Development and Evaluation of Rizatriptan benzoate Hybrid Nanoemulsion Loaded *In Situ* Nasal Gel for Migraine

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ABSTRACT

Background: Migraine is a disabling neurological disorder that demands rapid and effective therapeutic intervention. Rizatriptan benzoate (RZT), a Biopharmaceutics Classification System (BCS) Class III drug, exhibits limited oral bioavailability (40–45%) due to poor permeability and significant first-pass metabolism. **Aim:** This study aimed to develop a Hybrid Nanoemulsion (HNE) incorporated into an *in situ* nasal gel for nose-to-brain delivery of RZT. **Materials and Methods:** The RZT-HNE was formulated using probe sonication. The optimized HNE was integrated into an ion-sensitive *in situ* nasal gel. **Results and Discussion:** The optimized formulation (F8 with oleic acid 4ml and S_{mix} 1:1 ratio) exhibited a Particle size of 124 nm, and Entrapment Efficiency of 91%. Scanning Electron Microscopy confirmed spherical morphology. *In vitro* drug release studies revealed 74.3% release from F8 within 35 minutes, following Korsmeyer-Peppas kinetics ($R^2 = 0.9884$). An ion-sensitive *in situ* nasal gel formulated with gellan and xanthan gum, which demonstrated suitable viscosity, spreadability, and a rapid gelation time of 15 seconds. The *in situ* gel exhibited 53.6% drug release within 30 minutes and 78.1% cumulative release within 150 minutes, governed by non-Fickian diffusion ($R^2 = 0.9444$). **Conclusion:** These results indicate that the RZT-HNE *in situ* nasal gel offers a promising approach for enhancing bioavailability, circumventing first-pass metabolism, and providing a patient-centric, effective strategy for migraine management.

Keywords:
Migraine, Rizatriptan benzoate, Biopolymer, Hybrid nanoemulsion, *in situ* nasal gel, Gelling time, *in vitro* release.

INTRODUCTION

Migraine is a heterogeneous neurological disorder affecting approximately 15% of the global population, representing a significant public health burden.[1] It is characterized by recurrent, debilitating headaches often accompanied by nausea, photophobia, and phonophobia. The pathophysiology, though not fully elucidated, involves activation of the trigeminovascular system and neurogenic inflammation.[2, 3]

Rizatriptan benzoate (RZT) is a selective serotonin (5-HT1B/1D) receptor agonist effective in the acute treatment of migraine. Its mechanism involves cranial vasoconstriction, inhibition of nociceptive transmission, and reduction of neurogenic inflammation.[4, 5] However, as a BCS Class III drug (high solubility, low permeability), it suffers from limited oral bioavailability (approximately 47%) due to significant first-pass metabolism and pre-systemic degradation.[6, 7] This underscores the need for an alternative delivery route.

The intranasal route offers a non-invasive pathway for direct nose-to-brain delivery, bypassing the blood-brain barrier and hepatic first-pass metabolism.[8] Hybrid Nanoemulsions (HNEs), with their nanoscale droplet size, enhance drug solubility, mucosal permeability, and stability. Incorporating a nanoemulsion into an *in situ* gelling system can further improve residence time in the nasal cavity by undergoing a sol-to-gel transition upon contact with nasal fluid, thereby reducing mucociliary clearance and facilitating sustained drug release.[9, 10]

The objective of this study was to develop, characterize, and evaluate a novel hybrid nanoemulsion-loaded *in situ* nasal gel of Rizatriptan benzoate to achieve rapid and sustained drug delivery for effective migraine management.

MATERIALS AND METHODS

Materials:

Rizatriptan benzoate was obtained from J.K. Chemicals, Gujarat. Oleic acid was obtained from Finar Chemicals, Gujarat. Coconut oil was obtained from Kovai Agro Foods, Tiruppur. Tween 80, Tween 20, Polyethylene glycol 400, Sodium alginate, Poloxamer 407, HPMC K100M, Gellan gum, and Deionized water were obtained from The Precision Scientific Co., Coimbatore. Xanthan gum, Mannitol were obtained from SDFCL, Mumbai. All other chemicals and solvents used were of analytical grade.

Methods:

Preformulation Studies:

The drug was identified by its description, melting point, and solubility. A melting point apparatus (LABHOLIC LH-108) was used. Fourier Transform Infrared (FTIR) spectroscopy (JASCO 4600) was performed using the KBr pellet method to assess drug-excipient compatibility. Calibration curves of RZT were constructed in phosphate buffer (pH 6.8), distilled water, and simulated intranasal fluid using a UV-Vis spectrophotometer (SHIMADZU UV-1800) at λmax of 225 nm.[11-14]

Preparation of Hybrid Nanoemulsion:

Preparation of Drug-Biopolymer Complex:

Biopolymer-RZT (1:4 w/w) complexes were synthesized by blending the drug and biopolymer in deionized water and stirring magnetically at 25°C for 2 hours. This process yield ALG-RZT complexes, which served as the key active agents in the creation of hybrid nanoemulsions.

Preparation of Rizatriptan benzoate Hybrid Nanoemulsion (RZT-HNE):

A Rizatriptan-sodium alginate complex (1:4 w/w) was first prepared by magnetic stirring in deionized water for 2 hours. The RZT-HNE was then formulated using a probe sonicator (V-TECH VT-PROBE 250). Briefly, the drug-biopolymer complex was mixed with surfactant (Tween 20 or Tween 80) and co-surfactant (PEG 400) at different S_{mix} ratios (2:1 and 1:1). The oil phase (4 mL of oleic acid or coconut oil) was gradually added to the aqueous phase under continuous stirring, followed by probe sonication at 35°C with 45% amplitude for 30 minutes, as illustrated in Figure 1.[9, 15] Eight different formulations, designated as F1 to F8, were successfully prepared and systematically evaluated, as presented in Table 1.

Selection of Optimized RZT-HNE Based on Z-Average, Polydispersity Index (PDI) and Stability:

The prepared formulations were examined for Z-average, Polydispersity ex (PDI) and Stability.

Characterization of RZT-HNE:

Z-Average and Polydispersity Index:

Polydispersity index (PDI) and z-average particle size were determined using the Horiba SZ-100 analyzer at 25°C after 1:10 dilution in Milli-Q water. Mean ± SD values were recorded for three runs. PDI between 0.1–0.25 indicates uniform size distribution, while values above 0.5 reflect higher polydispersity.[16, 17]

Zeta Potential:

Zeta potential was evaluated using the Horiba SZ-100 instrument with a DTS1060 cuvette after 1:10 dilution. The measurement indicates particle stability through charge interactions, where values of ±30 mV or higher ensure sufficient electrostatic repulsion among droplets, preventing aggregation and improving nanoemulsion stability.[16]

Scanning Electron Microscopy (SEM):

Samples were dried and gold-sputtered before imaging under TESCAN MIRA3 XMU SEM at 20 kV. The analysis revealed spherical, uniform droplets with smooth surfaces, confirming the nanoemulsion's morphological integrity and successful dispersion without aggregation or surface irregularities.

pH:

The pH of the nanoemulsion was measured using a calibrated digital pH meter at 25°C. The undiluted sample was uniformly mixed, readings repeated thrice, and results reported as mean ± SD. The obtained values confirmed formulation suitability for nasal administration within physiological range.[18]

Drug Content:

A 0.2 mL aliquot was diluted to 2 mL with distilled water, centrifuged, and the supernatant analyzed at 225 nm using a UV–Vis spectrophotometer. Triplicate measurements provided mean ± SD values, confirming consistent and acceptable drug content within the nanoemulsion dispersion.[19]

$$\text{Drug content} = \frac{\text{Amount of drug obatined}}{\text{Total amount of drug added}} \text{X } 100$$

Encapsulation Efficiency:

Encapsulation efficiency (%EE) was evaluated using ultrafiltration-centrifugation. Briefly, 2 mL of the NLC dispersion was placed in centrifuge tubes and centrifuged at 10,000 rpm for 15 minutes at 20 °C. Free drug in filtrate was quantified at 225 nm, and %EE calculated by %EE = A/B × 100. Here, A represents the amount of RZT encapsulated, while B denotes the initial concentration of RZT, encapsulated drug A = (B – free drug) was determined. Results indicated efficient drug loading within the nanoemulsion matrix.[9]

Viscosity:

Viscosity of the nanoemulsion was assessed using a Brookfield viscometer with spindle 64 at 25°C across 10–100 rpm. Final viscosity at 100 rpm was recorded in centipoise (cP), confirming acceptable flow behavior suitable for nasal delivery consistency.[20]

***In vitro* Drug Release and Kinetics of RZT-HNE:**

Drug release was studied by the dialysis membrane method using phosphate buffer (pH 6.5) at 37 ± 0.5°C. A 5 mL nanoemulsion sample was placed inside the membrane sac and immersed in buffer. Aliquots were withdrawn every 5 minutes, replaced with fresh buffer, and analyzed at 225 nm to determine drug diffusion and sustained release profile.[21, 22] Release data were fitted into Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. These established rate constants, n-values, and mechanisms, distinguishing Fickian diffusion, non-Fickian transport, or case-II relaxation based on linear regression of cumulative drug release data.[23]

Preparation of RZT-HNE Loaded *In situ* Nasal Gel:

The optimized RZT-HNE(F8) was incorporated into an *in situ* nasal gel. Three distinct gel formulations, designated as G1, G2, and G3**,** were developed employing different gelling mechanisms: temperature-sensitive (Poloxamer 407 for G1), pH-sensitive (Carbopol 934P/HPMC K100M for G2), and ion-sensitive (Gellan gum/Xanthan gum for G3), as summarized in Table 2.[10, 24]

Characterization of RZT-HNE Loaded *In situ* Nasal Gel:

Physical Appearance:

Formulations were visually inspected for clarity, uniformity, and texture. Transparent and smooth appearance without any precipitation or coarse particles confirmed aesthetic quality and physical stability of the nasal gel preparation.

pH:

pH of formulations was determined using a calibrated digital pH meter at 25°C, performed in triplicate and expressed as mean ± SD. The results fell within the nasal physiological range, ensuring compatibility and non-irritancy upon administration.

Viscosity:

Viscosity was measured using the Brookfield viscometer with spindle 64 at 25°C. Values recorded across 10–100 rpm confirmed suitable consistency and rheology for facile extrusion and adequate nasal retention upon application.[20]

Homogeneity Study:

Homogeneity Study was performed by Visual inspection of formulations which confirms smooth texture and absence of lumps or granules, indicating uniform distribution of gel components and consistent homogeneity throughout the prepared nasal gel batch.

Syringeability:

Syringeability was examined by passing 1 mL of formulation through a 5 mL syringe fitted with a 20-gauge needle. Samples easily passing were marked "pass," verifying smooth flow and injectability of the nasal gel.

Spreadability:

Spreadability was determined by compressing gel between glass slides under a 1000 g weight for 5 minutes. The time required for slide movement indicated ease of spreading; higher values correlated with optimal spreadability and user comfort.

Gelling Time:

Gelling time was measured by adding nasal fluid to 2 mL of sol at 37°C. The time taken for sol-to-gel transformation was observed visually and recorded in seconds, ensuring rapid gelation upon administration.

Drug Content Estimation:

Gel formulations were diluted with phosphate buffer (pH 6.8) and analyzed spectrophotometrically at 225 nm. Triplicate readings were averaged to quantify the drug content, ensuring uniform drug incorporation across gel batches.

***In vitro* Drug Release and Kinetics of RZT-HNE *in situ* nasal gel:**

In vitro release was conducted using dialysis bag in phosphate buffer (pH 6.8) at 37 ± 0.5°C under 50 rpm stirring. Gel exposed to simulated nasal fluid was sampled at intervals, replaced with fresh buffer, and absorbance recorded at 225 nm. The results demonstrated controlled and prolonged drug release suitable for nasal absorption. Kinetic modeling of release data applied Zero-order, First-order, Higuchi, and Korsmeyer–Peppas equations. Regression (R^2) values identified release mechanism, typically diffusion-controlled, confirming sustained release behavior of the optimized gel formulation.[24, 25]

RESULTS

Preformulation Studies:

Identification of Drug by Description, Solubility and Melting Point:

The identification of Rizatriptan benzoate was confirmed through evaluation of its physical characteristics, solubility profile, and melting point. The drug appeared as a white to off-white crystalline powder with uniform texture and clarity, conforming to official standards. The melting point determined by the capillary method was 179.8ºC, which falls within the Indian Pharmacopoeia range of 178–182ºC, validating its purity and identity. Solubility assessment demonstrated high solubility in distilled water and appreciable solubility in methanol, DMSO, 0.1N HCl, and phosphate buffer (pH 6.8), indicating hydrophilic behavior and suitability for aqueous formulation systems. In contrast, limited solubility in ethanol suggests the necessity of alternative solvent systems for specific applications. These outcomes confirm the authenticity and consistency of the analyzed sample while providing insight into its physicochemical properties relevant to formulation design and stability across various pH conditions, particularly for nasal or oral delivery systems.

Calibration curve of Rizatriptan benzoate:

The maximum absorbance wavelength (λmax) of Rizatriptan benzoate was determined by UV scanning of a 10 µg/mL solution across distilled water, pH 6.8 phosphate buffer, and simulated intranasal fluid. A characteristic absorption peak was observed at 225 nm, indicating consistent spectral behavior across all media, which was used for subsequent analytical evaluations. Calibration curves constructed in pH 6.8 buffer, distilled water, and intranasal fluid within the 1–5 µg/mL concentration range exhibited linear relationships in accordance with Beer-Lambert's law. In pH 6.8 phosphate buffer, the regression equation was $y = 0.1287x + 0.0069$ with a correlation coefficient (R^2) of 0.9998, signifying high linearity and reliability. Distilled water and intranasal fluid showed correlation coefficients of 0.9984 and 0.9959, respectively, confirming excellent method reproducibility. These outcomes validate the selected wavelength (225 nm) and confirm the accuracy, linearity, and sensitivity of the UV spectrophotometric method for quantitative analysis of Rizatriptan benzoate

Compatibility Studies Using FT-IR Spectrophotometer:

The FTIR compatibility study confirmed no interaction between Rizatriptan benzoate and selected excipients. Characteristic peaks of the pure drug—N–H (3726, 3628 cm^{-1}), C=N (1340 cm^{-1}), and C=O (1745 cm^{-1}) were retained in all mixtures with sodium alginate, xanthan gum, and gellan gum. The absence of new or shifted peaks indicates no structural alteration, confirming chemical stability and compatibility for safe mucoadhesive or oral formulation development.

Development of Rizatriptan benzoate Hybrid Nanoemulsions:

The Rizatriptan benzoate Hybrid Nanoemulsions (RZT-HNEs) were formulated using the probe sonication method. RZT-HNEs was prepared as per the method suggested by Ribeiro LN *et al.,*2020 [9] Ahmad N *et al.,*2018 [15] with some modification. A basic advantage of this technique is its simplicity and low cost since there is no usage of organic solvents. Additionally, scale-up is simple with this method. The formulated RZT-HNEs were optimized based on Particle size, PDI, stability and characterized. Formulations are observed after a week (room temperature). Formulations containing coconut oil were phase separated and non-homogeneous.

Evaluation of Rizatriptan benzoate Hybrid Nanoemulsion:

Particle Size and Polydispersity Index:

The impact of the surfactant system and oil phase on the physicochemical properties of Rizatriptan benzoate Hybrid Nanoemulsions (RZT-HNEs) was comprehensively assessed. The mean globule size of the formulations (F1–F8) ranged between 124 and 209 nm, which falls within the ideal nanoscale range for effective nasal drug delivery, as presented in Table 3. The optimized concentrations remained within the safe limits specified in the Handbook of Pharmaceutical Excipients.

The observed PDI values ranging from 0.26 to 0.40, as presented in Table No. 4, indicate a narrow particle size distribution, confirming the formation of a uniform and stable nanoemulsion system. Typically, PDI values below 0.5 signify homogeneous dispersion with minimal particle aggregation, suggesting that the prepared formulations exhibited excellent uniformity and consistent droplet distribution throughout the system. [26]

Zeta Potential:

Zeta potential serves as a crucial indicator of nanoemulsion stability, reflecting the magnitude of electrostatic repulsion between dispersed droplets. Values exceeding ±30 mV typically signify robust stability and resistance to aggregation and phase separation (Mohammed *et al.*, 2020).[23] Among the tested formulations, F8 exhibited the highest negative zeta potential -32.5mV shown in Table No. 4, correlating with excellent physical stability. This observation aligns with Ribeiro *et al.,* (2020) [9], who reported that sumatriptan-loaded hybrid nanoemulsions with zeta potentials between −26 mV and −35 mV displayed improved dispersion and intranasal performance. The negative charge in F8 primarily arises from oleic acid, whose carboxylic group dissociates in aqueous media to produce negatively charged carboxylate ions ($–COO^-$). Furthermore, the presence of nonionic surfactants such as Tween 80 and PEG 400 may contribute to minor negative interfacial potential, enhancing droplet repulsion and stabilization.

Scanning Electron Microscopy:

A Scanning Electron Microscope (SEM) is an advanced analytical instrument that employs a focused beam of electrons to generate detailed surface images of solid materials. This technique provides high-resolution, three-dimensional-like visualization, enabling precise examination of surface morphology, texture, and topography. It is extensively utilized in fields such as materials science, nanotechnology, and pharmaceutical formulation to study particle size, shape, and structural characteristics.[27] Particle size and morphology of nanoparticles were studied by scanning electron microscopy (SEM). A detailed examination of the surface morphology demonstrated that the RZT-HNEs possessed a spherical shape with a smooth and uniform surface, as illustrated in Figure 2.

pH and Viscosity:

All RZT-HNE formulations displayed pH values between 4.8 and 6.3 (Table No. 4), which fall within the ideal nasal physiological range of 4.5–6.5. Among them, formulation F8 showed a pH of 6.3, indicating optimal compatibility with the nasal mucosa. [28, 29] Viscosity values ranged from 22 to 36 cP, with formulation F8 exhibiting the highest viscosity (36 cP), suggesting superior mucoadhesive properties and prolonged nasal residence time. [30]

Entrapment Efficiency and Drug Content:

Entrapment efficiency (%EE) and drug content are fundamental indicators of formulation stability and drug loading capacity. Formulation F4 showed an entrapment efficiency (%EE) of 85.2%, while F8 achieved a higher value of 91%, indicating superior drug encapsulation capability, as presented in Table 4**.** Drug content analysis showed 66% for F4 and 109% for F8, as shown in Table No. 4, within the acceptable 90–110% range (Johnson *et al.,* 2021).[33] Enhanced solubilization and uniform drug distribution accounted for the higher value.

***In Vitro* Drug release and Release Kinetics study:**

The *in vitro* drug release study revealed that formulation F8 exhibited a markedly higher and faster cumulative drug release compared to formulation F4 (Figure 3). At 10 minutes, F8 released 13.1% of the drug, whereas F4 released only 7.4%. After 35 minutes, the cumulative release reached 74.3% for F8 and 54.2% for F4 as shown in Figure 3.[36, 37, 38] Drug release kinetic modeling indicated that the Korsmeyer–Peppas model showed the highest correlation coefficient (r^2), suggesting a non-Fickian diffusion mechanism governed by both erosion and swelling processes.

Formulation of RZT-HNE loaded *In Situ* Nasal Gel:

The RZT-HNE loaded *in situ* nasal gels were formulated using the ionic gelation method, temperature and pH sensitive method under aseptic condition.[39] The formulation method and the best fit formulation of RZT-HNE loaded *in situ* nasal gel were selected based on gelation time and their characteristics. A basic advantage of this technique is its simplicity and low cost since there is no usage of organic solvents. Additionally, scale-up is simple with this method.

Characterization of RZT-HNE Loaded *In Situ* Nasal Gel:

Physicochemical Characterization:

Formulations G1 and G3 appeared white and homogeneous, while G2 was yellowish-white and non-homogeneous, indicating poor stability. Homogeneity studies confirmed that G1 and G3 were lump-free, but G2 contained small lumps, compromising uniformity. Syringeability tests showed G3 had smooth flow suitable for nasal use, whereas G1 had reduced and G2 failed syringeability. Spreadability values were G2 (58.9 $g \cdot cm \cdot sec^{-1}$), G1 (53 $g \cdot cm \cdot sec^{-1}$), and G3 (38.26 $g \cdot cm \cdot sec^{-1}$), with G3's lower value offset by rapid gelation and strength. pH values revealed G3 (6.0) within the nasal range, whereas G1 (6.8) and G2 (3.8) were beyond ideal limits, potentially affecting comfort.

Gelling Time:

In vitro gelation studies showed G3 had the fastest gelation time (15 seconds), attributed to gellan gum's ionotropic gelation in the presence of Na^+ and Ca^{2+}, while G1 required 75 seconds and G2 failed to gel properly.

Viscosity and Drug Content:

Viscosity analysis indicated G3 had low solution viscosity (30 cP) for ease of administration and high gel viscosity (767.8 cP) for sustained retention. Drug content evaluation showed G3 had the highest drug loading (93.4%), followed by G1 and G2.

***In Vitro* Drug Release:**

The *in vitro* release profile G3 showed a biphasic trend, featuring an initial burst release of 28.3% at 5 minutes and 42.5% at 15 minutes, followed by a sustained release reaching 61.3% at 60 minutes and 78.1% at 150 minutes, ideal for rapid onset and prolonged nasal delivery.[40, 43] The RZT-HNE loaded *in situ* nasal gel release profile was analyzed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models, with the highest r^2 value observed for the Korsmeyer–Peppas model, indicating non- Fickian diffusion involving both erosion and swelling mechanisms.

DISCUSSION

Hybrid Nanoemulsion:

Smaller globules enhance mucosal adhesion and facilitate permeation across the nasal epithelium, thereby improving absorption and therapeutic performance (Ullah *et al.*, 2023; Mahadev *et al.,* 2022).[25, 16] The surfactant-to-cosurfactant (S_{mix}) ratio strongly influenced droplet size and dispersion uniformity. Formulations with a 1:1 S_{mix} ratio yielded finer droplets and lower PDI (< 0.3) than those with a 2:1 ratio, as excessive surfactant concentrations destabilize the interfacial film, promoting coalescence (Kato and Nakamura, 2025; Luan *et al.,* 2019).[19, 18] The observed PDI values (0.26–0.40) as shown in Table No. 4 confirmed uniform nanoemulsion formation, consistent with findings by Mahadev *et al.* (2022).[16] The nature of the surfactant also affected system stability. Tween 20: PEG-400 combinations produced smaller globules than Tween 80: PEG-400, which is attributed to the higher hydrophilic-lipophilic balance (HLB = 16.7) of Tween 20, resulting in greater stabilization of hydrophilic drug-based emulsions (Ullah *et al.,* 2023; Branco *et al.,* 2020).[25, 21]

Oil phase studies showed that formulations with coconut oil exhibited phase separation within 24 hours, while oleic acid-based systems-maintained uniformity and physical integrity, as previously reported by Branco *et al.,* (2020) and Sarheed *et al.,* (2021).[21, 22] The improved stability is attributed to oleic acid's favourable polarity and viscosity. Additionally, incorporation of a sodium alginate–RZT complex increased continuous-phase viscosity, providing steric and electrostatic stabilization, thereby reducing droplet coalescence and Ostwald ripening, consistent with the work of Sarheed *et al.*, (2022).[22] Overall, optimized S_{mix} ratios, surfactant type, and oleic acid-based systems significantly enhanced droplet stability, confirming their suitability for nasal nanoemulsion formulations.

Mohammed *et al.,* (2020)[23] similarly observed a zeta potential of −31.92 mV in Tween 20-based Nigella sativa nanoemulsions, whereas Chuacharoen *et al*., (2019) [27] emphasized that optimal surfactant levels maintain balanced zeta potential essential for long-term stability. Collectively, these results confirm that controlled selection and concentration of lipids and surfactants are critical in establishing electrostatic stability. The high negative potential observed in F8 supports good colloidal dispersion, reduced coalescence, and enhanced pharmaceutical suitability for intranasal drug delivery. Scanning electron microscopy (SEM) analysis demonstrated that the RZT-HNEs were spherical with smooth and even surfaces, confirming the efficient formation of nanoemulsions. The high-resolution, three-dimensional images revealed uniform particle dispersion and consistent morphology, indicating excellent stability and structural uniformity of the developed nanoparticles (Figure 2).

The pH range observed ensures mucosal comfort and minimizes irritation, maintaining both drug stability and excipient compatibility (Sambhakar *et al.,* 2023; Elsewedy *et al.,* 2025). [28, 29] The enhanced viscosity of formulation F8 promotes improved mucoadhesion and sustained drug retention in the nasal cavity without affecting spreadability. Such rheological and physicochemical attributes are consistent with previous findings (Furubayashi *et al.,* 2007)[30], highlighting F8 as the most effective formulation for intranasal drug delivery.

For entrapment efficiency, The improvement in F8 is attributed to oleic acid and an optimized 1:1 S_{mix} ratio (Tween 80: PEG 400), which enhanced solubilization and interfacial stability. Oleic acid's ionizable carboxyl group aided in forming a stable lipid matrix, effectively entrapping the hydrophilic drug. Extended ultrasonication (40% amplitude) improved droplet uniformity, further increasing %EE. Similar enhancements were reported by Taher *et al.,* (2022) [31] and Eissa *et al.,* (2023).[32] For drug content, Comparable results were observed by Guareschi *et al.*, (2024) [34] and Siddique *et al.*, (2022) [35] in intranasal and micellar formulations. Overall, F8 demonstrated excellent entrapment efficiency and uniform drug content, supporting its suitability for stable and effective intranasal delivery of Rizatriptan benzoate.

The enhanced release behaviour of F8 can be attributed to its optimized composition containing oleic acid and a 1:1 S_{mix} ratio (Tween 80: PEG 400), which improved solubilization, droplet dispersion, and diffusion across the membrane. The presence of hydrophilic co-surfactant PEG-400 promoted efficient micelle formation and enhanced wettability, accelerating dissolution (Sarmad *et al.,* 2020).[36] Comparable findings by Jacob *et al.,* (2024)[37] and Das *et al.*, (2023)[38] also reported rapid release from nanoemulsions with reduced droplet size and improved interfacial stability. The faster release of F8 suggests improved drug diffusion and absorption, supporting its potential for rapid onset of action in acute migraine management. Conversely, the slower profile of F4 may result from higher polymeric content reducing diffusivity. Overall, F8's formulation attributes make it a promising candidate for intranasal delivery requiring efficient and immediate drug release.

***In situ* Nasal gel:**

The overall physicochemical evaluation confirmed G3 as the most optimized formulation for intranasal delivery of RZT-HNE. Its white, homogeneous appearance and physiological pH (6.0) ensure compatibility with nasal mucosa, minimizing irritation and maintaining formulation stability. The excellent syringeability and lump-free texture of G3 indicate superior uniformity and ease of administration compared to G1 and G2.

In vitro gelation studies showed distinct differences among formulations. G3 exhibited the fastest gelation time due to gellan gum's ionotropic gelation in the presence of Na^+ and Ca^{2+}, ensuring rapid *in situ* gel formation and mucosal retention (Qian *et al.,* 2025).[40] In contrast, G1 requires times, indicating slower temperature dependent sol–gel transition. G2 showed insufficient ion-induced gelation. Gadziński *et al.,* (2022) [41] confirmed that gellan-xanthan systems improve viscosity, while gellan drives rapid gelation.

Overall, G3 presented in Figure 4 possess optimized composition and fast gelation rate minimize leakage and enhance residence time, establishing its superiority for intranasal drug delivery applications. Viscosity and gelation studies confirmed G3 as the optimal formulation, showing low solution viscosity (30 cP) for easy administration and high gel viscosity (767.8 cP) for prolonged retention. Rapid gelation within 15 seconds, driven by gellan gum's ionotropic interaction with nasal cations, ensured effective mucoadhesion (Qian *et al.,* 2025).[40] In contrast, G1 showed slower gelation (75 seconds), and G2 failed to gel, consistent with Sherafudeen *et al.,* (2015).[42] G3's balanced viscosity and rapid gelation favor efficient nasal drug delivery.

G3 also demonstrated the highest drug content (93.4%), indicating uniform drug dispersion and formulation integrity. Despite slightly reduced spreadability, the rapid gelation and enhanced mucoadhesion compensate for this limitation.

The biphasic drug release profile observed in G3—characterized by an initial burst followed by sustained release—provides both rapid therapeutic onset and prolonged efficacy, which are ideal for managing acute migraine episodes. The burst phase, likely due to diffusion of surface or loosely bound drug molecules in the gellan gum matrix, aligns with Qian *et al.,*'s [40] findings of 30% release within 10 minutes in gellan-based nasal gels. The sustained phase, governed by diffusion and polymer relaxation, matches Lavania *et al*., [43] reports of 65–75% release over 2–3 hours, attributed to gellan's ion-activated gel network restricting drug release. Mahdi *et al.,*[44] noted similar biphasic kinetics, with gellan ensuring controlled release for enhanced bioavailability. G3's release profile, combining rapid therapeutic onset with sustained action, supports its potential for nasal administration.

CONCLUSION

A novel hybrid nanoemulsion-loaded *in situ* nasal gel of Rizatriptan benzoate was successfully developed and evaluated. The optimized nanoemulsion (F8 with oleic acid 4ml and S_{mix} 1:1 ratio) exhibited desirable nanometric properties and high encapsulation efficiency. The incorporation of this nanoemulsion into an ion-sensitive *in situ* gel (G3 formulated with gellan and xanthan gum) resulted in a formulation with suitable rheological properties, rapid gelation, and a biphasic drug release profile conducive for migraine treatment offering both rapid onset and sustained action. This innovative combinational approach holds significant promise for enhancing the nose-to-brain delivery of Rizatriptan benzoate, potentially improving therapeutic efficacy and patient compliance in the management of acute migraine attacks. Further *in vivo* studies are warranted to confirm these findings.

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Abbreviations:

RZT-HNE: Rizatriptan benzoate Hybrid Nanoemulsion.

BCS : Biopharmaceutical Classification System.

PDI : Polydispersity index.

FTIR : Fourier Transform Infrared spectroscopy.

SEM : Scanning Electron Microscope.

rpm : rotation per minute.

%EE : Entrapment Efficiency.

% CDR : Cumulative %drug release.

S_{mix} : Surfactant mixture.

PEG : Polyethylene glycol.

Conflict of Interest:

The author declares that there is no conflict of interest regarding the publication of this research work.

SUMMARY:

The present investigation aimed to design a novel intranasal drug delivery system for Rizatriptan benzoate to overcome the drawbacks of oral administration, such as low bioavailability and extensive first-pass metabolism. A hybrid nanoemulsion was developed using oleic acid as the oil phase and Tween 20 as the surfactant, employing the probe sonication technique for efficient emulsification. Among the prepared formulations, F8, containing a 1:1 ratio of Tween 20 and PEG 400 (Smix) with 4 mL oleic acid, exhibited superior properties, including a particle size of 124 nm, low polydispersity index (0.26), high zeta potential (–32.5 mV), and excellent entrapment efficiency (91%). In-vitro diffusion analysis using a dialysis bag indicated a rapid drug release of 74.3% within 35 minutes under nasal sink conditions. The optimized nanoemulsion was further incorporated into an ion-sensitive in-situ nasal gel formulated with gellan and xanthan gums to enhance mucoadhesion and residence time. The gel displayed a controlled release profile, with 53.6% of the drug released in 30 minutes and 78.1% at 150 minutes, fitting the Korsmeyer–Peppas model, confirming diffusion and polymer relaxation mechanisms. This hybrid nanoemulsion-loaded nasal gel provides an efficient, patient-friendly platform for rapid and sustained migraine management through improved nose-to-brain delivery.

FIGURES

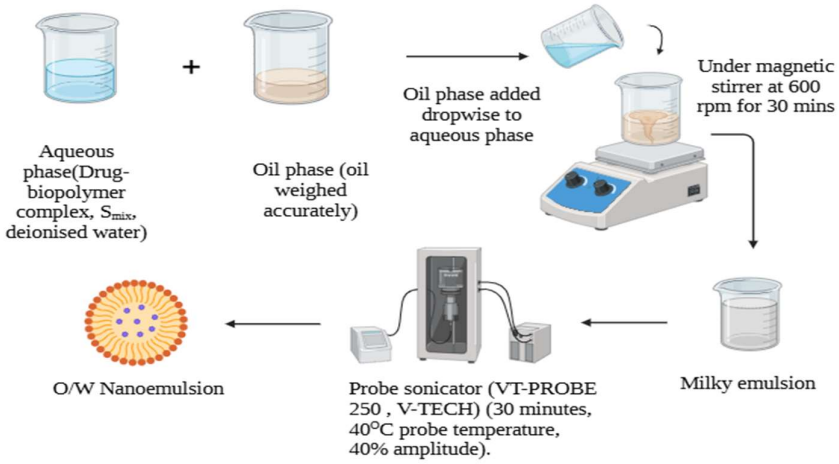

Figure 1.

Development of Rizatriptan benzoate Hybrid Nanoemulsion by probe sonication method

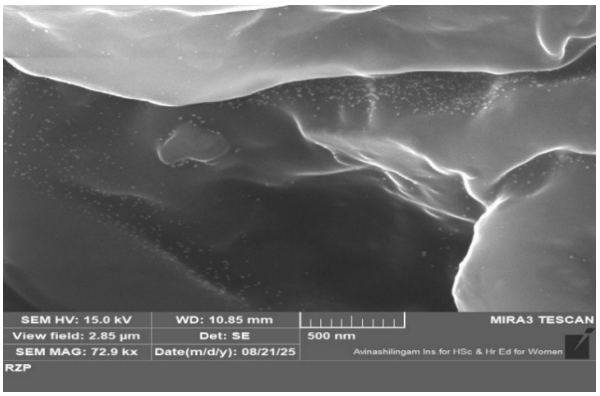

Figure. 2
SEM image of formulation F8

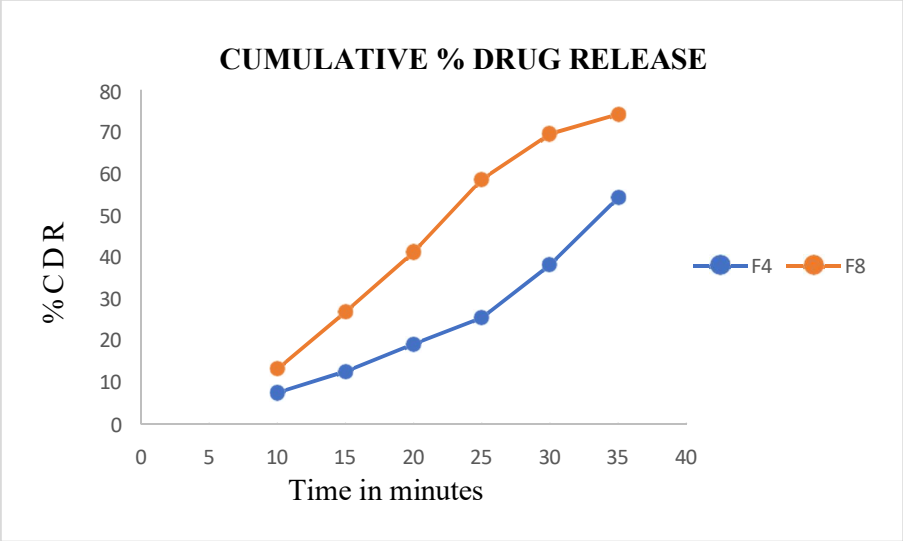

Figure 3.

Cumulative % drug release for formulation F8

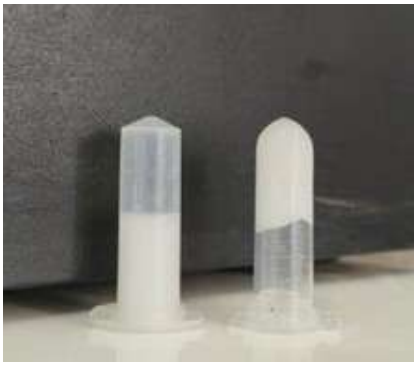

Figure 4.

Appearance of Sol and Gel

TABLES

Table 1.

Preparation of Rizatriptan benzoate Hybrid nanoemulsion

Formulation	Drug RZT (mg)	Biopolymer Sodium alginate (mg)	Oil (4ml)	S_{mix} Ratio (ml)	Deionized water
F1	10	2.5	Coconut oil	Tween-80:PEG 400(2:1)	Upto 50ml
F2	10	2.5	Coconut oil	Tween-20:PEG 400(2:1)	Upto 50ml
F3	10	2.5	Coconut oil	Tween-80:PEG 400(1:1)	Upto 50ml
F4	10	2.5	Coconut oil	Tween-20:PEG 400(1:1)	Upto 50ml
F5	10	2.5	Oleic acid	Tween-80:PEG 400(2:1)	Upto 50ml
F6	10	2.5	Oleic acid	Tween-20:PEG 400(2:1)	Upto 50ml
F7	10	2.5	Oleic acid	Tween-80:PEG 400(1:1)	Upto 50ml
F8	10	2.5	Oleic acid	Tween-20:PEG 400(1:1)	Upto 50ml

Table:2Preparation of Rizatriptan benzoate Hybrid nanoemulsion loaded *in situ* nasal gel

Trials	Gelling agent (%W/V)	Mannitol (% W/V)	PEG (% W/V)	Ethyl paraben (%W/V)	RZT-HNE (ml)	Deionized Water (upto 100mL)
G1	Poloxamer407: 18	0.15	0.2	0.1	20	q.s
G2	Carbopol 934P: 2 HPMC K100M: 0.5	0.15	0.2	0.1	20	q.s
G3	Gellan gum: 1.5 Xanthan gum: 0.25	0.15	0.2	0.1	20	q.s

Table 3.
Particle size of the formulated RZT-HNEs

Formulation	Particle size (nm)
F1	209
F2	196.7
F3	145.7
F4	134.2
F5	192.6
F6	174.7
F7	138.2
F8	124

Table 4.

Evaluation of Formulated RZT-HNEs

Parameters	Results	
	F4	**F8**
PDI	0.349	0.26
Zeta potential	-42.5mV	-32.5mV
pH	5.9	6.3
Viscosity	22cP	36cP
Entrapment Efficiency	85.2%	66%
Drug Content	91%	109%

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