

Development, Optimization and Characterization of a Thermosensitive In Situ Nasal Gel of Zolmitriptan for Sustained and Enhanced Drug Delivery

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Received: 25th Aug, 2026 | Revised: 1st Sep, 2026 | Accepted: 5th Sep, 2026 | Available Online: 12th Sep, 2026

Abstract

Background

Migraine is a prevalent and disabling neurological disorder in which the rapidity and reliability of drug delivery are particularly important during acute attacks. Although zolmitriptan is an established serotonin 5-HT_{1B/5-HT_{1D}} receptor agonist for acute migraine management, oral administration may be compromised by migraine-associated nausea, vomiting, gastrointestinal dysmotility, and presystemic metabolism. Intranasal delivery provides a rational alternative because of the highly vascularized nasal mucosa and the possibility of rapid systemic absorption while circumventing the gastrointestinal tract. Nevertheless, conventional nasal formulations may undergo rapid mucociliary clearance, limiting formulation residence and potentially restricting sustained drug–mucosa interaction.

Objective

The present study was undertaken to develop, optimize, and characterize a thermosensitive in situ nasal gel of zolmitriptan designed to combine the rapid-access advantages of intranasal administration with enhanced mucosal residence and controlled drug-delivery characteristics.

Methods

Thermosensitive formulations were prepared using Poloxamer 407 and Poloxamer 188 as thermoresponsive polymers, with low-molecular-weight chitosan and HPMC as mucoadhesive and viscosity-modifying components. HP-β-CD was incorporated as a solubility-enhancing excipient. Preformulation investigations included FTIR compatibility assessment, determination of λ_{max}, calibration-curve development, and saturation solubility studies. Five formulations (F1–F5) were prepared and comparatively evaluated for gelation temperature, gelation time, mucoadhesive strength, viscosity, drug content, pH, gelling capacity, sprayability, and stability. The formulation demonstrating the most balanced overall performance was selected for subsequent characterization.

Results

FTIR analysis demonstrated retention of the principal characteristic spectral features of zolmitriptan without emergence of distinct new functional-group bands, supporting the absence of major chemical incompatibility with the investigated excipients. Gelation temperatures ranged from 37.2 ± 0.6°C to 40.3 ± 0.3°C, whereas gelation times ranged from 34 ± 4 to 46 ± 6 s. Mucoadhesive strength ranged from 1012 ± 40 to 1450 ± 50 dyne/cm² and viscosity at 25°C ranged from 1550 ± 65 to 2005 ± 60 cP. F4, containing Poloxamer 407 (21% w/v), Poloxamer 188 (15% w/v), HPMC K4M (1% w/v), and zolmitriptan:HP-β-CD at a 1:6 molar ratio, demonstrated the most favorable overall balance among the investigated batches. F4 exhibited a gelation temperature of 39.8 ± 0.6°C, gelation time of 36 ± 5 s, mucoadhesive strength of 1280 ± 40 dyne/cm², and viscosity of 1920 ± 60 cP. During three months of accelerated storage at 40 ± 2°C/75 ± 5% relative humidity, relatively modest changes were observed in pH, viscosity, and drug content. However, gelation temperature increased progressively to 42.4 ± 0.8°C.

Conclusion

The study establishes the feasibility of a zolmitriptan thermosensitive in situ nasal platform and identifies F4 as the best-performing formulation among the investigated batches, while simultaneously identifying gelation temperature as the principal critical quality attribute requiring further optimization. The findings provide a rational

formulation-development foundation for subsequent optimization, release characterization, ex vivo nasal permeation studies, and in vivo pharmacokinetic evaluation.

Keywords: Zolmitriptan; migraine; intranasal delivery; thermosensitive in situ gel; Poloxamer 407; Poloxamer 188; chitosan; HPMC; hydroxypropyl- β -cyclodextrin; mucoadhesion; nasal drug delivery.

How to cite this article: Anil Budumurul Polepalli Sai Veera Venkata Samhitha^{2*} Dr. Shirisha V³ Dr. Aneesha⁴ B. Krishnakanth⁵ Dr. Hema N⁶. Development, Optimization and Characterization of a Thermosensitive In Situ Nasal Gel of Zolmitriptan for Sustained and Enhanced Drug Delivery. *Int J Drug Deliv Technol.* 2026;16(82s):1546-1555. DOI: 10.25258/ijddt.16.82s.179.

INTRODUCTION

Recurrent episodes of moderate-to-severe headache, often accompanied by nausea, vomiting, photophobia, phonophobia, and significant functional impairment, are the hallmark of migraine, a very common neurological condition. The condition has a significant negative impact on social functioning, healthcare systems, occupational productivity, and individual well-being. According to recent epidemiological data, migraine is still one of the major causes of disability in the globe, especially for working-age women^{1,2}.

Cortical excitability, trigeminovascular activation, neuropeptide release, vascular responses, and central pain-processing processes all dynamically interact in the intricate pathophysiology of migraine. Important aspects of migraine aetiology include the activation of trigeminal afferents innervating cranial tissues and the consequent release of vasoactive mediators, including calcitonin gene-related peptide (CGRP). Additionally, serotonergic signalling plays a key role in the pharmaceutical management of acute migraine, serving as the molecular basis for the creation of triptans³.

A second-generation triptan, zolmitriptan mainly acts as an agonist at 5-HT_{2B} and 5-HT_{4D} receptors. Its antimigraine action is linked to cranial vascular responses and trigeminal neurotransmission regulation, which suppresses key elements of the neurovascular cascade that underlies migraine attacks. With an absolute oral bioavailability of about 40%, pharmacokinetic studies have shown that zolmitriptan undergoes substantial presystemic metabolism after oral administration, giving a logical foundation for exploring other routes of administration⁴.

During a severe migraine attack, the limits of oral administration become very pertinent. Oral medication delivery may be hampered by nausea and vomiting, and the pace and predictability of gastrointestinal drug absorption may be impacted by migraine-related changes in stomach motility. Alternative pathways that might avoid the gastrointestinal tract and enable quick systemic exposure are therefore highly relevant from a therapeutic perspective.

Because the nasal mucosa is highly vascularised and has a comparatively large surface area that is suited for medication absorption, the nasal route is especially appealing. For systemically absorbed drugs, intranasal delivery can minimise the impact of hepatic first-pass metabolism, prevent

gastrointestinal degradation, and lessen reliance on gastric emptying⁵⁻⁷. Thus, the nasal cavity serves as a crucial conduit for the quick administration of many medicinal substances, such as antimigraine medications.

Intranasal zolmitriptan has been shown to be therapeutically effective in clinical trials. Zolmitriptan nasal spray showed a considerably higher headache response than a placebo at two hours in a large randomised, double-blind, placebo-controlled experiment. Therapeutic benefits were visible as early as fifteen minutes after treatment⁸. Similar quick systemic availability following intranasal treatment has been shown by pharmacokinetic investigations, which supports the nose route's applicability when early therapeutic exposure is preferred⁹.

The clinical utility of intranasal zolmitriptan has been further supported by more recent comparative data. The 5-mg zolmitriptan nasal spray was found to have favourable efficacy in a systematic review and network meta-analysis of intranasal treatments for acute migraine, especially in terms of pain freedom at 2 h¹⁰.

As a result, intranasal zolmitriptan is already a clinically proven method of administration. However, the nasal cavity's natural clearance systems limit the use of typical nasal treatments and sprays.

By continuously pushing mucus toward the nasopharynx, the nasal mucociliary apparatus quickly removes deposited materials, reducing the amount of time that formulation and mucosa are in contact^{11,12}. Rapid clearance is a serious obstacle to long-term intranasal medication delivery even though it is physiologically protective. Pharmaceutical research is now primarily focused on methods that can increase formulation residence without sacrificing nasal tolerability.

One such approach is the use of mucoadhesive medication delivery devices. Mucoadhesive polymers increase the likelihood of medication solubility and absorption by making close contact with the mucosal surface and perhaps delaying formulation removal^{16,13}. Because of its intrinsic mucoadhesive qualities, biocompatibility, biodegradability, and cationic nature, chitosan is very appealing. A physicochemical foundation for improved mucosal contact is provided by its protonated amino groups' ability to interact with negatively charged mucin components^{14,15}.

This method can be further improved with in situ gelling systems. When these systems are exposed to physiological ambient conditions, they undergo a sol-to-gel change after being supplied as relatively low-viscosity liquids. As a result, they aim to combine the retention qualities of gels with the administration benefits of liquid dosage forms. Because temperature-induced polymer organization can result in a quick rise in viscosity after delivery, thermally triggered nasal in situ gels have drawn a lot of interest¹⁶⁻¹⁸.

One of the most studied thermoresponsive medicinal polymers is poloxamer 407. It is a triblock copolymer with reversible temperature-dependent micellisation and gelation that is composed of poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) segments. The system stays reasonably fluid at lower temperatures, but as the temperature rises, micellar organization and formation are encouraged, leading to increased viscosity and gel formation¹⁹.

Nevertheless, Poloxamer 407 by itself might not always produce the best thermogel for every medication or route. The polymer content, ionic environment, drug loading, and interactions with secondary excipients all affect its gelation temperature, viscosity, gel strength, and release characteristics. These properties can be changed and the formulation design space expanded by adding Poloxamer 188 and mucoadhesive polymers^{19,20}.

Another method of formulation is the use of cyclodextrins. Hydroxypropyl- β -cyclodextrin can improve formulation compatibility and apparent water solubility by creating non-covalent inclusion complexes with appropriate drug molecules^{21,22}. Therefore, homogenous zolmitriptan incorporation into an aqueous thermoresponsive polymeric matrix may be made easier by cyclodextrin-assisted solubilisation.

Thus, the combination of zolmitriptan, HP- β -CD, thermoresponsive poloxamers, and mucoadhesive polymers has a complex scientific basis. Poloxamer 407 offers temperature-responsive gelation, Poloxamer 188 controls the thermoresponsive matrix, HP- β -CD allows drug solubilisation, and chitosan/HPMC contribute mucoadhesive and rheological functionality. The drug gives the proven pharmacological action. An appropriate platform for improving intranasal medication delivery performance might be offered by such a multifunctional formulation architecture.

Significantly, prior research has previously shown that thermoreversible zolmitriptan intranasal systems are feasible. The phase-transition temperature reported in a work employing zolmitriptan-loaded nanoethosomes integrated into Poloxamer 407-based thermoreversible gels was roughly 32–33°C, which closely resembles nasal physiological conditions²³. This discovery offers a crucial standard for the development of

thermosensitive zolmitriptan formulations in the future.

However, a formulation shouldn't be evaluated just based on the gelation temperature. The administration viscosity, gelation temperature, gelation kinetics, mucoadhesion, drug loading, release behaviour, sprayability, isotonicity, pH, and stability must all be rationally balanced in an efficient nasal in situ gel. Thus, the identification of essential quality qualities and a methodical comprehension of formulation-performance correlations are key components of modern pharmaceutical development²⁴.

In light of this, the goal of the current study was to create and evaluate a thermosensitive in situ nasal gel containing zolmitriptan using Poloxamer 407 and Poloxamer 188 together with mucoadhesive polymers and HP- β -CD. The physicochemical and functional properties of the formulations were rigorously screened. The study determines that a zolmitriptan thermosensitive in situ nasal platform is feasible and that F4 is the formulation that performs the best among the batches under investigation. It also identifies gelation temperature as the primary critical quality attribute that needs to be further optimised.

MATERIALS AND METHODS

Materials

The active pharmaceutical ingredient for the formulation development was zolmitriptan, which was purchased from a licensed pharmaceutical and chemical supplier. Sigma-Aldrich (USA) supplied the thermoresponsive gelling agents Poloxamer 407 and Poloxamer 188. While HPMC K4M and HPMC K15M were purchased from Loba Chemie (India) and utilised as mucoadhesive and viscosity-modifying polymers, respectively, low-molecular-weight chitosan was purchased from CDH (India). As a solubility-enhancing agent, hydroxypropyl- β -cyclodextrin (HP- β -CD) was purchased from an appropriate pharmaceutical-grade supplier.

Analytical-grade methanol, sodium hydroxide, hydrochloric acid, and glacial acetic acid were purchased from Merck, SRL, and CDH. Sodium chloride was utilised to regulate isotonicity, and benzalkonium chloride was obtained and employed as a preservative. In the lab, double-distilled water was created. Simulated nasal fluid (SNF) and phosphate-buffered saline (PBS, pH 6.4) were made in-house using normal laboratory techniques. Spectroscopic-grade potassium bromide (KBr) was utilised for FTIR analysis, and dialysis membrane was purchased for in vitro drug-release investigations. Every chemical, polymer, and other material used in the study was of laboratory, analytical, or pharmaceutical quality.

Preformulation Studies

FTIR	Spectroscopic	Drug-Excipient
Compatibility		

To determine whether zolmitriptan was compatible with the chosen excipients, FTIR spectroscopy was used. Compressed into translucent pellets, pure zolmitriptan, individual excipients, and physical mixes of zolmitriptan with the corresponding excipients were all triturated with KBr in an approximate ratio of 1:100.

A PerkinElmer Spectrum Two FTIR spectrometer operating between 4000 and 400 cm^{-1} at a resolution of 4 cm^{-1} was used to obtain the spectra. Zolmitriptan's primary absorption bands were found and contrasted with bands in the physical mixes. Evidence against significant chemical incompatibility was regarded as the preservation of the main characteristic bands without the loss of important spectral characteristics or the introduction of distinct new bands.

Determination of λ_{max} and Calibration Curve

A UV-visible spectrophotometer was used to find zolmitriptan's maximum absorption wavelength. 10 mg of zolmitriptan were precisely weighed, dissolved in methanol, and the volume was adjusted with 0.1 N hydrochloric acid to provide a stock solution of 100 $\mu\text{g/mL}$. Working solutions with concentrations between 5 and 25 $\mu\text{g/mL}$ were made by dilution. The wavelength that corresponded to maximal absorption was found by scanning the solutions between 200 and 400 nm. The λ_{max} found through experimentation was 225 nm. After measuring absorbance at 225 nm, absorbance was plotted versus concentration to create a calibration curve. To find the regression equation and correlation coefficient, linear regression was used.

Saturation Solubility

The equilibrium shake-flask method was used to measure saturation solubility. Stoppered glass vials containing 10 mL of PBS (pH 6.4) were filled with an excess of zolmitriptan. After a quick vortex, samples were kept at $37 \pm 0.5^\circ\text{C}$ and 100 rpm for 72 hours.

Samples were filtered using a 0.22- μm membrane filter after equilibration. The filtrates were measured spectrophotometrically at 225 nm after being appropriately diluted. The formulation technique utilising HP- β -CD was supported by the resulting solubility data.

Preparation of Zolmitriptan Thermosensitive In Situ Nasal Gel

Preparation of Poloxamer Base

Precooled double-distilled water kept at about 4°C was used to progressively disseminate the necessary amounts of Poloxamer 407 and Poloxamer 188, which were precisely weighed. To ensure full hydration and deaeration, the dispersion was kept at 4°C for 24 hours after being constantly stirred at 500 rpm for two hours.

Preparation of Mucoadhesive Polymer Solutions

With constant stirring, low-molecular-weight chitosan was dissolved in 1% v/v glacial acetic acid. 1 N sodium hydroxide was used to bring the pH

down to about 5.5. A 0.45- μm membrane filter was used to filter the resultant solution. With constant stirring at 500 rpm, HPMC K4M or K15M was progressively distributed in filtered water kept at about 60°C . The polymeric solution was cooled to room temperature following full dispersion.

Preparation of Zolmitriptan-HP- β -CD Inclusion Complex

HP- β -CD and zolmitriptan were mixed in molar ratios of 1:1, 1:2, and 1:3. The precisely weighed ingredients were kneaded for 30 minutes after being triturated with a small amount of ethanol. The resultant mass was ground up after being vacuum-dried at 40°C . To evaluate drug-cyclodextrin interactions and related solid-state modifications, the produced complexes were characterised using FTIR and DSC. The thermosensitive formulation was then chosen to include the optimised complex.

Preparation of Final Formulations

Under constant stirring, the optimised zolmitriptan-HP- β -CD complex was progressively added to the hydrated Poloxamer base. An Ultra-Turrax T25 homogeniser was used to homogenise the preparation for three minutes at 10,000 rpm.

0.1 N sodium hydroxide or hydrochloric acid was used to bring the pH down to 5.5–6.5. Sodium chloride (0.9% w/v) was used to modify the isotonicity, and benzalkonium chloride (0.01% w/v) was added as a preservative. After final homogenisation at 15,000 rpm, the product was put into amber-colored, sterile nasal spray vials.

Formulation Development and Optimization

Five formulations, designated F1–F5, were prepared by varying the concentrations of Poloxamer 407, Poloxamer 188, and the selected secondary polymeric components.

The formulations were comparatively evaluated for:

1. Gelation Temperature
2. Gelation Time
3. Viscosity
4. Mucoadhesive Strength
5. pH
6. Drug Content
7. Gelling Capacity
8. Sprayability
9. Actuation Volume and
10. Stability

For further characterisation, the formulation with the most balanced overall performance was chosen as the best-performing batch.

Physicochemical Characterization

Gelation Temperature and Gelation Time

A test tube containing around 5 mL of the formulation was put in a water bath with a thermostat. The temperature rose at a rate of about 0.5°C each minute. The temperature at which the formulation stopped flowing after the tube was inverted at intervals of thirty seconds was noted as the gelation temperature. The amount of time needed

for the visible sol-to-gel transformation at the desired physiological temperature was measured as the gelation time.

Rheological Evaluation

A Brookfield DV-II+ Pro viscometer equipped with spindle No. 4 was used to evaluate rheological characteristics. At spinning speeds of 10, 20, 50, and 100 rpm, viscosity was measured at 25°C and 34°C. To describe flow behaviour, the connection between shear stress and shear rate was assessed. The hysteresis loop produced during uphill and downward shear-rate measurements was used to evaluate thixotropic behaviour.

Drug Content

After precisely weighing the formulation, about 1 g was added to 10 mL of methanol. After 15 minutes of sonication, the sample was passed through a 0.45- μ m membrane filter. The filtrate was spectrophotometrically measured at 225 nm after being appropriately diluted. The calibration curve was used to compute the drug content, which was then expressed as a percentage of the theoretical drug concentration.

pH

A digital pH meter that had been calibrated was used to measure the pH at room temperature. Measurements were made in triplicate and reported as mean $\pm$ standard deviation.

Visual Appearance and Clarity

On black and white backgrounds, formulations were visually inspected for colour, homogeneity, turbidity, visible particle matter, and phase separation.

In Vitro Gelling Capacity

Two millilitres of SNF kept at pH 6.4 and 37°C were mixed with one millilitre of formulation. After gently mixing the formulation, gel formation was monitored. The rate of gel formation, structural integrity, and resistance to early erosion were taken into consideration when evaluating gelling capacity.

In Vitro Drug Release

A dialysis membrane diffusion approach was used to assess the in vitro drug-release profile. The donor and receptor compartments were separated by the constructed dialysis membrane. The donor compartment was filled with a fixed amount of formulation that contained the same dose of zolmitriptan. The receptor compartment was kept at $37 \pm 0.5^\circ\text{C}$ with constant stirring after being supplied with an appropriate release media. Aliquots were taken out at prearranged intervals and promptly replaced with equal amounts of brand-new, preheated medium. Samples were spectrophotometrically examined at 225 nm after being suitably diluted.

Nasal Sprayability and Actuation Volume

The chosen nasal spray device was used to assess the optimised formulation's spray properties. Nasal spray vials equipped with metered-dose actuators were filled with the formulation. The formulation

was sprayed over Whatman filter paper at a distance of around 3 cm in order to assess the spray pattern.

The homogeneity, circularity, tailing, and uneven deposition of the spray pattern were assessed. Gravimetric analysis of repeated actuations yielded the actuation volume, which was then reported as mean $\pm$ standard deviation.

Accelerated Stability Study

The optimized F4 formulation was stored at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ relative humidity.

Samples were evaluated at 0, 1, 2, and 3 months for:

- Visual Appearance
- Clarity
- pH
- Viscosity
- Drug Content
- Gelation Temperature
- Gelation Time
- Sprayability
- Actuation Volume
- Microbiological Quality

Fluid Thioglycollate Medium and Soybean-Casein Digest Medium were used in approved pharmacopeial techniques to assess microbiological quality.

Because ICH Q1A(R2) typically calls for six months of accelerated testing at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH for the general case, along with an acceptable long-term stability assessment, the accelerated stability protocol was viewed as preliminary.

Statistical Analysis

The mean $\pm$ standard deviation was used to express the experimental observations, which were collected in suitable duplicates. The proper statistical software was used to conduct the statistical analysis. The statistical approach was used in accordance with the data distribution and experimental design. A statistically significant p-value was one that was less than 0.05.

RESULTS

FTIR Compatibility Assessment

The reference spectrum was the FTIR spectra of pure zolmitriptan, which demonstrated the drug's distinctive absorption profile. The physical combination of Poloxamer 188 and zolmitriptan showed slight variations in peak position and intensity. In the O–H/N–H stretching region, the zolmitriptan–HPMC spectrum showed widening. More spectrum overlap and widening were shown by the combination of zolmitriptan, Poloxamer 188, and Poloxamer 407.

However, zolmitriptan's primary distinctive spectral areas were preserved. There were no noticeable extra absorption bands that corresponded to recently formed functional groupings. Therefore, rather than chemical incompatibility, the spectrum changes are better understood as potential physical intermolecular interactions, such as hydrogen bonds and van der Waals interactions. All, the FTIR results validated zolmitriptan's compatibility with the

chosen formulation ingredients and supported their advancement into formulation development.

Development of Thermosensitive Formulations

Poloxamer 407, Poloxamer 188, and secondary polymeric components were used in varying amounts and combinations to create five formulations, F1–F5. Viscosity, mucoadhesive strength, gelation temperature, and gelation kinetics were all clearly affected by variations in polymer composition.

To investigate the impact of cyclodextrin incorporation on the formulation profile, the zolmitriptan:HP- β -CD ratio was gradually changed throughout the formulation series. Instead of focusing on maximising a single response, the formulation-development technique aimed to achieve a multidimensional balance.

Gelation Temperature and Gelation Time

The range of gelation temperatures for F1–F5 was $37.2 \pm 0.6^\circ\text{C}$ to $40.3 \pm 0.3^\circ\text{C}$. The temperature at which F1 and F2 gelled was $37.2 \pm 0.6^\circ\text{C}$ and $37.5 \pm 0.7^\circ\text{C}$, respectively. At $40.3 \pm 0.3^\circ\text{C}$, F3 showed the highest transition temperature, whereas F4 and F5 showed values of $39.8 \pm 0.6^\circ\text{C}$ and $39.2 \pm 0.4^\circ\text{C}$, respectively.

The gelation period varied between 34 ± 4 and 46 ± 6 s. At 34 ± 4 seconds, F3 had the shortest gelation time, followed by F4 at 36 ± 5 seconds, F5 at 39 ± 9 seconds, F2 at 40 ± 7 seconds, and F1 at 46 ± 6 seconds. Changes in polymer concentration, hydration, micellar organization, and polymer–polymer interactions may be responsible for the variations in thermoresponsive behaviour. Temperature-dependent micellisation and gel formation occur in poloxamer 407, and secondary polymers have the ability to significantly alter the transformation behaviour.

Interestingly, not a single formulation showed a transition within the commonly desired $32\text{--}34^\circ\text{C}$ range. Previous zolmitriptan thermoreversible systems have reported phase-transition temperatures about $32\text{--}33^\circ\text{C}$, which makes this finding significant from a scientific standpoint. As a result, the current data not only demonstrate thermoresponsive behaviour but also point to gelation temperature as a significant formulation-development obstacle.

Mucoadhesive Strength

Mucoadhesive strength varied between 1012 ± 40 and 1450 ± 50 dyne/cm². F1 had the lowest mucoadhesive strength, while F3 had the highest. F2 demonstrated 1200 ± 45 dyne/cm², F4 1280 ± 40 dyne/cm², and F5 1270 ± 45 dyne/cm². Increased mucin-polymeric matrix interaction is responsible for the improved mucoadhesive efficacy of the polymer-containing formulations. A physicochemical foundation for improved adherence is provided by chitosan's cationic nature and ability to interact electrostatically with negatively charged mucosal components. When mucoadhesion was taken into account together with

gelation time and viscosity, F4 provided a better-balanced formulation profile even though F3 showed the highest mucoadhesive strength.

Rheological Evaluation

At 25°C , the formulations' viscosities varied from 1550 ± 65 to 2005 ± 60 cP. F1 had the lowest viscosity at 1550 ± 65 cP, while F3 had the highest viscosity at 2005 ± 60 cP. F2 and F4 had viscosities of 1830 ± 40 and 1920 ± 60 cP, respectively. F5 showed 1610 ± 37 cP of viscosity. The observed variations align with the impact of polymeric chain tangling and polymer concentration on flow resistance. F4 showed respectable spray performance despite a comparatively high viscosity. This is crucial because an intranasal in situ gel needs to balance two seemingly incompatible needs: high enough post-administration structural integrity to withstand quick clearance and low enough viscosity for repeatable administration. In the development of nasal in situ gels, such formulation balance is a known difficulty.

Table 1. Composition of the Investigated Thermosensitive Nasal Gel Formulations

Formulation	Poloxamer 407	Poloxamer 188	Mucoadhesive/viscosity modifier	Zolmitriptan:HP- β -CD
F1	As per formulation design	As per formulation design	As per formulation design	1:3
F2	As per formulation design	As per formulation design	As per formulation design	1:3
F3	As per formulation design	As per formulation design	As per formulation design	As per formulation design
F4	21% w/v	15% w/v	HPMC K4M 1%	1:6
F5	As per formulation design	As per formulation design	As per formulation design	1:9

Table 2. Comparative Physicochemical Characteristics of F1–F5

Formulation	Gelation temperature (°C)	Gelation time (s)	Mucoadhesive strength (dyne/cm ²)	Viscosity at 25°C (cP)
F1	37.2 ± 0.6	46 ± 6	1012 ± 40	1550 ± 65
F2	37.5 ± 0.7	40 ± 7	1200 ± 45	1830 ± 40
F3	40.3 ± 0.3	34 ± 4	1450 ± 50	2005 ± 60
F4	39.8 ± 0.6	36 ± 5	1280 ± 40	1920 ± 60
F5	39.2 ± 0.4	39 ± 9	1270 ± 45	1610 ± 37

Selection of F4 as the Best-Performing Formulation

F4 was selected as the best-performing formulation among the investigated batches based on its integrated physicochemical profile.

Its composition was:

Component	Concentration/ratio
Poloxamer 407	21% w/v
Poloxamer 188	15% w/v
HPMC K4M	1% w/v
Zolmitriptan:HP-β-CD	1:6
Benzalkonium chloride	0.01% w/v
Sodium chloride	0.9% w/v

Its principal characteristics were:

Parameter	F4
Gelation temperature	39.8 ± 0.6°C
Gelation time	36 ± 5 s
Mucoadhesive strength	1280 ± 40 dyne/cm ²
Viscosity at 25°C	1920 ± 60 cP

F4 therefore demonstrated a favourable compromise among gelation kinetics, viscosity, and mucoadhesive performance.

Importantly, the term best-performing formulation is used here to denote comparative superiority within the experimental formulation space investigated and does not imply that all critical quality attributes have reached their final target values.

Accelerated Stability Study

The stability profile of F4 is presented in Table 3.

Table 3: Stability Profile of F4

Parameter	Initial	1 Month	2 Month	3 Month
pH	6.10 ± 0.02	6.08 ± 0.03	6.05 ± 0.02	6.02 ± 0.03
Viscosity (cP)	1920 ± 60	1900 ± 60	1805 ± 55	1840 ± 65
Drug content (%)	104.1 ± 2.3	102.6 ± 2.0	100.8 ± 1.9	100.7 ± 2.0

Gelation temperature (°C)	39.8 ± 0.6	40.7 ± 0.6	40.9 ± 0.7	42.4 ± 0.8
Gelation time (s)	36 ± 5	37 ± 6	38 ± 7	40 ± 9

During the early phases of storage, F4 maintained visual homogeneity. At three months, there was some turbidity, but no discernible phase separation was noted. The pH steadily dropped from 6.10 ± 0.02 to 6.02 ± 0.03, suggesting that the formulation's acid–base environment was very slightly altered.

At two months, viscosity decreased from 1920 ± 60 cP to 1805 ± 55 cP; at three months, it slightly increased to 1840 ± 65 cP. Three months later, the drug content dropped from 104.1 ± 2.3% to 100.7 ± 2.0%.

On the other hand, after three months, the gelation temperature increased steadily from 39.8 ± 0.6°C to 42.4 ± 0.8°C. The gelation time went from 36 ± 5 s to 40 ± 9 s, a little increase.

Throughout the evaluation period, there were no documented microbiological growths in the formulation. The formulation showed a consistent circular spray pattern with little tailing during the three-month assessment. Within the designated goal range of 0.05–0.10 mL/spray, the actuation volume was 0.083 ± 0.006 mL/spray.

The formulation showed Grade 0 clarity, instantaneous gel formation in about 30 seconds, a reported gel duration of about 1 hour, and a gelling capacity rating of +++.

DISCUSSION

The present study was undertaken to establish a scientifically rational thermosensitive in situ nasal delivery platform for zolmitriptan. The formulation strategy was predicated upon the complementary functionality of thermoresponsive polymers, mucoadhesive polymers, and cyclodextrin-mediated solubilization. Rather than attempting to reproduce the function of a conventional nasal spray, the study sought to engineer a formulation capable of undergoing physicochemical transformation after administration and thereby providing a more persistent drug-delivery microenvironment.

Pharmacokinetic and clinical data support the justification for intranasal zolmitriptan. In the early phases of an acute migraine attack, conventional intranasal zolmitriptan can provide clinically significant relief and achieve rapid systemic exposure^{8–10}. Therefore, figuring out whether formulation engineering can enhance residence and adjust release without sacrificing administration features is the main pharmaceutical problem rather than proving that zolmitriptan can be administered through the nasal route.

Preliminary proof of drug–excipient compatibility was provided by the FTIR results. The retention of distinctive zolmitriptan spectrum areas implies that the drug's basic chemical structure did not change after physical mixing with the polymers under

investigation. Hydrogen bonding and other non-covalent interactions within the formulation matrix may be linked to slight changes and band broadening. FTIR cannot determine the extent or pharmacological relevance of such interactions, although they may affect drug dispersion and polymer hydration.

The formulation screening showed that the composition of the polymer had a significant impact on the properties of gelation. It is known that poloxamer 407 undergoes reversible temperature-dependent micellisation, whereby rising temperatures encourage the production of micelles and the polymeric system's subsequent three-dimensional organization¹⁹.

By changing the hydrophilic–hydrophobic balance and polymeric interactions, Poloxamer 188 and secondary polymers can change this process. One of the study's most significant scientific discoveries is the gelation-temperature results. The gelation temperature for F4 was $39.8 \pm 0.6^\circ\text{C}$. The number is higher than the typically preferred physiological nasal range, despite the fact that this validates thermoresponsive behaviour.

This is a crucial distinction. It is not necessary for a formulation to be maximally thermosensitive for nasal administration in order to be classified as thermosensitive. The pharmacological goal is not just to gel at a high temperature; rather, the transition should happen in a way that is sufficiently similar to the physiological conditions that arise following nasal injection while maintaining fluidity during application.

Previous study on zolmitriptan formulation highlights the importance of this issue. Zolmitriptan-loaded nanoethosomes in a thermoreversible intranasal formulation based on Poloxamer 407 showed a phase-transition temperature of roughly $32\text{--}33^\circ\text{C}$ ²³. The difference between that system and the current F4 formulation suggests that there is still room for improvement in the polymeric composition employed here.

The particular quantity and ratio of Poloxamer 407 and Poloxamer 188, the presence of HPMC, the cyclodextrin complex, ionic components, or interactions between these constituents may all be responsible for the higher transition temperature. Therefore, rather than being the final formulation, the formulation should be considered a promising prototype within the explored design area.

Nevertheless, F4 showed a comparatively quick gelation time of $36 \pm 5\text{ s}$. Because it can potentially shorten the time that the injected liquid is susceptible to nasal clearance, rapid gel formation is desirable. However, gelation temperature and gelation duration must always be taken into consideration. The formulation problem is not entirely solved by rapid production at an incorrect transition temperature.

The mucoadhesive results were more positive. F3 showed the greatest value of $1450 \pm 50\text{ dyne/cm}^2$, whereas F4 showed a mucoadhesive strength of $1280 \pm 40\text{ dyne/cm}^2$. As a well-known multipurpose mucoadhesive polymer, chitosan's interaction with mucin can improve formulation retention^{14,15}.

The nasal mucociliary clearance system's constant activity is the source of mucoadhesion's physiological relevance. Mucus and deposited particle matter are efficiently transported by the nasal cavity to the nasopharynx^{11,12}. For prolonged intranasal administration, extending the time of formulation–mucosa interaction is therefore a crucial design goal.

Excessive mucoadhesion is not always beneficial, though. A formulation must not significantly impair physiological mucociliary function and must preserve sufficient mucosal compatibility. Therefore, rather than just choosing the formulation with the highest measured adhesive force, F4's moderate mucoadhesive profile could be preferred.

This multifaceted formulation approach is supported by the rheological results. At 25°C , the viscosity of F4 was $1920 \pm 60\text{ cP}$. Viscosity is a crucial factor in determining administration and post-administration performance since poloxamer-based systems exhibit significant temperature-dependent rheological behavior^{19,20}.

Spray formation, actuation repeatability, and patient acceptability could all be jeopardised by a too viscous formulation. On the other hand, a formulation with insufficient viscosity might be quickly expelled from the nasal cavity. The fact that F4 was able to successfully generate a relatively uniform spray pattern and an actuation volume of $0.083 \pm 0.006\text{ mL/spray}$ indicates that, under the tested conditions, its rheological qualities remained compatible with the chosen delivery mechanism.

The goal of adding HP- β -CD was to solve zolmitriptan's solubility and dispersion needs in the aqueous polymeric system. Cyclodextrins can form dynamic inclusion complexes with specific medicinal molecules because of their hydrophilic exterior surface and somewhat hydrophobic cavity^{21,22}. This kind of complexation can enhance formulation versatility and perceived aqueous solubility.

However, complementing solid-state and phase-solubility characterisation should ideally be used to prove the existence of an inclusion complex. Quantitative phase-solubility analysis would provide a more reliable evaluation of the complexation behaviour, while FTIR and DSC offer supporting data.

F4 was chosen as the top-performing batch based on the comparative formulation study. No single parameter's highest value served as the basis for this choice. For instance, F3 showed the highest viscosity and highest gelation temperature together with the highest mucoadhesive strength and the

quickest gelation duration. F4 offered a profile that was rather balanced.

This strategy is in line with modern pharmaceutical development principles, which state that rather than depending just on single-response optimisation, formulation optimisation should take into account interactions among important quality attributes²⁴.

The stability results showed that a number of formulation properties changed in comparatively small ways. Over the course of the three months, the pH just slightly dropped, indicating that the formulation environment remained largely stable. Overall, viscosity changed very little, and the medication content was rather constant.

It is important to give serious thought to the initial drug content of $104.1 \pm 2.3\%$. Before drawing firm conclusions, an initial assay number above the nominal 100% level should be examined in relation to analytical method accuracy, calibration, sampling, and formulation uniformity, even though successive values neared 100%.

The rise in gelation temperature from $39.8 \pm 0.6^\circ\text{C}$ to $42.4 \pm 0.8^\circ\text{C}$ was the most significant stability observation. This gradual change points to a change in the thermoresponsive polymeric microenvironment during storage. Since the gelation temperature was already beyond the intended physiological range at baseline, this finding is very significant. The likelihood of good in situ gelation after nasal delivery may be decreased by an additional upward shift.

As a result, "the formulation was s" is not a sufficient summary of the stability findings. Under the examined accelerated conditions, F4 showed generally acceptable short-term physicochemical stability while exhibiting a progressive change in its thermoresponsive transition behaviour, according to a more scientifically accurate interpretation. Careful qualification is also necessary for the length of the current accelerated stability investigation. ICH Q1A(R2) proposes six months of accelerated data for the general case and defines $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ as the general accelerated condition²⁵. As a result, the three-month information should be regarded as preliminary and should not be utilised to determine a final shelf life.

There was no documented microbial development over the examined time, and the microbiological results were positive. However, because the nasal route exposes the formulation directly to delicate mucosal tissues, intranasal medicines necessitate strict microbiological quality control. Thus, as part of future development, preservative efficacy, container-closure integrity, and device compatibility should be assessed. It is also necessary to properly interpret the formulation's therapeutic relevance. Intranasal zolmitriptan is effective, according to available clinical data⁸⁻¹⁰. There is currently no proof that thermosensitive gelation enhances clinical efficacy

or bioavailability in the current formulation. Rather, the current studies show a logical pharmacological platform that might change drug-release and residence behaviour.

Similarly, direct nose-to-brain transport cannot be deduced from the current formulation data alone, even though the nasal cavity has been studied as a possible route for central nervous system administration through olfactory and trigeminal pathways^{5,6}.

It would take specific pharmacokinetic, biodistribution, or imaging investigations to prove direct CNS transit.

Therefore, formulation engineering is the main contribution of the current work. It shows that a multifunctional thermosensitive nasal system with quantifiable mucoadhesive, rheological, and sprayability properties may be integrated with zolmitriptan. Simultaneously, the study pinpoints a particular and experimentally verifiable constraint—gelation temperature—that offers a clear path for further optimisation.

Poloxamer 407 concentration, Poloxamer 188 concentration, secondary polymer concentration, and HP- β -CD ratio should all be considered formulation variables in future development, while gelation temperature, viscosity, mucoadhesive strength, sprayability, drug release, and stability should be considered critical responses^{24,25}.

With this method, the current formulation would become a scientifically defined formulation design space rather than an empirically chosen prototype.

CONCLUSION

The current investigation determines if it is feasible to create a thermosensitive in situ nasal administration platform for zolmitriptan by combining Poloxamer 407, Poloxamer 188, HPMC, and HP- β -CD.

FTIR research confirmed that zolmitriptan was compatible with the chosen formulation ingredients. Viscosity, mucoadhesive performance, and gelation behaviour were all significantly impacted by polymer composition, according to a methodical screening of five formulations.

With a gelation time of $36 \pm 5 \text{ s}$, mucoadhesive strength of $1280 \pm 40 \text{ dyne/cm}^2$, and viscosity of $1920 \pm 60 \text{ cP}$ at 25°C , batch F4 showed the best overall formulation profile among the batches under investigation. During the assessed stability period, F4 also demonstrated microbiological quality, drug-content retention, actuation volume, and acceptance spray characteristics.

The study determines that a zolmitriptan thermosensitive in situ nasal platform is feasible and that F4 is the formulation that performs the best among the batches under investigation. It also identifies gelation temperature as the primary critical quality attribute that needs to be further optimised.

However, after three months of accelerated storage, the gelation temperature of F4 rose from $39.8 \pm 0.6^\circ\text{C}$ to $42.4 \pm 0.8^\circ\text{C}$. This result emphasises a well-defined formulation-development problem and suggests that further polymer composition optimisation is necessary.

Therefore, rather than being a definitive final formulation, F4 should be considered a promising developing prototype. Reducing the transition temperature toward the physiological nasal range, establishing the full in vitro drug-release profile, figuring out release kinetics, analysing ex vivo nasal penetration, gauging nasal mucosal safety, and contrasting pharmacokinetic performance with traditional intranasal zolmitriptan should be the main goals of future research.

Nevertheless, the current research offers a logical pharmacological basis for future development of a thermoresponsive, patient-friendly zolmitriptan nasal administration method.

Benefits and Limitations

Despite these drawbacks, the study shows that creating a thermosensitive in situ nasal delivery platform for zolmitriptan is feasible, with F4 showing a good balance of mucoadhesive strength, viscosity, quick gel formation, drug-content retention, sprayability, and short-term physical stability. These results offer a good basis for additional optimisation targeted at enhancing nasal residence and regulated medication delivery.

The main drawbacks included F4's higher-than-ideal gelation temperature, the short three-month stability period, and the lack of comprehensive drug-release, permeation, toxicity, pharmacokinetic, and clinical data. Future research should therefore concentrate on lowering the gelation temperature by statistically guided optimisation and confirming the optimised formulation through comparative pharmacokinetic, ex vivo, in vivo, and extended stability tests.

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