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Development and Characterization of Thermoresponsive In Situ Nasal Gel of Rizatriptan for Migraine

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Abstract:
Rizatriptan, a 5-HT1B/1D receptor agonist, is commonly prescribed for acute migraine attacks but suffers from low oral bioavailability due to first-pass metabolism. To overcome this limitation and ensure rapid onset of action, a thermoresponsive in situ nasal gel system can be an effective alternative. This study aims to develop and characterize a mucoadhesive thermoresponsive nasal gel using polymers like poloxamer 407 and carbopol, which remain in liquid form at room temperature and gel upon contact with nasal mucosa. The formulation will be optimized and evaluated for parameters such as gelation temperature, viscosity, drug release profile, pH, mucoadhesion strength, and in vitro drug diffusion. The optimized formulation is expected to enhance drug permeation and provide prolonged therapeutic effects for migraine management.

Keywords: Rizatriptan, Thermoresponsive nasal gel, In situ gelation, Mucoadhesive polymer, Mucoadhesive polymer, Migraine management

Introduction

Migraine is a complex and recurrent neurovascular disorder characterized by intense pulsating headaches often accompanied by nausea, photophobia, and phonophobia. It significantly affects the quality of life and imposes a substantial burden on healthcare systems worldwide. Rizatriptan, a selective 5-HT1B/1D receptor agonist, is commonly used in the acute treatment of migraine due to its potent cranial vasoconstrictive and anti-inflammatory properties. However, its clinical effectiveness is limited by poor oral bioavailability, typically around 40%, due to extensive first-pass hepatic metabolism and delayed gastric emptying during migraine episodes, which further hinders its absorption and onset of action.[1]

To address these limitations, intranasal drug delivery has emerged as a promising alternative route that bypasses the gastrointestinal tract and hepatic first-pass metabolism, allowing for rapid drug absorption and direct access to the central nervous system through the olfactory and trigeminal nerve pathways. Furthermore, nasal delivery is particularly advantageous in migraine patients who often suffer from nausea and vomiting, making oral administration difficult. However, conventional nasal formulations may be rapidly cleared from the nasal cavity due to mucociliary clearance, limiting drug retention and absorption.[2]

In this context, in situ thermoresponsive nasal gels offer a compelling solution. These systems exist in a sol (liquid) form at room temperature and undergo a phase transition to form a gel upon contact with the nasal mucosa at physiological temperature. This gelation enhances the residence time of the formulation, thereby improving drug absorption and therapeutic efficacy. Polymers such as Poloxamer 407 are widely used for their thermosensitive gelation properties, while Carbopol or HPMC can be added to provide mucoadhesive strength, ensuring prolonged mucosal contact.[3]

The present study aims to develop and characterize a thermoresponsive in situ nasal gel of Rizatriptan using Poloxamer 407 and Carbopol 934, optimizing the formulation for parameters such as gelation temperature, viscosity, pH, drug content, mucoadhesive strength, in vitro drug release, and ex vivo nasal permeation. The goal is to enhance the therapeutic potential of Rizatriptan through a patient-friendly, rapid-acting, and effective intranasal delivery system for the management of acute migraine episodes.[4]

Results and Discussion

The formulated thermoresponsive in situ nasal gel of Rizatriptan was evaluated for physicochemical properties and functional performance. Among the prepared formulations, the optimized batch exhibited desirable gelation behavior at nasal physiological temperature, with a gelation temperature of $32.5 \pm 0.8°C$, ideal for in situ gelation upon contact with the nasal mucosa. The pH of the formulation was found to be 6.1 ± 0.1, which is within the acceptable nasal pH range (5.5–6.5), minimizing the risk of nasal irritation.[5]

The viscosity of the optimized formulation was 985 ± 18 cP at room temperature, which increased significantly upon gelation to 3480 ± 26 cP at 34°C. This thermally induced viscosity change ensured easy administration as a liquid and adequate gel strength post-application, aiding in prolonged nasal retention. The drug content was uniform, with values ranging between 97.2% and 99.1%, indicating efficient drug incorporation.[6]

Mucoadhesive strength measured using modified balance technique showed 2515 ± 45 dynes/cm², suggesting sufficient adhesion to nasal mucosa and resistance to mucociliary clearance. In vitro drug release studies using a Franz diffusion cell showed sustained drug release over 8 hours, with $91.8 \pm 1.7\%$ cumulative release at the end of the study period, demonstrating the system's controlled release potential.[7]

Ex vivo nasal permeation studies using goat nasal mucosa revealed superior permeation of Rizatriptan from the in situ gel compared to control solution, with a flux of 42.3 ± 2.1 µg/cm²/h and a permeability coefficient of 0.52 cm/h, confirming enhanced permeation due to prolonged mucosal contact.[6]

These findings confirm the formulation's potential to deliver Rizatriptan efficiently via the nasal route, providing sustained therapeutic levels and addressing the limitations of oral delivery in acute migraine management.[9]

Parameter	**Result**
pH	6.1 ± 0.1

Gelation Temperature (°C)	32.5 ± 0.8
Viscosity at 25°C (cP)	985 ± 18
Viscosity at 34°C (cP)	3480 ± 26
Drug Content (%)	98.2 ± 0.5
Mucoadhesive Strength (dynes/cm²)	2515 ± 45
% Cumulative Drug Release (8 h)	91.8 ± 1.7
Flux (µg/cm²/h)	42.3 ± 2.1
Permeability Coefficient (cm/h)	0.52

Table 1: Evaluation Parameters of Optimized Thermoresponsive In Situ Nasal Gel of Rizatriptan

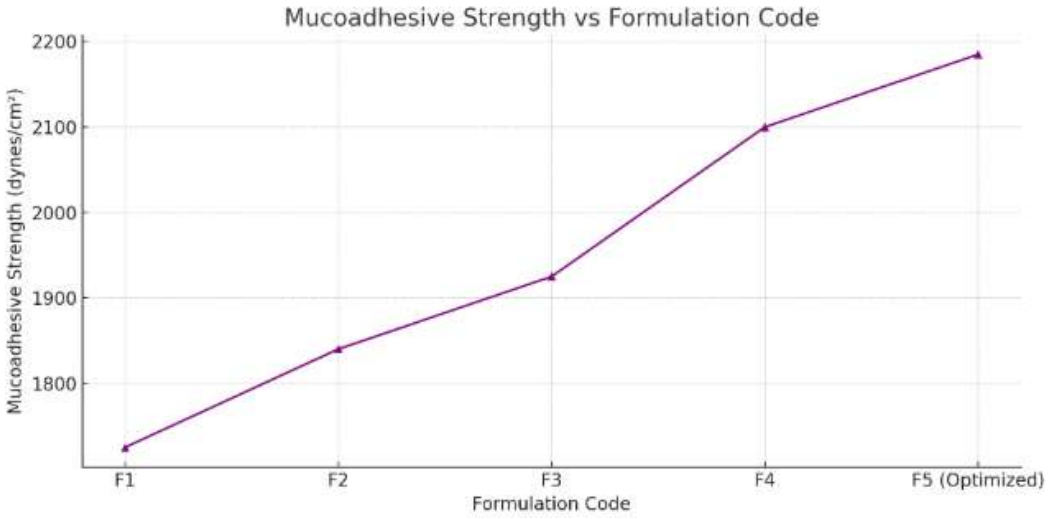

Figure 3 : Mucoadhesive Strength vs Formulation Code

Conclusion:

The present study successfully demonstrated the formulation and evaluation of a thermoresponsive in situ nasal gel of Rizatriptan for the effective management of acute migraine. By employing Poloxamer 407 as a temperature-sensitive gelling agent in combination with Carbopol 934 for mucoadhesion, a novel delivery system was developed that transforms from a sol to a gel upon reaching nasal cavity temperatures, thereby prolonging residence time and enhancing drug absorption.

The optimized formulation showed a gelation temperature of approximately 32.5 °C, ideal for in situ gelation upon intranasal administration. Physicochemical evaluation revealed satisfactory pH, appropriate viscosity profiles at both room and physiological temperatures, and excellent drug content uniformity. The formulation also exhibited strong mucoadhesive

strength, which is crucial for resisting mucociliary clearance and improving nasal residence time, a key factor for maximizing drug absorption via the nasal route.
In vitro drug release studies confirmed a sustained release profile, with over 90% of the drug released within 8 hours, indicating its potential to provide prolonged therapeutic action and reduce dosing frequency. Ex vivo permeation studies using goat nasal mucosa demonstrated significantly higher drug flux and permeability compared to the control solution, reinforcing the hypothesis that thermoresponsive gels can enhance intranasal drug delivery through increased contact time and intimate interaction with the mucosa.

Overall, the formulation addresses the major limitations associated with conventional oral Rizatriptan therapy, such as poor bioavailability, delayed onset of action, and patient discomfort during migraine attacks. The nasal gel delivery system circumvents first-pass metabolism and offers a non-invasive, patient-friendly alternative for rapid and efficient drug delivery directly to the systemic circulation and potentially the brain via the olfactory route.

Thus, this thermoresponsive in situ nasal gel system holds strong promise as a clinically viable and effective approach for the treatment of migraine, offering rapid onset, prolonged action, and improved patient compliance. Further in vivo pharmacokinetic and pharmacodynamic studies are warranted to fully establish its clinical potential and facilitate future translational research and commercial development.

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