a clear solution.

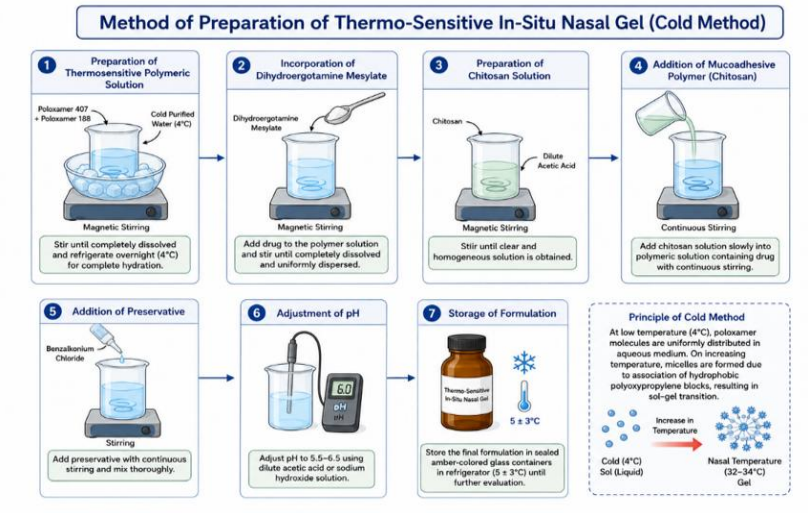

Figure No: 3. Methods of Preparation

Dihydroergotamine Mesylate was accurately weighed and incorporated into the chilled polymeric solution with continuous stirring until uniformly dissolved. Separately, the required quantity of chitosan was dissolved in dilute acetic acid to obtain a homogeneous solution. The chitosan solution was slowly added to the drug-polymer solution with continuous stirring.

Benzalkonium chloride was then added as a preservative and mixed uniformly. The pH was adjusted to approximately **5.5–6.5** using diluted acetic acid or sodium hydroxide. The final volume was adjusted to 10 mL with purified water. The prepared formulations were filled into sealed amber-colored containers and stored at **5 ± 3°C** until further evaluation.

Principle of Cold Method

Solubility of poloxamers is dependent on temperature. At lower temperatures (4°C), poloxamer molecules are uniformly distributed in aqueous medium and produce a clear liquid solution. At increasing temperature, poloxamer molecules become associated due to increased interaction among hydrophobic polyoxypropylene blocks, which leads to formation of micelles. Cold process ensures complete hydration of polymer molecules and prevents premature gelling.

Step 1: Preparation of Thermosensitive Polymeric Solution

Cold filtered water held at a temperature of 4°C was slowly incorporated with accurately measured quantities of Poloxamer 407 and Poloxamer 188.

In order to avoid formation of aggregates and ensure complete disintegration, gradual addition of the polymers while simultaneously stirring them magnetically continued until they dissolved completely.

Following this, the solution containing the polymers was allowed to stay in the refrigerator overnight at 4°C in order to ensure full hydration of the solution.

Purpose

- Complete hydration of polymers.
- Formation of a clear thermosensitive solution.
- Prevention of polymer aggregation.
- Achievement of uniform viscosity.

Step 2: Incorporation of Dihydroergotamine Mesylate

Dihydroergotamine Mesylate was precisely weighed and incorporated into the cooled polymer solution in a predetermined quantity.

The mixture was continuously stirred until the drug was fully dissolved and well dispersed.

Purpose

- Uniform drug loading.
- Homogeneous distribution of drug molecules.
- Prevention of drug precipitation.

Step 3: Preparation of Chitosan Solution

The amount of chitosan required was then dissolved in a solution of acetic acid to form chitosan solution separately.

Agitation was done until a clear and consistent chitosan solution was obtained.

Purpose

- Complete dissolution of chitosan.
- Development of mucoadhesive characteristics.
- Enhancement of nasal retention.

Step 4: Addition of Mucoadhesive Polymer

The polymeric solution containing DHE was gradually mixed with the prepared chitosan solution while being continuously stirred. The process of mixing was carried out until a consistent formulation was achieved.

Purpose

- Enhancement of mucoadhesive strength.
- Improvement of nasal residence time.
- Increased drug permeation through nasal mucosa.
- Stabilization of the formulation.

Step 5: Addition of Preservative

After precisely weighing benzalkonium chloride, it was added to the mixture while being constantly stirred.

To guarantee that the preservative was distributed evenly, the recipe was completely blended.

Purpose

- Prevention of microbial contamination.
- Improvement of product safety.
- Enhancement of storage stability.

Step 6: Adjustment of pH

A digital pH meter was used to determine the formulation's pH.

A solution of sodium hydroxide or diluted acetic acid was used to bring the pH down to about 5.5–6.5.

Purpose

- Compatibility with nasal mucosa.
- Prevention of nasal irritation.
- Maintenance of drug stability.
- Optimization of mucoadhesive properties.

Step 7: Storage of Formulation

After the finished mixture was put into sealed amber-colored glass containers, it was kept in a refrigerator at 5 ± 3°C until further testing.

Purpose

- Prevention of premature gelation.
- Maintenance of physicochemical stability.
- Protection from environmental degradation.

Evaluation Parameters

The prepared formulations were evaluated for appearance, pH, viscosity, gelation temperature, gelation time, gel strength, drug content, mucoadhesive strength, spreadability, in-vitro drug release, ex-vivo nasal permeation, and stability.

RESULTS

The preformulation, formulation evaluation, in vitro drug release, ex vivo permeation, and stability investigations of the created thermosensitive in-situ nasal gel of Dihydroergotamine Mesylate are presented in this chapter. In order to comprehend how formulation variables, specifically the concentrations of Poloxamer 407, Poloxamer 188, and chitosan, affected the nasal gel system's performance, the results were thoroughly examined. The most appropriate formulation was chosen based on

overall performance after the results were compared with published literature.

I. In-Vitro Drug Release:

- Drug release was studied using a **Franz Diffusion Cell** with phosphate buffer pH 6.4 for **8 hours**.
- **F1** showed faster drug release due to its lower polymer concentration and less dense gel structure.
- **F3** showed slower and controlled drug release because of its stronger polymeric matrix.
- The optimized **F3 formulation released approximately 93–94% drug in 8 hours**.
- F3 demonstrated **effective sustained drug release**, which may help maintain therapeutic drug levels and reduce dosing frequency.

1. In-Vitro Drug Release Results

Table 2: Percentage Cumulative Drug Release

Time (h)	F1 (%)	F2 (%)	F3 (%)
1	18.5 ± 0.8	15.2 ± 0.7	12.4 ± 0.6
2	35.6 ± 1.2	29.8 ± 1.1	24.5 ± 0.9
3	58.4 ± 1.5	51.2 ± 1.4	46.8 ± 1.2
4	70.2 ± 1.4	74.5 ± 1.3	81.4 ± 1.5
5	79.5 ± 1.2	87.6 ± 1.1	93.8 ± 1.0

II. Ex-Vivo Permeation Release:

- Ex-vivo permeation was studied using sheep nasal mucosa in a Franz Diffusion Cell.
- Flux increased with increasing chitosan concentration, indicating enhanced drug permeation.
- F3 showed the highest flux, confirming effective permeation of Dihydroergotamine Mesylate.
- The permeability coefficient was highest for F3, indicating improved nasal absorption.
- Overall, chitosan enhanced nasal permeation, while the thermosensitive gel supported effective drug delivery.

1. Ex-Vivo Permeation Results

Table 3: Ex-Vivo Permeation Parameters

Parameter	F1	F2	F3
Drug Permeation (%)	73.4 ± 1.5	84.8 ± 1.3	91.5 ± 1.2
Flux (µg/cm²/hr)	72.5 ± 2.4	84.7 ± 2.2	96.8 ± 2.1
Permeability Coefficient (cm/hr ×10⁻³)	0.071	0.084	0.096

III. Selection of Optimized Formulation:

Table 4: Evaluation Parameters

Evaluation Parameter	F1	F2	F3
pH	Acceptable	Acceptable	Excellent
Drug Content	Good	Very Good	Excellent
Gelation Temperature	Higher	Suitable	Optimum
Viscosity	Low	Moderate	High
Mucoadhesion	Moderate	Good	Excellent
Drug Release	Fast	Controlled	Sustained
Permeation	Good	Very Good	Excellent
Stability	Good	Very Good	Excellent
Overall Rank	III	II	I

DISCUSSION

Effect of Polymer Concentration on Gelation: Increasing Poloxamer 407 concentration decreased the gelation temperature due to enhanced micelle formation. This allowed the formulation to rapidly form a gel at nasal physiological temperature.

Effect on Viscosity and Drug Release: Higher polymer concentration increased viscosity and formed a denser gel network, resulting in slower and prolonged drug release. Lower polymer concentration produced lower viscosity and faster drug release.

Comparison with Literature: The findings were consistent with reported studies showing that higher Poloxamer 407 concentration improves gelation, viscosity, mucoadhesion, and sustained drug release. Chitosan also enhanced nasal permeation.

Selection of Optimized Formulation: F3 was selected as the optimized formulation due to its suitable gelation temperature, high viscosity, strong mucoadhesion, improved permeability, prolonged drug release, and good stability. Overall, F3 showed good potential for effective intranasal delivery of Dihydroergotamine Mesylate.

CONCLUSION

All experimental observations and analytical data were methodically collated and put through the proper statistical analysis following the successful completion of formulation development, assessment, optimization, and stability studies. In order to evaluate the impact of formulation variables like Poloxamer 407, Poloxamer 188, and chitosan on the physicochemical properties, gelation behavior, mucoadhesive qualities, drug release profile, and permeation performance of the thermosensitive in-situ nasal gel, the obtained results were carefully interpreted.

Numerous factors, such as pH, viscosity, gelation temperature, gel strength, drug content, mucoadhesive strength, in-vitro drug release, ex-vivo penetration, and stability, were assessed for the generated formulations. The optimized formulation outperformed the other created formulations in terms of suitable gelation at nasal physiological temperature, sufficient viscosity, superior mucoadhesive qualities, high drug content, prolonged drug release, improved nasal penetration, and acceptable stability during storage. These results validated the designed thermosensitive nasal gel system's appropriateness for efficient intranasal administration of Dihydroergotamine Mesylate.

To confirm the formulation approach and determine the importance of the current study, the

experimental results were further compared with previously published literature. The efficiency of Poloxamer-Chitosan-based formulations for enhancing nasal residence time and drug absorption was supported by the observed results, which were found to be compatible with published studies on thermosensitive and mucoadhesive nasal drug delivery systems.

The created thermo-sensitive in-situ nasal gel has considerable potential as an alternate delivery strategy for Dihydroergotamine Mesylate in the treatment of migraine, according to the overall findings. Rapid start of action, avoidance of hepatic first-pass metabolism, extended nasal cavity residence duration, increased bioavailability, better patient compliance, and long-lasting therapeutic effect are only a few benefits of the formulation. Ultimately, all of the study results were arranged and methodically recorded in a dissertation. The Introduction, Review of Literature, Aim and Objectives, Plan of Work, Drug Profile, Materials and Methods, Experimental Work, Evaluation Parameters, Results and Discussion, Conclusion, and References were the different chapters that made up the dissertation. The results were supported by relevant tables, figures, graphs, release profiles, FTIR spectra, DSC thermograms, penetration tests, and statistical analyses. The finished dissertation offers a thorough scientific account of the research and makes a significant contribution to the fields of migraine treatment and nasal medication delivery.

6. EXPECTED OUTCOMES

A stable thermo-sensitive in-situ nasal gel should:

- Remain clear and homogeneous.
- Maintain pH within the acceptable range.
- Retain drug content above 95%.
- Exhibit gelation temperature close to nasal physiological temperature.
- Show minimal changes in viscosity.

Table 5: Sample Stability Study Observation Table

Parameter	Initial	1 Month	2 Months	3 Months
Appearance	Clear	Clear	Clear	Clear
pH	5.8 ± 0.1	5.8 ± 0.1	5.7 ± 0.1	5.7 ± 0.1
Drug Content (%)	99.2 ± 0.5	98.9 ± 0.4	98.5 ± 0.6	98.1 ± 0.5
Gelation Temperature (°C)	33.2 ± 0.3	33.3 ± 0.2	33.4 ± 0.2	33.5 ± 0.3
Viscosity (cP)	3450 ± 45	3438 ± 40	3425 ± 38	3412 ± 42

Statistical Analysis

All experiments were performed in triplicate (n = 3).

Results were expressed as:

Mean ± Standard Deviation (SD)

Statistical analysis was performed using:

- One-way ANOVA
- Student's t-test (where applicable)

A p-value less than 0.05 was considered statistically significant.

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