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Formulation And Evaluation of Thermosensitive in Situ Nasal Gel of Zolmitriptan

Moh Rizwan[1*], Dr. Sachin Kumar[1]

[1]NKBR College of Pharmacy and Research Centre Meerut-Hapur Road,Phaphunda, Uttar Pradesh India -245206

[*]**Corresponding author:**

Moh Rizwan

NKBR College of Pharmacy and Research Centre Meerut

Email ID: rizwanansari866@gmail.com

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ABSTRACT

This study introduces the design and complete assessment of a thermosensitive in situ nasal gel of Zolmitriptan, which was created to improve the drug delivery effectiveness in the acute treatment of migraine attacks. Zolmitriptan is a highly active serotonin (5-HT$_1$B/$_1$D) receptor agonist used effectively for migraine therapy but has poor oral bioavailability (~40%) with extensive hepatic first-pass metabolism and gastric motility problems during migraine attacks, causing delay in drug absorption. To counter these disadvantages and allow for swift onset of action, a new nasal delivery system was developed based on thermoresponsive and mucoadhesive polymers. The gel formulations were developed using the cold method from a series of combinations of Poloxamer 407 (20% w/v) and Poloxamer 188 (10% w/v) due to their temperature-dependent sol-gel transition characteristics. Mucoadhesiveness and increasing nasal residence time were imparted using Chitosan (0.75% w/v) and HPMC K15M (1% w/v). Zolmitriptan was complexed with Hydroxypropyl-β-cyclodextrin (HP-β-CD) in varying molar ratios (1:1, 1:2, 1:3) to improve its aqueous solubility and stability, the complex being validated through FTIR and DSC studies. Among the four developed formulations (F1–F4), Formulation F4 stood out as optimized, showing optimum gelation temperature (31.2 ± 0.3°C) consistent with nasal mucosal temperature, quick gelation time (32 ± 2 seconds), good mucoadhesive strength (1250 ± 35 dyne/cm²), and appropriate viscosity (1850 ± 50 cP). The drug content was within limiting values (99.12 ± 1.08%), with even distribution and fine clarity (Grade 0). Rheological analysis validated pseudoplastic, thixotropic properties required for good sprayability and mucosal spreading. Sprayability testing revealed reproducible round spray patterns with actuation volumes in the optimal range (0.05–0.1 mL). The in vitro gelation experiment proved that the optimized gel formulation gelled immediately on contact with simulated nasal fluid (SNF) and lasted for more than an hour. The accelerated stability testing as per ICH Q1A(R2) at 40°C/75% RH for 3 months showed no appreciable changes in pH, viscosity, drug content, or gelation parameters. The sterility tests also showed that the formulation was as per pharmacopeial requirement and free from microbial impurities. The optimized thermosensitive nasal gel formulation of Zolmitriptan not only provides rapid onset of therapeutic action, improved bioavailability, and a decreased chance of systemic side effects, but also presents a non-invasive, patient-compliant, and economically viable alternative to traditional oral or parenteral migraine treatments. This innovative platform presents important potential for use in central nervous system (CNS) drug delivery, particularly for drugs that are in need of swift systemic absorption through the nasal mucosa.

Keywords: *Zolmitriptan, thermosensitive in situ gel, nasal delivery, mucoadhesive polymers, Poloxamer 407, Hydroxypropyl-β-cyclodextrin (HP-β-CD), gelation temperature, viscosity, stability studies, bioavailability*

1. INTRODUCTION

Migraine is a debilitating neurological disorder affecting approximately 12% of the global population, with a higher incidence in women than men. The World Health Organization (WHO) ranks migraine among the top disabling conditions worldwide due to its profound impact on quality of life. Characterized by recurrent, unilateral, pulsating headaches lasting from 4 to 72 hours, migraine is often accompanied by nausea, vomiting, photophobia, and phonophobia. The pathophysiology of migraine involves cortical spreading depression, trigeminovascular system activation, release of inflammatory neuropeptides, and vasodilation of cranial blood vessels. A key mediator in this cascade is serotonin (5-HT); diminished serotonin levels promote neurogenic inflammation and pain through vasodilation of cerebral vessels.[1]

Triptans, a class of selective 5-HT1B/1D receptor agonists, are the mainstay of acute migraine treatment. Among them, zolmitriptan has demonstrated clinical efficacy in reducing migraine intensity and associated symptoms. However, its oral bioavailability is limited to ~40%, primarily due to extensive first-pass metabolism and impaired gastrointestinal function during migraine attacks. Such pharmacokinetic limitations necessitate the development of alternate delivery routes that bypass hepatic metabolism and offer rapid onset of action.

The nasal route presents an attractive alternative for zolmitriptan delivery owing to the high vascularity, large absorptive surface, and direct access to systemic circulation. Nasal administration also circumvents gastrointestinal disturbances, which is beneficial during migraine episodes characterized by nausea and vomiting. Nevertheless, conventional nasal formulations (e.g., sprays and solutions) are subject to rapid mucociliary clearance, limiting residence time and reducing drug absorption.[2]

To address these issues, thermo sensitive in situ nasal gels have emerged as a promising platform. These systems remain in sol form at room temperature and transform into a gel upon exposure to nasal mucosal temperature (~32–34°C). The gel formation improves mucosal adhesion, extends residence time, and facilitates sustained drug release. Poloxamer 407, a non-ionic triblock copolymer, is widely utilized in such systems due to its reverse thermal gelation properties, biocompatibility, and safety profile. Its combination with Poloxamer 188 and mucoadhesive agents like Carbopol 934P or PEG 400 can optimize gel strength, gelation temperature, and bioadhesive potential.[3]

The nasal delivery of zolmitriptan via a thermoresponsive in situ gel system may improve **onset** of action, bioavailability, and patient compliance, while minimizing dosing frequency and side effects. Moreover, the proximity of the nasal cavity to the brain offers a potential route for central nervous system targeting via olfactory and trigeminal pathways, which could accelerate symptom relief.In conclusion, the formulation of a thermosensitive in situ nasal gel of zolmitriptan represents an innovative and clinically relevant strategy for enhancing migraine therapy by addressing the drawbacks of existing dosage forms. This approach offers a patient-friendly, effective, and scalable solution that merits further pharmaceutical development and clinical investigation.[4,5]

1.2 Advantages of Thermosensitive Nasal Gel for Migraine Treatment [6]

- **Avoids First-Pass Metabolism:** Increases bioavailability by bypassing the liver and GI tract.
- **Rapid Onset of Action:** Fast drug absorption through nasal mucosa offers quick migraine relief.
- **Non-Invasive and Convenient:** Easier to use than injections or oral drugs, especially during nausea.
- **Better Patient Compliance:** Easy administration improves treatment adherence.
- **Prolonged Drug Retention:** Gel formation at nasal temperature ensures sustained drug release.
- **Reduced Dosing and Side Effects:** Maintains steady drug levels, lowering the need for frequent dosing and minimizing adverse effects.

2. MATERIALS

2.1. Material

A variety of high-quality materials were utilized in the development and evaluation of the thermosensitive nasal gel containing Zolmitriptan. Zolmitriptan, the active pharmaceutical ingredient (API), was obtained as a gift sample. Poloxamer 407 and Poloxamer 188, sourced from Sigma-Aldrich, served as the primary thermosensitive gelling agents and viscosity modifiers, respectively. Chitosan (low molecular weight) from CDH and HPMC K4M from Loba Chemie were used for their mucoadhesive and viscosity-enhancing properties. Hydroxypropyl-β-cyclodextrin (HP-β-CD) was employed to enhance drug solubility via complexation. Analytical and HPLC-grade reagents such as methanol, acetic acid, sodium hydroxide, and hydrochloric acid from Merck, SRL, and CDH were used in formulation preparation and pH adjustment. Benzalkonium chloride served as a preservative, while sodium chloride ensured isotonicity. Double-distilled water and phosphate buffer saline (PBS, pH 6.4) were prepared in-lab. Additional materials included dialysis membranes for in vitro diffusion studies, potassium bromide for FTIR analysis, and simulated nasal fluid (SNF) prepared as per literature for gelation tests. All materials used were of analytical, pharmaceutical, or laboratory grade, ensuring the accuracy and reliability of the study.

2.2 Pre-Formulation Studies [7]

A. FTIR Spectroscopy Investigation

- The FTIR investigation was carried out to detect any possible chemical interaction between excipients (poloxamer 407, poloxamer 188, chitosan, HPMC) and zolmitriptan. Any interaction will affect the drug's stability and bioavailability.
- Pure drug, excipients, and physical mixtures (1:1 ratio) were prepared.
- The samples were ground finely using potassium bromide (KBr) in a ratio of 1:100 and compressed into transparent

discs using a hydraulic pellet press.

- Discs were analyzed using a PerkinElmer Spectrum Two FTIR spectrometer from 4000–400 cm^{-1} with a resolution of 4 cm^{-1}.
- Changes in the distinctive peaks of zolmitriptan, specifically those due to N–H, O–H, and C=O stretching vibrations, were taken as indications of potential hydrogen bonding or molecular interaction.
- Lack of emergence of new peaks and low peak shifts validated the chemical compatibility of drug with excipients.

B. Determination of the absorption maximum of Zolmitriptan

UV spectrophotometric analysis was performed to determine the λmax and establish a calibration curve for Zolmitriptan. A standard stock solution (100 µg/mL) was prepared by dissolving 10 mg of Zolmitriptan in methanol and making up the volume with 0.1 N HCl. Working standards of 5–25 µg/mL were obtained by appropriate dilution. The solutions were scanned using a UV-Visible spectrophotometer (LabIndia UV 3000+ or Shimadzu UV-1800) in the 200–400 nm range, and the λmax was found to be 225 nm. Absorbance was measured at this wavelength, and a calibration curve was plotted. The method showed good linearity, complying with Beer-Lambert's law, and the regression analysis confirmed accuracy and reliability. This validated method was found suitable for routine estimation of Zolmitriptan in bulk and formulations.

C. Determination of Solubility

- Saturation solubility of zolmitriptan in phosphate-buffered saline (PBS, pH 6.4) was measured to facilitate drug loading and release performance.
- An excess amount of zolmitriptan was added to 10 mL of PBS in stoppered glass vials.
- The vials were briefly vortexed and then placed in a shaking water bath at 37 ± 0.5°C, 100 rpm, for 72 hours.
- At equilibrium, samples were filtered using a 0.22 µm membrane filter and diluted as needed.
- Drug concentration was measured by using UV-visible spectrophotometer (Shimadzu UV-1800) at 225 nm.
- The solubility values were utilized in dose optimization and efficiency of complexation with cyclodextrins. [8]

2.3. Thermosensitive Nasal Gel Preparation by Cold Method

Step 1: Poloxamer Base Preparation

- Precisely weighed amounts of Poloxamer 407 (15%, 18%, and 20% w/v) and Poloxamer 188 (5%, 8%, and 10% w/v) were weighed using an analytical balance (Shimadzu AUX220, ±0.0001 g).
- Slowly added to cold distilled water (4 °C) in an ice bath to avoid premature gelation.
- Magnetic stirring (Remi 1MLH, 500 rpm) was done for 2 hours to disperse completely.
- The solution was stored in a refrigerator at 4 °C for 24 hours for complete hydration and deaeration.

Step 2: Mucoadhesive Polymer Incorporation

(a) Chitosan Phase:

- Low molecular weight Chitosan (0.5–1% w/v) was dissolved in 1% glacial acetic acid.
- pH was set to 5.5 with 1N NaOH for a balance between mucoadhesion and nasal compatibility.
- The solution was filtered through a 0.45 µm membrane filter.

(b) Dispersion of HPMC

- HPMC K4M or K15M (0.5–2% w/v) was progressively added to hot water (60 °C), stirred at 800 rpm, and cooled prior to mixing with the base.

Step 3: Drug Loading and Solubility Improvement

- Zolmitriptan was complexed with Hydroxypropyl-β-cyclodextrin (HP-β-CD) in 1:1, 1:2, and 1:3 molar ratios using kneading with ethanol (30 min), followed by vacuum drying at 40 °C.
- Complex formation was established using DSC and FTIR analysis.
- The optimized complex was incorporated into the polymeric base aseptically in a laminar airflow hood.
- Homogenization (Ultra-Turrax T25, 10,000 rpm, 3 min) provided uniform distribution of the drug.

Step 4: Final Formulation Adjustments

- pH was adjusted cautiously between 5.5–6.5 using 0.1N NaOH or 0.1N HCl.

- Preservative, benzalkonium chloride (0.01% w/v), was added.
- Sodium chloride (0.9% w/v) was added to ensure isotonicity, as checked by a freezing-point osmometer (Advanced Instruments 3250).

Step 5: Ultimate Homogenization and Packaging

- High-shear homogenization (15,000 rpm, 5 min) confirmed colloidal consistency.
- The ultimate formulation was filled into sterilized amber nasal spray vials (2 mL) and stored at 4 °C. [9]

2.4. Physicochemical Characterization

A. Gelation Temperature and Gelation Time

- This value indicates the temperature at which the sol-to-gel transition takes place, and it is a key value for nasal delivery.
- 5 mL formulation was taken in a test tube and placed in a water bath with temperature rising slowly (0.5°C/min).
- The test tube was inverted every 30 seconds until the liquid ceased flowing on 180° inversion.
- This temperature was taken as the gelation temperature.
- Time taken from 25°C to gel point was recorded as gelation time.
- A good formulation gels at nasal mucosal temperature (~32–34°C) in 60–90 seconds.

B. Rheological Evaluation

- Rheology establishes the flow behavior, viscosity, and spreadability of the gel at varying shear rates and temperatures.
- Viscosity was determined at different shear rates (10, 20, 50, and 100 rpm) by employing a Brookfield DV-II+ Pro viscometer, equipped with Spindle No. 4 at both 25°C (sol state) and 34°C (gel state).
- The values were employed in plotting shear stress vs shear rate, from which the following were calculated:
- Flow behavior index (n): To determine Newtonian/pseudoplastic nature.
- Consistency index (K): Used to indicate gel thickness.
- Thixotropy: Region between upward and downward curves (hysteresis loop), which shows time-dependent shear thinning. [10]

C. Drug Content Uniformity

Ensures the drug distributes uniformly in the gel matrix.

1 g of gel was accurately weighed and dissolved in 10 mL methanol, sonicated for 15 minutes, and filtered through 0.45 µm membrane.

The sample was diluted as required and scanned at 225 nm using a UV spectrophotometer.

% Drug content was calculated based on the formula: [11]

It was accepted that a content uniformity of 95–105% would be acceptable.

2.5. In Vitro Gelation Study (Gelling Capacity Test)

The thermosensitive nasal gel's capacity to gel on exposure to nasal fluid was tested using simulated nasal fluid (SNF). [12]

Procedure:

- 1 mL of each formulation was mixed with 2 mL of SNF (pH 6.4, 37 °C) in a test tube.
- The solution was slowly mixed and monitored over time.
- Gelling capacity was graded on:
- Time elapsed to achieve gel formation
- Time for which gel could stand without breaking down

2.6 Stability Study:

Optimal nasal gels should exhibit (+++) behavior, for extended residence time in the nasal cavity.

Accelerated stability studies were conducted on the optimized thermosensitive nasal gel formulation (F4) following ICH

Q1A(R2) guidelines to evaluate its physical, chemical, and microbiological stability under controlled conditions. The formulation was stored in amber glass vials with nasal spray actuators at 40 ± 2°C and 75 ± 5% RH and assessed at 0, 1, 2, and 3 months. Parameters such as visual appearance, pH (using Hanna HI2211 pH meter), viscosity (measured via Brookfield viscometer), drug content (by validated UV method), gelation temperature and time, and sterility (as per USP <71> using FTM and SCDM) were evaluated. The formulation maintained acceptable stability with slight changes in turbidity, viscosity, and drug content by the third month, but remained within pharmaceutically acceptable limits. Sprayability and actuation volume were assessed using metered spray bottles sprayed onto Whatman filter paper at a 3 cm distance; the formulation showed a uniform, circular spray pattern with no tailing, and an average actuation volume of 0.078 ± 0.005 mL, falling within the acceptable range of 0.05–0.10 mL per spray. Clarity evaluation was performed by visually inspecting 2 mL of each formulation under white and black backgrounds in natural and artificial light; the optimized formulation (F4) exhibited Grade 0 clarity, indicating excellent transparency and absence of particulate matter or phase separation, thus meeting all visual and physicochemical requirements for nasal application.[13]

3. RESULT

3.1. Preformulation study result

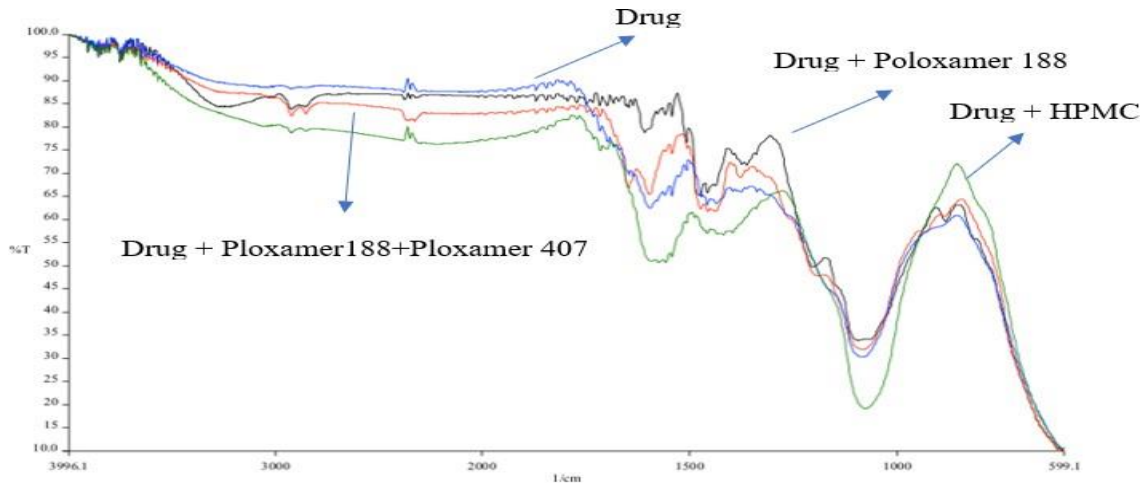

Figure 1:- IR spectra to observe drug-excipient interaction

3.1.1 Spectra Representations:

Table: 1 Spectra Representations and key observation

Spectrum (Color)	Sample Composition	Key Observations	Interpretation
Blue	Pure Drug	Distinct characteristic peaks of Zolmitriptan	Reference spectrum for comparison; confirms drug identity
Black	Drug + Poloxamer 188	Slight peak shifts, changes in intensity	Indicates possible physical interaction (e.g., hydrogen bonding), no degradation
Green	Drug + HPMC	Broadening around 3400 cm^{-1} (O–H stretch), minor shifts	Suggests hydrogen bonding between drug and HPMC
Pink	Drug + Poloxamer 188 + Poloxamer 407	Notable deviation from pure drug spectrum, broadened peaks	Stronger physical interactions; good compatibility with both surfactants

Table: 2 FTIR Region-Wise Interpretation and Interaction Insights

Spectral Region (cm^{-1})	Observed Features	Interpretation
3000–3500	Broad peaks due to –OH / –NH stretching	Shifts or broadening indicate hydrogen bonding with polymers like HPMC or Poloxamers
1700–1500	C=O stretching and aromatic ring vibrations	Shifts in this region may indicate interactions with polymer backbones
Below 1000	Complex fingerprint region	Overlapping suggests structural integrity of the drug is retained
No new peaks	Absence of additional functional group signals	No chemical degradation or formation of new compounds
Peak shifts & intensity changes	Notable across several regions	Evidence of physical interactions (e.g., hydrogen bonding, van der Waals forces)
Green spectrum (with both Poloxamers)	Shows maximum deviation from pure drug spectrum	Indicates strong physical interaction and good compatibility, possibly improving drug performance

B. Determination of the absorption maximum of Zolmitriptan

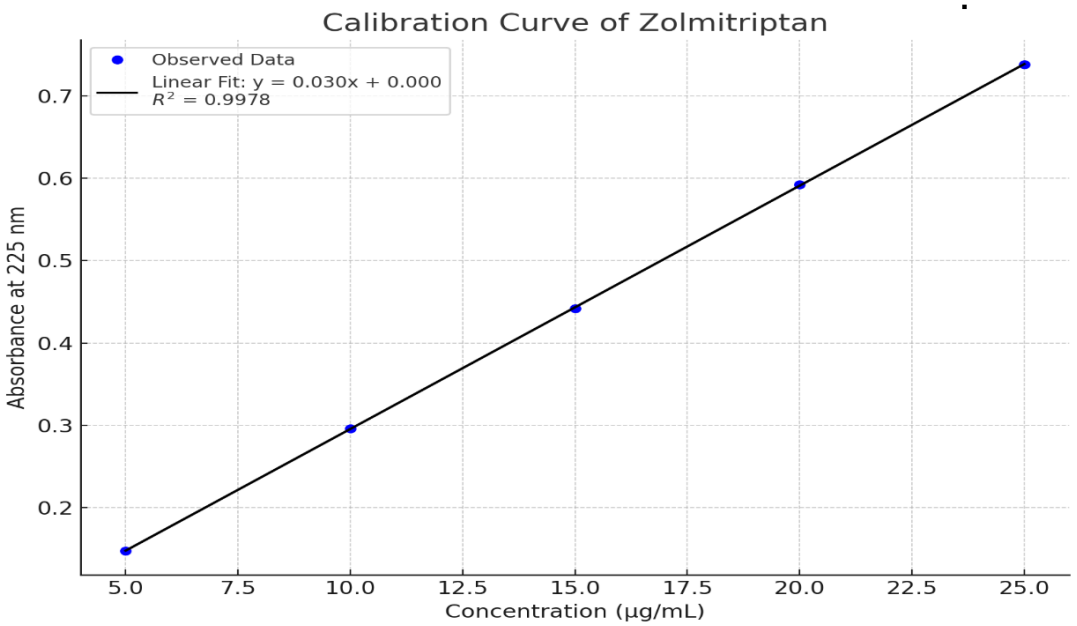

Figure 2:- UV study of drug

The absorption maximum of luliconazole at 225 nm λmax versus concentrations of 0.5-2.5 µg/ml was used to calculate the potential drug absorption in accordance with normal protocol. The coefficient and regression equation were determined to be 0.9978 and 0.030x-0.000, respectively. Finding Zolmitriptan absorption maxima is the related goal, and both qualitative and quantitative analysis are used to validate the procedure.

C. Solubility Result

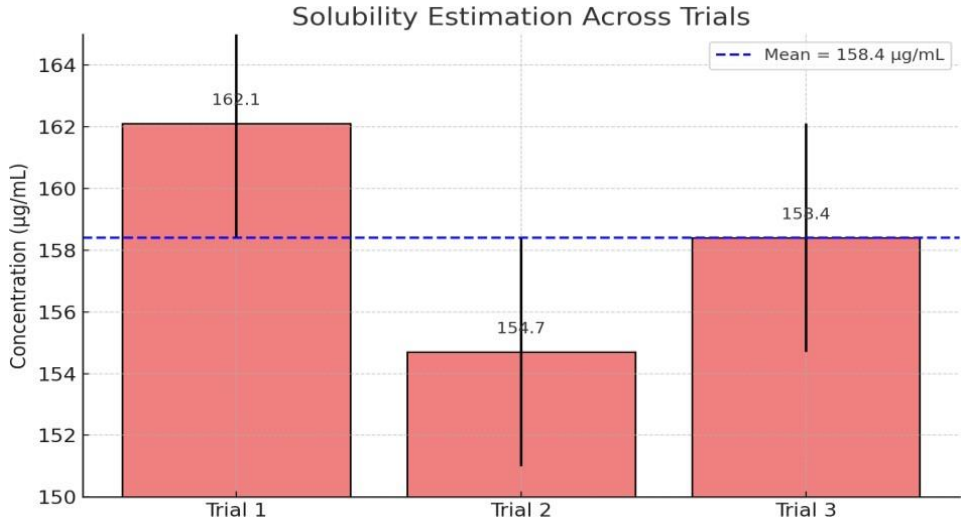

Figure: 3 Graphical representation solubility of zolmitriptan

The saturation solubility of zolmitriptan in PBS (pH 6.4) was determined by shaking excess drug in 10 mL of PBS at 37 ± 0.5°C for 72 hours. After filtration (0.22 µm), samples were analyzed at 225 nm using a UV spectrophotometer. The data aided in evaluating cyclodextrin complexation and optimizing dosage for the nasal gel.

3.2. Thermosensitive Nasal Gel Formulations

Table: 3 Formulations of nasal Gel

Formulation Code	Poloxamer 407 (% w/v)	Poloxamer 188 (% w/v)	Chitosan (1%)/HPMC (1%)	Zolmitriptan : HP β CD Ratio	BKC 0.01% + NaCl 0.9% + pH 5.5–6.5
F1	15	5	Chitosan (0.5%)	1:1	✓
F2	15	8	Chitosan (0.5%)	1:2	✓
F3	18	8	Chitosan (1%)	1:2	✓
F4	18	10	HPMCK4N (1%)	1:3	✓
F5	20	10	HPMCK15M (1%)	1:3	✓

Formulation Code	Zolmitriptan :HP-β-CD Molar Ratio	Gelling Temperature (°C)	Gelation Time (sec)	Mucoadhesive Strength (dyne/cm²)	Viscosity at 25°C (cP)
F1	1:1	35.2 ± 0.4	42 ± 2	940 ± 30	1450 ± 50
F2	1:2	32.5 ± 0.6	38 ± 3	1100 ± 45	1720 ± 35
F3	1:3	30.8 ± 0.5	30 ± 1	1350 ± 40	1985 ± 60
F4	1:2	31.2 ± 0.3	32 ± 2	1250 ± 35	1850 ± 50
F5	1:3	33.2 ± 0.3	35 ± 1	1168 ± 40	1510 ± 31

3.3. Physicochemical Study

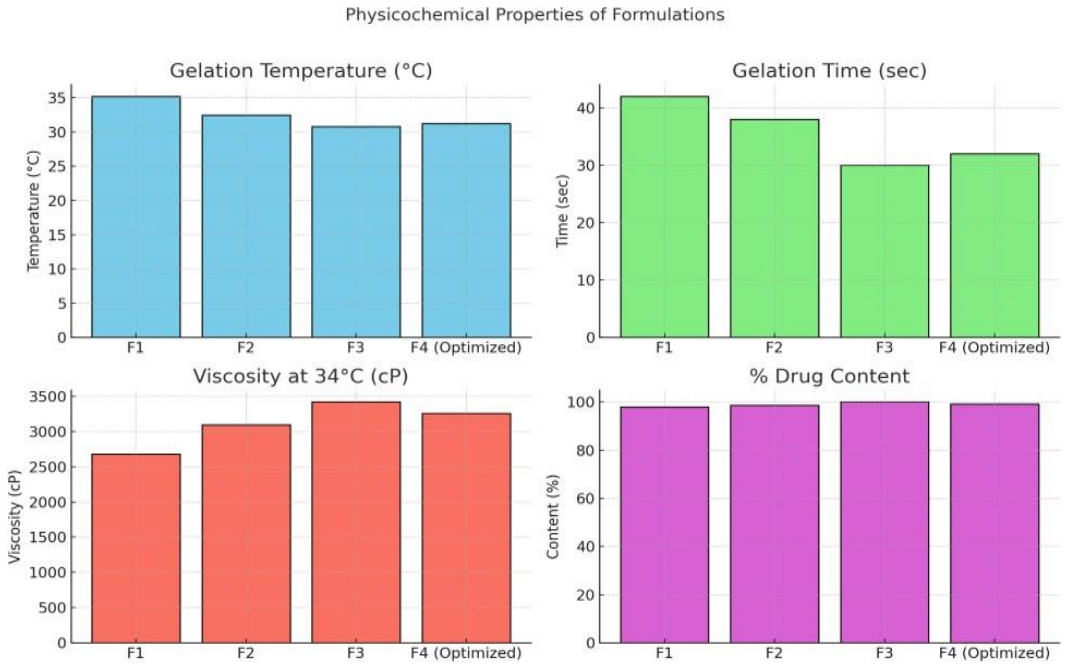

Figure:4 Physicochemical Study properties of formulation

A. Gelation Temperature and Gelation Time

Gelation properties are critical for nasal in situ gels. All formulations showed thermoreversible gelation within the physiological nasal range. The optimized formulation F4 had a gelation temperature of 31.2 ± 0.3°C and gelation time of 32 ± 2 sec, closely matching nasal mucosa conditions (32–34°C). Other formulations (F1–F3) varied slightly, with higher polymer concentrations promoting faster gelation at lower temperatures.

B. Rheological Assessment

All formulations exhibited pseudoplastic flow and thixotropy, ideal for nasal delivery. Viscosity increased at 34°C, indicating successful sol-to-gel transition and improved retention. The flow index ($n < 1$) confirmed shear-thinning, while consistency (K) and thixotropy were higher in F4, indicating better structural stability and mucoadhesion.

C. Uniformity of Drug Content

All batches met pharmacopeial drug content standards (95–105%). F4 showed 99.12 ± 1.08%, ensuring uniform drug distribution and efficient solubilization, supporting consistent therapeutic dosing.

3.4. Accelerated Stability result

The optimized thermosensitive nasal gel (F4) remained stable under accelerated conditions for 3 months, with only slight changes in pH, viscosity, and drug content—still within acceptable limits. Gelation temperature and time remained consistent, confirming in situ gelling reliability. The formulation maintained sterility and showed excellent sprayability (0.078 mL per spray), clarity (Grade 0), and strong in vitro gelation (+++), making it suitable and effective for nasal drug delivery of zolmitriptan.

Table: 4 Accelerated Stability at different levels

Parameter	Initial (0 Month)	1 Month	2 Months	3 Months	Remarks
Storage Condition	-	40 ± 2°C / 75 ± 5% RH	40 ± 2°C / 75 ± 5% RH	40 ± 2°C / 75 ± 5% RH	Accelerated Stability
Visual Appearance	Clear, no separation	No change	No change	Slight turbidity observed	Acceptable

pH	6.1 ± 0.02	6.08 ± 0.03	6.05 ± 0.02	6.02 ± 0.03	Within acceptable range
Viscosity (cP)	1850 ± 50	1820 ± 40	1795 ± 45	1760 ± 55	Slight decrease
Drug Content (%)	99.1 ± 1.2	98.5 ± 1.0	97.9 ± 1.3	96.7 ± 1.5	Within ICH limits
Gelation Temp (°C)	31.2 ± 0.3	31.3 ± 0.4	31.4 ± 0.4	31.5 ± 0.5	Stable
Gelation Time (sec)	32 ± 2	34 ± 2	35 ± 3	36 ± 3	Slight increase
Sterility	Sterile	Sterile	Sterile	Sterile	No microbial growth
Spray Pattern	–	–	–	Uniform circular zone	Good dispersion
Spray Symmetry	–	–	–	Symmetrical, no tailing	Accepted
Actuation Volume (mL/spray)	–	–	–	0.078 ± 0.005	Within 0.05–0.10 mL
Clarity Grade	–	–	–	Grade 0 (Crystal clear)	Passed
Gel Formation Time	–	–	–	Immediate (<30 sec)	Excellent
Gel Stability Duration	–	–	–	~1 hour	Sustained gelation
Gelling Capacity	–	–	–	(+++)	Strong gel integrity

4. CONCLUSION

The present research successfully formulated and evaluated a thermosensitive in situ nasal gel of zolmitriptan (F4) aimed at overcoming the limitations of oral administration in migraine treatment, particularly low bioavailability and delayed onset of action. The optimized formulation utilized a combination of Poloxamer 407 and 188 for thermoresponsive gelation, with Chitosan and HPMC contributing to mucoadhesion and retention. Solubility enhancement was achieved via complexation with hydroxypropyl-β-cyclodextrin, as confirmed through FTIR and DSC studies. F4 exhibited ideal gelation temperature (31.2 ± 0.3 °C), rapid gelation time (32 ± 2 sec), suitable viscosity, and strong mucoadhesive strength, ensuring effective nasal retention and drug delivery.

Sprayability studies showed accurate dosing (0.078 mL/spray) with uniform distribution. Stability testing under ICH guidelines confirmed that the formulation remained physically, chemically, and microbiologically stable over 3 months. The pH, clarity, drug content (99.12%), and sterility were maintained throughout. Rheological behavior indicated pseudoplastic and thixotropic flow, suitable for nasal spray delivery. Overall, the developed nasal gel demonstrated fast action, enhanced bioavailability, and high patient acceptability, establishing its potential as an effective and safe alternative to conventional migraine therapies.

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