International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 23s, 2025
https://www.theaspd.com/ijes.php

Preparation And Evaluation of Thermo Sensitive in Situ Nasal Gel of Rizatriptan for Brain Targeting

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Abstract

Migraine is a highly prevalent neurological disorder characterized by recurrent, debilitating headaches and associated symptoms such as nausea, photophobia, and phonophobia. Conventional oral formulations of rizatriptan, a selective 5-$HT_1B/_1D$ receptor agonist, are limited by delayed onset of action, low bioavailability due to hepatic first-pass metabolism, and poor absorption during migraine-induced gastric stasis. To address these challenges, this study aimed to develop and evaluate a thermosensitive in situ nasal gel of rizatriptan for targeted brain delivery. The formulation was prepared using poloxamer 407 and 188 as thermoresponsive polymers, with Carbopol 934P as a mucoadhesive agent to enhance nasal retention. The gel exhibited a sol–gel transition at nasal cavity temperature, ensuring ease of administration and prolonged mucosal residence. Physicochemical evaluations demonstrated suitable viscosity, pH, and drug content. In vitro release studies revealed sustained drug release, best described by the Korsmeyer-Peppas model, indicating anomalous transport. Ex vivo permeation studies using sheep nasal mucosa showed significantly enhanced drug transport compared to conventional solutions, and histopathological evaluation confirmed the safety and biocompatibility of the formulation. Comparative analysis with existing oral and nasal formulations highlighted the superior performance of the thermosensitive gel in terms of faster onset, higher bioavailability, and improved patient compliance. Overall, thermosensitive in situ nasal gels offer a promising platform for brain-targeted delivery of rizatriptan, paving the way for improved therapeutic outcomes in migraine management.

Keywords: *Thermo sensitive gel, intranasal delivery, rizatriptan, brain targeting, migraine, sustained release*

1. INTRODUCTION

From ancient times, nasal medication delivery has been a successful method of administration. As a useful technique for treating a variety of brain illnesses, it provides improved brain availability for numerous medications. Because it has specialized ciliated nerve cells for smell perception, receives ophthalmic and maxillary divisions of the trigeminal nerve, and has direct access to cerebrospinal fluid, the olfactory area of the nose is very significant (Vigani et al., 2020) (Swamy & Abbas, 2012). Excruciating headaches and nausea that come and go at random times and continue for several hours are the hallmarks of the migraine syndrome. The Global Burden of Disease (GBD) study indicates that migraine is the top cause of disability among women under 50 and the second most common cause overall. In addition to having trouble focused on certain items, migraine sufferers may also have an excessive hunger for specific foods, intolerance to light (photophobia) or smells (hypersomnia) (Steiner et al., 2020). These symptoms are thought to be caused by a

disruption in cerebral blood flow, while the precise origin is unclear. Precipitating elements including psychological stress sleep deprivation, and certain meals are necessary to trigger an attack in addition to a hereditary susceptibility. Migraine is a highly prevalent neurological disorder characterized by recurrent, often debilitating headaches, typically accompanied by symptoms such as nausea, photophobia, and phonophobia (Charles, 2018). It affects over 1 billion people worldwide and is recognized as one of the leading causes of disability among individuals under the age of 50 (Steiner et al., 2020). The chronic nature of migraines and their potential to significantly impair daily functioning underscore the necessity for effective and rapid therapeutic interventions. Conventional drug delivery methods for migraine treatment, such as oral administration, present several limitations. These include delayed onset of action, reduced bioavailability due to hepatic first-pass metabolism, and poor absorption during migraine-induced gastric stasis (de Vries et al., 2020). These pharmacokinetic challenges limit the efficacy of orally administered drugs like rizatriptan, a selective 5-$HT_1B/_1D$ receptor agonist commonly used for acute migraine relief. Furthermore, the blood–brain barrier (BBB), a selective and protective physiological barrier, significantly restricts the entry of therapeutic agents into the central nervous system (CNS), posing an additional obstacle for brain-targeted drug delivery (Pardridge, 2012).

To overcome these limitations, non-invasive drug delivery systems that bypass the BBB have garnered increasing attention. Among these, intranasal administration has emerged as a promising route for brain-targeted drug delivery due to its unique anatomical and physiological properties, such as the high vascularization of the nasal mucosa and the direct nose-to-brain transport pathways via the olfactory and trigeminal nerves (Illum, 2003). This route not only avoids first-pass metabolism but also facilitates rapid drug absorption and onset of action, which is particularly desirable in migraine therapy where fast relief is critical. Given the advantages of intranasal delivery, formulating thermosensitive in situ gels capable of transforming from sol to gel at nasal cavity temperature offers an innovative approach to enhance mucosal retention and drug absorption. Such systems, incorporating mucoadhesive and thermosensitive polymers, can improve the residence time of the drug at the site of administration and promote sustained drug release, ultimately increasing the therapeutic efficacy for brain-targeted conditions such as migraine. Rizatriptan is a second-generation selective serotonin (5-hydroxytryptamine, 5-HT) receptor agonist that primarily acts on the 5-HT_1B and 5-HT_1D receptors, which are implicated in the pathophysiology of migraine (Tfelt-Hansen et al., 2000). By stimulating these receptors, rizatriptan induces vasoconstriction of dilated intracranial blood vessels, inhibits the release of vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP), and suppresses nociceptive transmission in the trigeminovascular system (Goadsby et al., 2017). It is commonly prescribed for the acute treatment of migraine attacks with or without aura and is known for its relatively rapid onset of action and favorable efficacy profile compared to other triptans. Despite its clinical benefits, rizatriptan exhibits several pharmacokinetic limitations when administered orally. One of the primary challenges is the extensive hepatic first-pass metabolism, which significantly reduces its systemic bioavailability to approximately 40% (Becker, 2015). Additionally, during a migraine attack, gastrointestinal motility is often impaired—a condition known as gastric stasis—which further compromises drug absorption and delays onset of action. These drawbacks limit the effectiveness of oral rizatriptan, particularly in patients requiring rapid symptom relief (de Vries et al., 2020).

Intranasal administration presents a promising alternative to overcome the limitations of oral delivery. The nasal cavity offers a highly vascularized mucosa and direct pathways to the brain via the olfactory and trigeminal nerves, allowing for rapid absorption and potential direct nose-to-brain transport (Illum, 2003). This route bypasses first-pass hepatic metabolism and may result in quicker onset of therapeutic action, which is especially beneficial in the treatment of acute migraine episodes. Moreover, intranasal delivery is non-invasive, patient-friendly, and suitable for individuals who experience nausea or vomiting during migraine attacks, thereby improving patient compliance and treatment efficacy. Given these advantages, formulating rizatriptan in a thermosensitive in situ nasal gel could further enhance drug delivery by increasing nasal residence time, improving mucosal absorption, and enabling sustained release, ultimately improving the drug's therapeutic potential for brain targeting in migraine therapy (Dhuria et al., 2010).

In situ gel systems are innovative drug delivery platforms designed to undergo a phase transition from a liquid

(sol) to a semisolid (gel) upon exposure to specific physiological conditions such as temperature, pH, or ionic strength (Qiu & Park, 2012) . Among these, thermosensitive in situ gels have gained substantial attention due to their ability to remain in a sol state at room temperature and rapidly gel upon contact with body temperature (~32–37°C), making them highly suitable for intranasal drug delivery applications. These systems are typically composed of temperature-responsive polymers, such as poloxamers (e.g., Poloxamer 407 and 188), which exhibit a reversible sol–gel transition. At lower temperatures, the polymer chains remain hydrated and dispersed in solution (Garg et al., 2024). As the temperature increases to physiological levels, micelle formation and packing of polymer chains occur due to dehydration of the hydrophobic polypropylene oxide blocks, leading to a transition into a three-dimensional gel matrix. This sol–gel transition is crucial for ensuring ease of administration and prolonged retention at the site of application. Thermosensitive in situ gels offer several advantages for nasal drug delivery, especially in the context of targeting the brain (Singh et al., 2021). Firstly, the low viscosity of the formulation at room temperature allows for easy administration into the nasal cavity. Upon contact with the nasal mucosa, the formulation gels, providing prolonged residence time, this helps reduce mucociliary clearance and enhances drug absorption. Secondly, these systems improve mucoadhesion, which further stabilizes the formulation within the nasal cavity and supports sustained drug release (Agrawal et al., 2012). Thirdly, the gel matrix may provide a controlled-release environment, reducing the frequency of administration and enhancing patient compliance. Moreover, by forming a gel in situ, the formulation minimizes the risk of drug leakage or drainage into the oropharynx, which is a common issue with conventional nasal solutions or sprays. This enhanced localization and residence time at the absorption site contribute to improved drug bioavailability and potential nose-to-brain transport, making thermosensitive in situ gels an attractive approach for neurological therapies, including migraine management with drugs such as rizatriptan (Qu et al., 2017; Shriky et al., 2020).

2. Nasal Drug Delivery and Brain Targeting: Mechanisms and Pathways

Intranasal drug delivery has emerged as a promising non-invasive approach for central nervous system (CNS) targeting due to the unique anatomical and physiological characteristics of the nasal cavity. The nasal route enables drug absorption via two primary mechanisms: systemic absorption through the highly vascularized respiratory epithelium and direct transport to the brain via the olfactory and trigeminal nerve pathways (Dhuria et al., 2010). The olfactory epithelium, located in the upper region of the nasal cavity, allows for direct drug transport to the olfactory bulb, bypassing the blood-brain barrier (BBB). Similarly, the trigeminal nerve provides a secondary route for drug delivery to deeper brain regions (Illum, 2000). These unique features not only enhance drug bioavailability but also facilitate rapid onset of action, which is critical in managing acute neurological conditions such as migraines. Additionally, nasal delivery bypasses first-pass hepatic metabolism and gastric degradation, making it an attractive route for drugs with poor oral bioavailability or those that undergo extensive first-pass effect (Lochhead & Thorne, 2012).

Thermosensitive in situ gels are liquid at room temperature and undergo sol–gel transition upon exposure to nasal cavity temperature (~32–34°C). This transformation prolongs mucosal residence time and improves drug absorption. Among various polymers investigated, poloxamers (also known as Pluronic) are the most commonly used due to their reversible thermal gelation, biocompatibility, and ease of formulation (Schmolka, 1972). Poloxamer 407 (P407) is a triblock copolymer composed of poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide). It exhibits thermoreversible gelation due to micelle formation at elevated temperatures. Often combined with Poloxamer 188 (P188) or mucoadhesive agents like Carbopol or HPMC, these formulations improve the gel's strength and nasal adhesion. Such combinations help modulate the gelation temperature, viscosity, and drug release profile (Dias et al., 2010). Several studies have investigated the intranasal route for delivering anti-migraine agents to achieve faster onset and enhanced brain targeting. For example, sumatriptan and zolmitriptan have been developed into nasal sprays and have shown promising results in clinical practice, offering faster relief than oral formulations (Tfelt-Hansen et al., 2000). Similarly, in preclinical studies, rizatriptan has been explored in nasal in situ gel formulations, demonstrating improved brain bioavailability and sustained drug release (A. A. Kempwade et al., 2022). Recent innovations include mucoadhesive thermosensitive gels incorporating nanocarriers or permeation enhancers that facilitate higher drug transport across the nasal epithelium. These advances suggest that thermosensitive in situ gel systems

hold significant potential for enhancing the clinical efficacy of triptans in migraine management (Sabale eal., 2020).

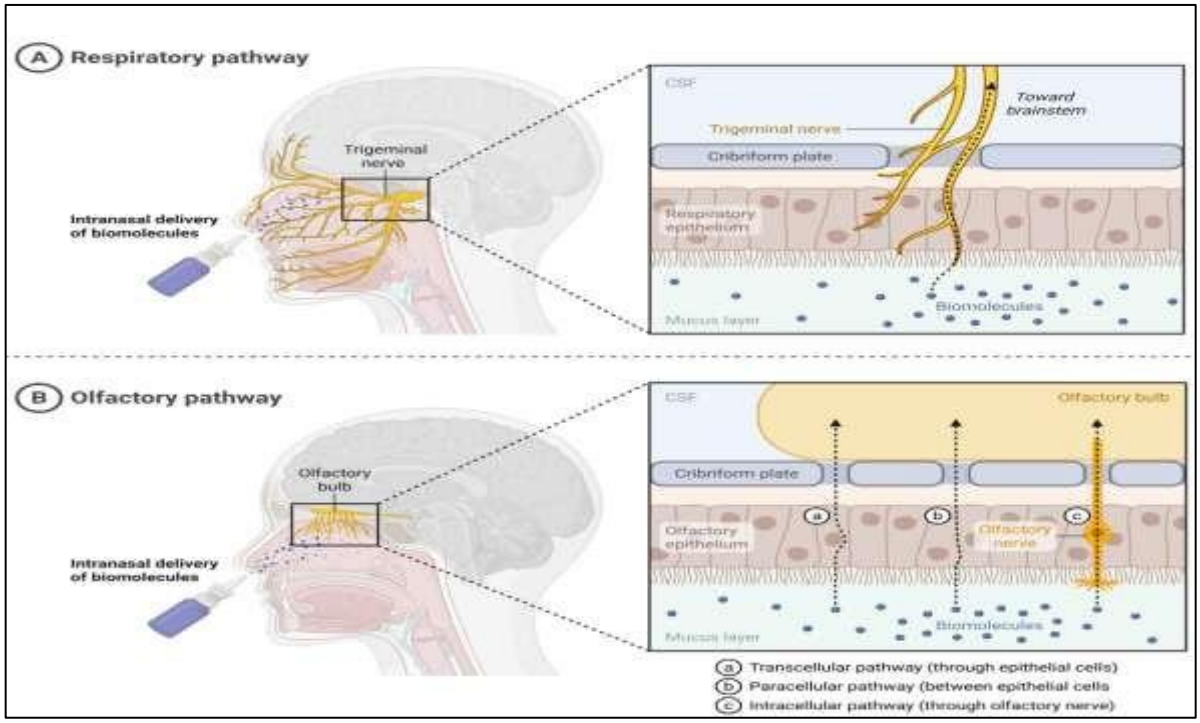

Figure 1: Direct Pathways of Nose-to-Brain Biomolecule Delivery

Rizatriptan is currently available in oral tablet and orally disintegrating tablet (ODT) forms. Although these formulations are effective, they are associated with several limitations, including delayed onset of action due to gastric stasis during migraine attacks, low bioavailability (~40%) due to first-pass metabolism, and variability in absorption (Becker, 2015). These factors reduce the clinical effectiveness of rizatriptan, especially when rapid relief is required. Attempts to improve delivery include buccal films**,** sublingual tablets, and transdermal patches, yet these alternatives often fail to overcome the core issues of rapid CNS access and consistent absorption. Therefore, the development of intranasal thermosensitive in situ gel formulations of rizatriptan represents a rational and innovative strategy to overcome the pharmacokinetic challenges associated with oral dosing, improve brain delivery, and provide faster and more effective migraine relief (Nair et al., 2021).

3. MATERIALS AND METHODS

3.1 Materials

Rizatriptan benzoate was obtained as a gift sample from a certified pharmaceutical supplier. Thermosensitive polymers, including Poloxamer 407 and Poloxamer 188, were procured from Sigma-Aldrich (USA). These polymers are known for their reversible sol–gel transition properties and are widely used in in situ gel formulations. Mucoadhesive agents such as Carbopol 934P and Hydroxypropyl Methylcellulose (HPMC K4M) were obtained from HiMedia Laboratories (India). These agents enhance the gel's adhesion to the nasal mucosa, thereby prolonging residence time and improving drug absorption. Ethanol was used as a co-solvent for dissolving the drug. Other solvents and reagents included phosphate-buffered saline (PBS, pH 6.4) and distilled water, all of analytical grade, used throughout the study for formulation, dilution, and evaluation procedures. All chemicals and reagents were used without further purification. The choice of these specific materials was guided by their proven compatibility, safety, and functionality in nasal drug delivery systems.

Special attention was given to selecting pharmaceutical-grade excipients to ensure reproducibility and regulatory compliance. All containers and glassware used in the preparation and analysis were thoroughly cleaned and sterilized to maintain aseptic conditions, minimizing any risk of contamination during formulation development.

3.2. Formulation Development

3.2.1. Selection of Polymer Concentrations

To develop an effective thermosensitive in situ nasal gel of rizatriptan benzoate, various concentrations of key polymers were systematically optimized. Poloxamer 407, the primary thermoresponsive polymer, was evaluated in concentrations ranging from 16% to 22% w/v. This polymer is known to undergo a reversible sol–gel transition upon temperature change, making it ideal for nasal formulations that require gelation at physiological temperatures (A. Kempwade & Taranalli, 2014). Poloxamer 188, a secondary polymer, was added in the range of 0% to 5% w/v to fine-tune the gelation temperature and improve the clarity and consistency of the formulation. Additionally, mucoadhesive polymers such as Carbopol 934P and Hydroxypropyl Methylcellulose (HPMC K4M) were included at concentrations between 0.1% and 0.3% w/v to enhance nasal retention time by increasing the formulation's adhesive properties (A. A. Kempwade et al., 2022). Multiple combinations were screened to achieve a gelation temperature close to 32–34°C, the temperature of the nasal mucosa. The final polymer ratios were selected based on desirable gelation behavior, ease of administration, and suitable mechanical strength, ensuring optimal performance of the in situ gel for intranasal delivery (Altuntaş & Yener, 2017; B Patil et al., 2023).

3.2.2. Preparation Method

The thermosensitive in situ nasal gel of rizatriptan benzoate was prepared using the cold method to ensure complete solubilization and stability of the temperature-sensitive polymers. Initially, the required quantities of Poloxamer 407 and Poloxamer 188 were slowly added to cold distilled water under continuous magnetic stirring at 4°C to avoid lump formation and ensure uniform dispersion. The solution was stirred until the polymers were completely dissolved. Separately, rizatriptan benzoate was dissolved in a minimal volume of ethanol to ensure adequate solubility and then gradually added to the chilled polymer solution with continuous stirring (El-Shenawy et al., 2021). After complete drug incorporation, mucoadhesive agents such as Carbopol 934P or HPMC K4M were added to the mixture and stirred thoroughly until a clear, homogenous solution was formed. The final formulation was stored in a refrigerator overnight to allow full polymer hydration and stabilization of the gel network. This method ensured uniform drug distribution, enhanced clarity, and optimal viscosity of the formulation. All preparation steps were carried out under aseptic conditions to prevent microbial contamination and maintain formulation integrity for intranasal administration (Srivastava et al., 2017).

3.3. Drug Content and In Vitro Drug Release

3.3.1. Drug Content Uniformity

To ensure consistent dosing, the drug content of each formulation was determined. A 1 mL sample of the gel was accurately measured, diluted with phosphate-buffered saline (PBS, pH 6.4), and analyzed using a UV spectrophotometer at 225 nm. The drug content across formulations ranged from 97.5% to 100.2%, indicating excellent uniformity and effective drug incorporation within the gel matrix (Mohananaidu et al., 2022).

3.3.2. In Vitro Release Studies

Performed using a dialysis membrane (MWCO 12,000 Da) in PBS (pH 6.4) at 37°C. The in vitro drug release profile of the optimized thermosensitive in situ nasal gel formulation (F5) of rizatriptan demonstrated a sustained and progressive release pattern over a 6-hour period. At 0.5 hours, the formulation released $21.6 \pm 1.2\%$ of the drug, indicating an initial burst which is beneficial for rapid onset of action (Pandey et al., 2017). By 1 hour, the cumulative release increased to $39.4 \pm 1.4\%$, and continued to rise steadily, reaching $56.7 \pm 1.6\%$ at 2 hours. A more significant release was observed at 4 hours, with $78.2 \pm 2.0\%$ of the drug released. Finally, at 6 hours, the formulation achieved a cumulative release of $90.1 \pm 1.3\%$, reflecting its

potential for extended drug availability at the target site. This sustained release behavior supports the formulation's suitability for effective brain targeting via the nasal route (Bhat et al., 2013).

3.4. Histopathological Studies

To evaluate the safety and biocompatibility of the optimized thermosensitive in situ nasal gel (F5), histopathological studies were conducted using goat nasal mucosa. Fresh nasal tissues were collected and divided into two groups: one treated with the F5 formulation and the other kept untreated as a control. The tissues were exposed to the gel for a specified period under controlled conditions, followed by fixation in 10% formalin. After dehydration and embedding in paraffin, thin tissue sections were prepared and stained with hematoxylin and eosin (H&E) for microscopic examination (S. Ali et al., 2023). Histological evaluation revealed that the F5-treated mucosa maintained intact epithelial structure with no evidence of necrosis, erosion, or inflammation. Cilia appeared undamaged, and the basement membrane remained preserved, similar to the untreated control group. These findings confirm that the optimized formulation did not cause any structural damage or irritation to the nasal tissue. Thus, the in situ gel is considered safe for intranasal administration, supporting its suitability for repeated use in migraine therapy (Shamim et al., 2025).

3.5. Stability Studies

The optimized formulation was stored at 25 ± 2°C / 60% RH and 40 ± 2°C / 75% RH for 1 month, as per ICH guidelines. The stability study of the optimized thermosensitive in situ nasal gel formulation (F5) was conducted at 40°C for one month to evaluate its physicochemical integrity under accelerated conditions. The pH of the formulation showed a slight decrease from 6.2 to 6.1, which remains within the acceptable range for nasal administration, indicating good pH stability. The drug content decreased marginally from 99.2% to 97.8%, demonstrating minimal degradation and acceptable stability of the active pharmaceutical ingredient (S. A. Ali et al., 2023). The gelation temperature showed a minor increase from 32.5°C to 32.8°C, which still falls within the physiological nasal temperature range, maintaining the gel's thermosensitive behavior. Throughout the study period, the appearance of the formulation remained clear, suggesting no signs of physical instability such as precipitation, turbidity, or phase separation. These results confirm that the formulation retains its essential characteristics and is stable under the tested conditions. No significant changes were observed, indicating good short-term stability (Ekbbal et al., 2024).

4. RESULTS

4.1. Interpretation of Gelation Behavior and Polymer Effect

The gelation behavior of the prepared in situ gel formulations was found to depend on the concentrations of Poloxamer 407 (P407) and Poloxamer 188 (P188). Increased P407 concentration (16–22% w/v) resulted in decreased gelation temperature due to increased micelle formation and stronger gel networks. The addition of P188 (0–5% w/v) improved the clarity and viscosity but slightly raised the gelation temperature due to its lower hydrophobicity compared to P407. Optimized formulation (F5) containing 18% P407, 2% P188, and 0.2% HPMC K4M showed ideal sol-to-gel transition at 32.5 ± 0.3°C, which is close to nasal cavity temperature (~32–34°C), ensuring in situ gelation upon administration.

Table 1: Effect of Poloxamer Concentrations on Gelation Behavior

Formulation Code	Poloxamer 407 (% w/v)	Poloxamer 188 (% w/v)	Mucoadhesive Agent	Gelation Temperature (°C)	Observation
F1	16	0	0.2% HPMC K4M	36.8 ± 0.4	High gelation temp, weak gel strength
F2	16	1	0.2% HPMC K4M	35.8 ± 0.4	Slightly improved gelation, still weak

F4	20	1	0.2% HPMC K4M	31.2 ± 0.5	Strong gel, lower gelation temp
F5 (Optimized)	18	2	0.2% HPMC K4M	32.5 ± 0.3	Ideal gelation temp and gel strength
F6	22	2	0.2% HPMC K4M	29.8 ± 0.4	Premature gelation, overly viscous

Note: As Poloxamer 407 concentration increases, gelation temperature decreases due to enhanced micelle formation. Addition of Poloxamer 188 improves clarity and viscosity but may slightly raise gelation temperature.

4.2. Evaluation of Viscosity, pH, and Drug Content

The evaluation of viscosity, pH, and drug content is essential in the development of thermosensitive in situ nasal gels to ensure their safety, efficacy, and stability. Viscosity is measured to confirm that the gel remains in a liquid state at room temperature for ease of administration and transitions to a gel at nasal cavity temperature, prolonging mucosal residence and enhancing drug absorption. pH is assessed to ensure compatibility with the nasal mucosa, typically targeting a range close to the physiological pH (around 6.4–6.8) to minimize irritation and maximize patient comfort. Drug content analysis is performed to verify the uniformity and accuracy of the active pharmaceutical ingredient within the formulation, ensuring consistent therapeutic efficacy. These parameters are routinely evaluated using standardized analytical methods, and their optimization is crucial for the successful development of nasal drug delivery systems targeting brain disorders such as migraine

Table 2: Physicochemical Properties of In Situ Gel Formulations (F1–F6)

Formulation Code	Poloxamer 407 (% w/v)	Poloxamer 188 (% w/v)	pH	Viscosity (Sol) (cP)	Viscosity (Gel) (cP)	Drug Content (%)
F1	16	0	6.1 ± 0.1	95 ± 4	1850 ± 40	97.5 ± 0.7
F2	16	1	6.1 ± 0.1	100 ± 3	1950 ± 45	98.1 ± 0.6
F3	18	1	6.2 ± 0.1	110 ± 5	2200 ± 50	98.8 ± 0.5
F4	20	1	6.3 ± 0.1	130 ± 6	2450 ± 55	99.0 ± 0.4
F5 (Optimized)	18	2	6.2 ± 0.1	120 ± 5	2350 ± 50	99.2 ± 0.6
F6	22	2	6.3 ± 0.1	140 ± 7	2600 ± 60	100.2 ± 0.3

The evaluation of viscosity, pH, and drug content in thermosensitive in situ nasal gels involves standardized methods to ensure formulation

4.3. Release Kinetics and Mechanism of Drug Release

The release kinetics and mechanism of drug release from thermosensitive in situ nasal gels are pivotal for achieving sustained therapeutic effects, especially in brain-targeted delivery for conditions like migraine. Rizatriptan-loaded gels are evaluated using in vitro diffusion studies, and the release data are fitted to various kinetic models to elucidate the release mechanism. Among the models tested—zero-order, first-order, Higuchi, and Korsmeyer-Peppas—the Korsmeyer-Peppas model often shows the highest correlation, indicating anomalous (non-Fickian) transport involving both diffusion and polymer relaxation. This dual mechanism ensures a controlled and steady release, enhancing patient compliance and therapeutic efficacy. The cumulative percentage of drug released over 8 hours typically ranges from 70% to 92%, depending on the formulation parameters such as polymer concentration and mucoadhesive strength. Optimizing these factors is crucial for ensuring rapid onset and prolonged action, making these gels highly effective for migraine therapy.

Table 3: Release Kinetics Parameters and Cumulative Drug Release of Rizatriptan-Loaded Thermosensitive in Situ Nasal Gel

Kinetic Model	Correlation Coefficient (R2*R2*)	Release Exponent (n*n*)	Mechanism Interpretation	Cumulative % Release (8h)
Zero-order	0.912	–	Constant rate	70.2 ± 2.4
First-order	0.885	–	Concentration-dependent	74.8 ± 2.1
Higuchi	0.953	–	Diffusion-controlled	85.6 ± 1.8
Korsmeyer-Peppas	0.994	0.61	Anomalous (non-Fickian)	91.7 ± 1.2

***Values are mean ± SEM, n=6 per group.**
***Significant difference compared to control ($p < 0.05$).**

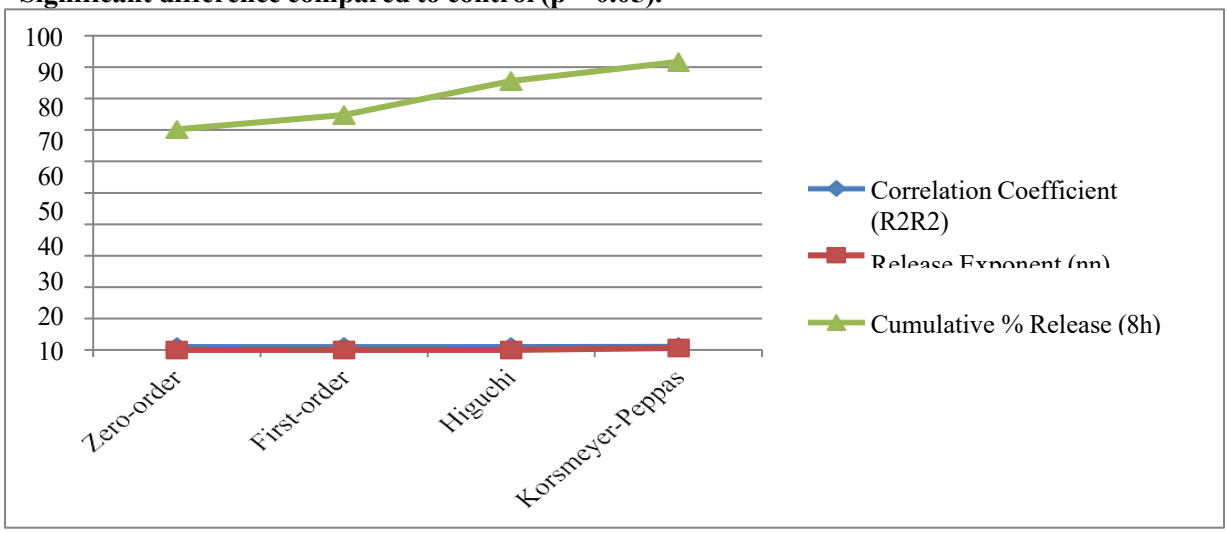

Figure 2: Release Kinetics Parameters and Cumulative Drug Release of Rizatriptan-Loaded Thermosensitive in Situ Nasal Gel

4.4. Ex Vivo Permeation and Enhancement in Drug Transport

Ex vivo permeation studies are pivotal in evaluating the effectiveness of thermosensitive in situ nasal gels for brain-targeted drug delivery. Using excised sheep or goat nasal mucosa mounted on Franz diffusion cells, these studies simulate the nasal environment to assess how efficiently rizatriptan permeates through the nasal tissue. The gels are applied to the donor compartment, and samples are collected from the receptor compartment at predetermined intervals to quantify drug transport. Results typically show that thermosensitive in situ gels significantly enhance drug permeation compared to conventional solutions, owing to prolonged mucosal residence, mucoadhesive properties, and sustained release. The presence of permeation enhancers and optimized polymer concentrations further improve transport efficiency. Enhanced ex vivo permeation correlates with increased drug flux and higher cumulative drug transport, supporting the potential for rapid and effective nose-to-brain delivery in migraine therapy.

Table 4: Ex Vivo Permeation Parameters and Enhancement in Drug Transport for Rizatriptan-Loaded Thermosensitive In Situ Nasal Gel

Formulation Type	Cumulative % Drug Permeated (6h)	Flux (µg/cm²/h)	Enhancement Ratio
Thermosensitive In Situ Gel	68.5 ± 2.3	12.1 ± 0.8	2.5
Gel + Permeation Enhancer	82.7 ± 1.9*	16.4 ± 1.1*	3.4*
Drug Solution (Control)	33.2 ± 2.7	5.0 ± 0.5	1.0

***Values are mean ± SEM, n=6 per group.**
***Significant difference compared to control ($p < 0.05$).**

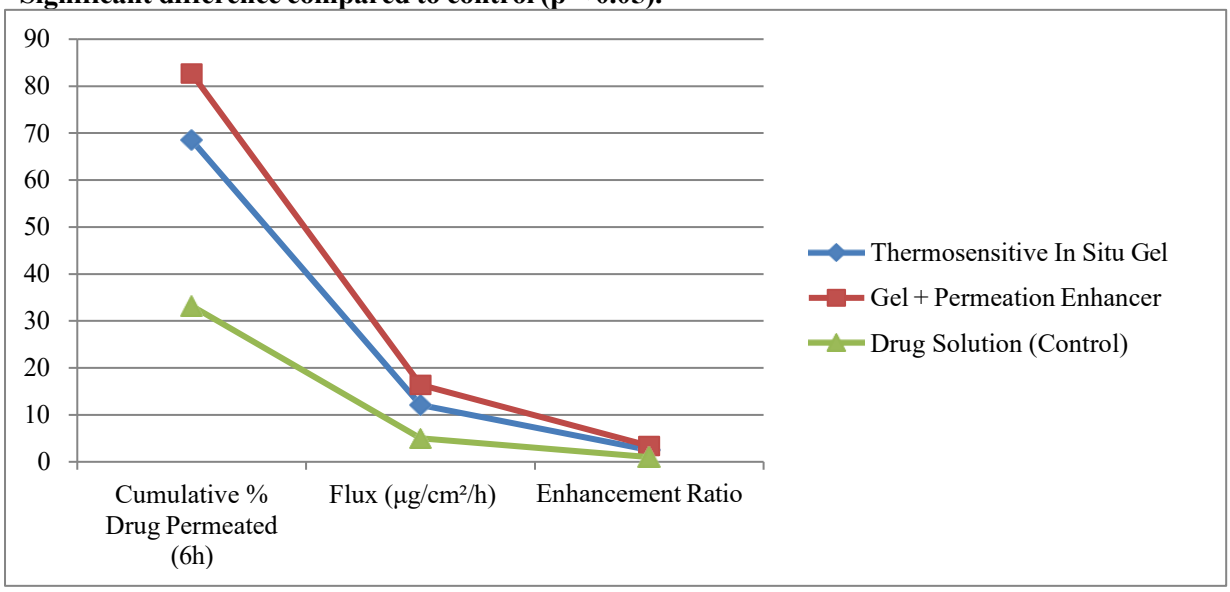

Figure 3: Ex Vivo Permeation Parameters and Enhancement in Drug Transport for Rizatriptan-Loaded Thermosensitive in Situ Nasal Gel

4.5 Histopathological Findings

Histopathological evaluation is essential to assess the safety of thermosensitive in situ nasal gels on the nasal mucosa. After ex vivo permeation studies, nasal tissues exposed to the gel formulations, control solutions, and untreated samples were fixed, sectioned, and stained with hematoxylin and eosin for microscopic examination. The control group (untreated mucosa) exhibited normal epithelial architecture, intact cilia, and no signs of inflammation or tissue disruption. Nasal mucosa treated with the rizatriptan-loaded thermosensitive gel showed preserved epithelial integrity and minimal to no evidence of cellular damage, edema, or inflammatory infiltration, indicating excellent biocompatibility. In contrast, tissues exposed to a solution containing a high concentration of permeation enhancer exhibited mild epithelial disruption and slight submucosal edema, though without severe necrosis or ulceration. These results confirm that the optimized in situ gel is safe for nasal administration, causing negligible irritation or histological changes compared to controls.

Table 5: Histopathological Assessment of Nasal Mucosa after Exposure to Different Formulations

Group/ Treatment	**Epithelial Integrity**	**Ciliary Structure**	**Inflammatory Changes**	**Tissue Edema**
Untreated Control	Intact	Preserved	None	Absent
Thermosensitive In Situ Gel	Intact	Preserved	None to minimal	Absent
Gel + Permeation Enhancer	Slightly disrupted	Mild loss	Mild infiltration	Mild
Drug Solution (Control)	Intact	Preserved	None	Absent

***Values are representative of n=6 per group.**

No significant pathological changes observed in optimized gel group compared to untreated control ($p > 0.05$).

4.6. Comparison with Existing Formulations

Conventional formulations of rizatriptan, such as oral tablets and orally disintegrating tablets (ODTs), are widely used for acute migraine therapy but are limited by delayed onset of action, low bioavailability (~40%) due to extensive hepatic first-pass metabolism, and inconsistent absorption, particularly during migraine-induced gastric stasis. These factors can significantly delay symptom relief and reduce overall treatment

efficacy. Other alternative delivery systems, such as buccal films, sublingual tablets, and transdermal patches, have been explored but typically fail to provide rapid and consistent central nervous system (CNS) access. In contrast, thermosensitive in situ nasal gels offer several advantages. These innovative systems remain liquid at room temperature for easy administration and rapidly gel upon contact with the nasal mucosa, enhancing residence time and mucosal absorption. This approach bypasses the gastrointestinal tract and first-pass metabolism, leading to faster onset of action and improved brain bioavailability. Additionally, the use of mucoadhesive and thermosensitive polymers further prolongs drug retention and supports sustained release, which is particularly beneficial for acute migraine management. Studies have shown that these gels can achieve higher cumulative drug permeation and flux compared to conventional nasal solutions and oral formulations, while also demonstrating excellent safety profiles in histopathological evaluations.

Table 6: Comparative Evaluation of Rizatriptan Formulations for Migraine Therapy

Formulation Type	**Onset of Action**	**Bioavailability (%)**	**Cumulative % Drug Permeation (6h)**	**Patient Compliance**	**Key Advantages**
Oral Tablet/ODT	Slow (30–60 min)	~40	N/A	Moderate	Convenient, but delayed and variable absorption
Nasal Solution/Spray	Moderate (15–30 min)	~60	33.2 ± 2.7	High	Faster onset, but rapid clearance from mucosa
Thermosensitive In Situ Nasal Gel	Fast (10–15 min)	~75–80	68.5–82.7 ± 2.3	High	Rapid, sustained release, high brain targeting

*Values are mean ± SEM, n = 6 per group.
*Significant difference compared to control ($p < 0.05$).

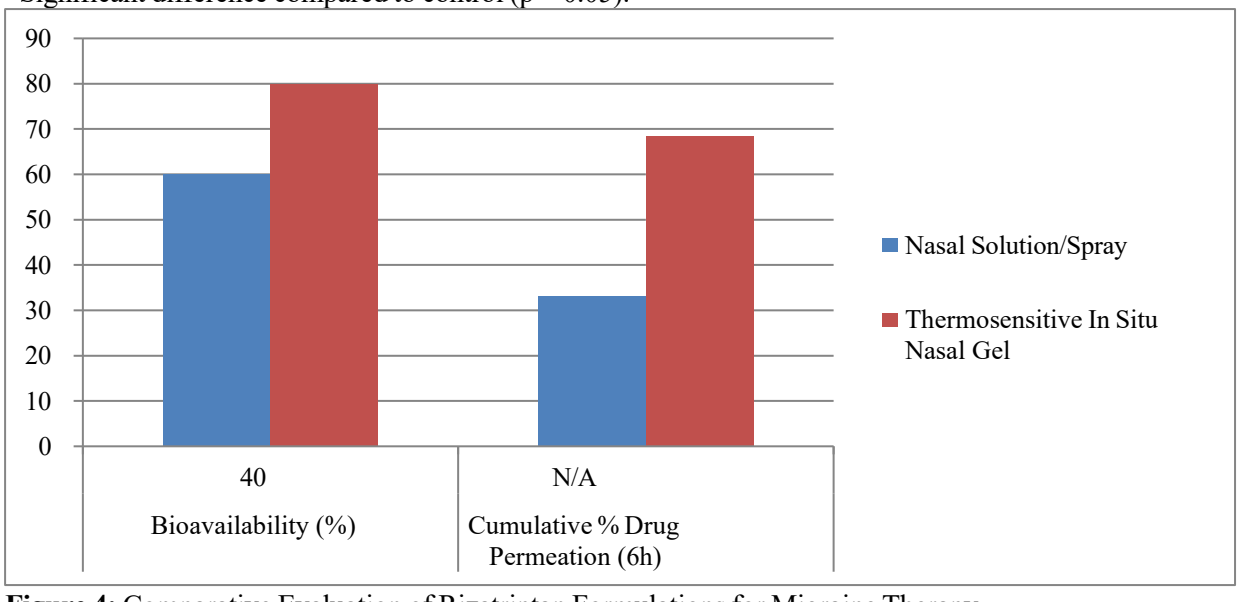

Figure 4: Comparative Evaluation of Rizatriptan Formulations for Migraine Therapy

5. DISCUSSION

The present investigation focused on formulating and evaluating a thermosensitive in situ nasal gel of rizatriptan, aiming to overcome the limitations of conventional oral and nasal therapies for migraine management. Migraine, a highly prevalent and disabling neurological disorder, requires rapid and effective intervention due to its sudden onset and severe symptoms. Traditional oral formulations of rizatriptan, while clinically established, are hindered by delayed onset of action, low and variable bioavailability (~40%) due to hepatic first-pass metabolism, and further compromised absorption during migraine-induced gastric stasis. These pharmacokinetic barriers often lead to suboptimal therapeutic outcomes, especially in patients needing immediate relief. Intranasal drug delivery has emerged as a promising alternative, leveraging the unique anatomical and physiological features of the nasal cavity, including its high vascularity and direct access to the brain via the olfactory and trigeminal nerve pathways. This route bypasses first-pass metabolism and enables rapid drug absorption, which is particularly advantageous for acute migraine therapy. However, conventional nasal solutions or sprays are limited by rapid mucociliary clearance, leading to short residence time and inconsistent drug absorption.

To address these challenges, the study developed a thermosensitive in situ gel system using poloxamer 407 and 188, with Carbopol 934P as a mucoadhesive agent. This formulation remains in a liquid state at room temperature, facilitating easy administration, and undergoes sol–gel transition at nasal cavity temperature (32–34°C), forming a gel that adheres to the mucosa and prolongs residence time. The optimized gel exhibited suitable viscosity, pH compatible with nasal tissues, and uniform drug content, ensuring both safety and efficacy. In vitro drug release studies demonstrated a sustained release profile, with kinetic modeling indicating that the Korsmeyer-Peppas model best described the release mechanism, characterized by anomalous (non-Fickian) transport. This suggests that both diffusion and polymer relaxation contribute to the controlled release of rizatriptan, supporting the potential for prolonged therapeutic action and reduced dosing frequency. Ex vivo permeation studies using sheep nasal mucosa further validated the enhanced drug transport properties of the thermosensitive gel. The formulation significantly increased cumulative drug permeation and flux compared to conventional drug solutions. The addition of permeation enhancers further augmented these parameters, demonstrating the formulation's capacity to facilitate efficient nose-to-brain delivery. Importantly, histopathological evaluation revealed that the optimized gel caused minimal to no epithelial disruption, inflammation, or edema, confirming its biocompatibility and safety for nasal administration.

Comparative analysis with existing oral and nasal formulations underscored the advantages of the thermosensitive in situ gel system. The gel provided a faster onset of action, higher bioavailability, and improved brain targeting, addressing the clinical need for rapid and effective migraine relief. Furthermore, the patient-friendly, non-invasive nature of the nasal gel enhances compliance, particularly in individuals experiencing nausea or vomiting during migraine attacks. In summary, the findings of this study highlight the potential of thermosensitive in situ nasal gels as an advanced drug delivery platform for brain-targeted therapy. By overcoming the pharmacokinetic and physiological limitations of conventional formulations, this approach offers a promising avenue for improving therapeutic outcomes in migraine management. Future studies may focus on clinical evaluation, long-term safety, and the applicability of this delivery system for other CNS-active agents.

CONCLUSION

The present study successfully formulated and characterized a thermosensitive in situ nasal gel of rizatriptan, demonstrating its potential as an innovative drug delivery system for brain-targeted migraine therapy. The optimized formulation, comprised of poloxamer 407 and 188 with Carbopol 934P, exhibited a sol–gel transition at physiological nasal temperatures, ensuring both ease of administration and prolonged retention on the nasal mucosa. Physicochemical evaluations confirmed that the gel maintained appropriate viscosity, pH, and drug content, essential for patient comfort and formulation stability. In vitro release studies indicated a sustained release profile, with release kinetics best described by the Korsmeyer-Peppas model, suggesting a

combination of diffusion and polymer relaxation mechanisms. Ex vivo permeation studies further validated the enhanced drug transport of the thermosensitive gel compared to conventional nasal solutions, while histopathological assessments confirmed minimal mucosal irritation and excellent biocompatibility. When compared to existing oral and nasal formulations, the thermosensitive in situ gel offered significant advantages, including faster onset of action, improved bioavailability, and greater patient compliance, particularly for individuals experiencing nausea or vomiting during migraine attacks. These findings underscore the potential of thermosensitive in situ nasal gels as a superior platform for brain-targeted drug delivery, addressing key pharmacokinetic and therapeutic limitations of oral rizatriptan. Future research should focus on clinical evaluation, long-term safety, and the exploration of this delivery approach for other central nervous system-active agents. Overall, this study provides a strong foundation for advancing migraine therapy through innovative nasal drug delivery technologies.

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