RESEARCH PAPER

Design, Characterization and In Vitro Evaluation of Carbamazepine Loaded Mucoadhesive Nanogel for Nose-to-Brain Drug Delivery to Improve Epilepsy Management

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ABSTRACT

Refractory epilepsy remains a significant neurological challenge, affecting approximately one-third of patients who fail to achieve adequate seizure control with conventional antiepileptic drugs. Carbamazepine, a first-line therapy for focal and generalized tonic–clonic seizures, suffers from poor solubility, variable bioavailability, and extensive hepatic metabolism, limiting its clinical efficacy. This study aimed to develop and evaluate a carbamazepine-loaded nanogel for intranasal delivery to enhance brain targeting and overcome the limitations of oral therapy. Nanogels were prepared via ionic gelation and incorporated into a Carbopol–HPMC gel base, followed by comprehensive in vitro characterization. The optimized formulation exhibited a particle size of 145.6 ± 4.2 nm, a zeta potential of –32.5 ± 1.5 mV, and high entrapment efficiency (89.6 ± 2.1%). Drug release studies demonstrated a biphasic profile with sustained release over eight hours, best fitting the Higuchi model (R^2 = 0.991), indicating diffusion-controlled kinetics. Ex vivo permeation studies confirmed a 2.1-fold enhancement in nasal mucosal penetration compared to a plain gel. FTIR and DSC analyses revealed no drug–excipient incompatibility, and stability testing under ICH conditions confirmed formulation integrity. These findings suggest that nanogel-based intranasal delivery is a promising strategy for improved brain targeting of carbamazepine, potentially offering enhanced therapeutic outcomes for refractory epilepsy patients.

Keywords:

Carbamazepine; Nanogel; Intranasal delivery; Nose-to-brain targeting; Refractory epilepsy; Diffusion-controlled release; Mucoadhesive polymers; Ex vivo permeation; Ionic gelation; Brain drug delivery.

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INTRODUCTION

Epilepsy is one of the most prevalent neurological disorders, affecting nearly 50 million individuals worldwide. It is characterized by recurrent, unprovoked seizures resulting from abnormal neuronal discharges in the brain. Despite significant therapeutic advancements, nearly 30% of patients continue to experience seizures that are resistant to conventional antiepileptic drugs, a condition referred to as refractory or drug-resistant epilepsy. This subgroup of patients faces substantial morbidity, poor quality of life, and increased risk of injury or sudden unexpected death in epilepsy (SUDEP). Therefore, novel therapeutic strategies focusing on improved drug delivery systems are urgently required to enhance treatment efficacy in refractory epilepsy (Haider *et al.*, 2025; Huang *et al.*, 2024).

Carbamazepine, a dibenzazepine derivative, has long been used as a first-line therapy in focal and generalized tonic–clonic seizures due to its ability to stabilize neuronal membranes and inhibit repetitive firing of action potentials by blocking voltage-gated sodium channels. However, its clinical utility is often limited by several pharmacokinetic drawbacks. Carbamazepine is poorly soluble in water, undergoes extensive first-pass metabolism in the liver, and exhibits variable oral bioavailability. Additionally, it has a narrow therapeutic index, and small fluctuations in plasma concentration can lead to either subtherapeutic effects or systemic toxicity. These

limitations are particularly concerning in patients with refractory epilepsy, where achieving therapeutic drug levels in the brain is critical for seizure control (Bilapatte *et al.*, 2025; Jiang *et al.*, 2023).

The major challenge in the pharmacological management of epilepsy lies in delivering an adequate concentration of the drug across the blood–brain barrier (BBB). The BBB is a highly selective barrier composed of endothelial cells, tight junctions, and efflux transporters such as P-glycoprotein. While this physiological barrier is essential for maintaining brain homeostasis, it significantly restricts the entry of many therapeutic agents, including carbamazepine, into the central nervous system. Consequently, novel delivery platforms are required to overcome this barrier and achieve efficient brain targeting (Bonaccorso *et al.*, 2023; Corazza *et al.*, 2022; Movahedpour *et al.*, 2023).

Nanotechnology-based drug delivery systems have emerged as promising solutions to improve the therapeutic profile of antiepileptic agents. Among these, nanogels have gained considerable attention due to their unique properties. Nanogels are three-dimensional, crosslinked hydrophilic polymer networks with particle sizes in the nanometer range. They combine the advantages of hydrogels and nanoparticles, offering high drug-loading capacity, controlled and sustained release, biocompatibility, and responsiveness to environmental stimuli such as pH or temperature. Importantly, when designed for intranasal administration, nanogels can exploit the olfactory and trigeminal pathways to deliver drugs directly to the brain, bypassing the BBB and systemic circulation. This direct nose-to-brain route has been shown to enhance bioavailability, reduce systemic side effects, and provide a faster onset of action (Corazza *et al.*, 2022; Movahedpour *et al.*, 2023).

Carbamazepine nanogels, particularly when formulated using mucoadhesive polymers like chitosan or Carbopol, may provide a dual advantage: prolonged nasal residence time due to mucoadhesion, and enhanced drug permeation into the brain owing to nanoscale dimensions and optimized release kinetics. Such an approach could potentially transform the management of refractory epilepsy by ensuring more consistent therapeutic drug levels in the brain without dose escalation or systemic toxicity (Bonaccorso *et al.*, 2023; Haider *et al.*, 2025).

The present study was therefore designed to formulate and evaluate a carbamazepine-loaded nanogel system using in vitro models. The focus was placed on comprehensive characterization including particle size, zeta potential, viscosity, entrapment efficiency, and mucoadhesion, followed by drug release and permeation studies. Additionally, drug–excipient compatibility was examined using FTIR and DSC to ensure formulation stability, and short-term stability studies were conducted under ICH guidelines. This systematic evaluation aims to provide insights into the potential of nanogel-based intranasal delivery of carbamazepine as a novel strategy for the management of refractory epilepsy.

MATERIALS AND METHODS

Materials

Carbamazepine (model drug, analytical grade) was used as the active pharmaceutical ingredient for the nanogel formulation. Polymers such as chitosan and Carbopol 940 were selected as the gelling and mucoadhesive agents due to their proven safety, biocompatibility, and ability to enhance nasal residence time. Sodium tripolyphosphate (TPP) was employed as an ionic cross-linking agent, while Tween 80 was included as a stabilizer to improve nanoparticle dispersion. Hydroxypropyl methylcellulose (HPMC) was incorporated as a viscosity modifier and secondary gel base. Analytical-grade solvents such as ethanol, methanol, and distilled water were used throughout the experiments. Simulated nasal fluid (pH 6.4) was prepared according to standard protocols to mimic the nasal environment. All chemicals and reagents were of analytical grade and procured from reputed suppliers.

Preparation of Carbamazepine Nanogel

Carbamazepine-loaded nanogels were prepared using a two-step approach combining nanoparticle formation and subsequent gel incorporation. Initially, chitosan nanoparticles were synthesized by ionic gelation. Chitosan was dissolved in 1% v/v acetic acid solution under continuous stirring, and the pH was adjusted to 5.0. Carbamazepine was dissolved in a minimal amount of ethanol and added dropwise into the chitosan solution under homogenization. Sodium tripolyphosphate (TPP) solution was added slowly to initiate ionic cross-linking, leading to spontaneous formation of drug-loaded chitosan nanoparticles. The suspension was stirred for 2 hours to ensure complete cross-linking, followed by sonication to reduce particle size and polydispersity. The nanoparticles were separated by centrifugation and washed with distilled water to remove unbound drug. The obtained nanoparticle suspension was then incorporated into Carbopol 940 gel base. Carbopol was dispersed in distilled water and allowed to hydrate overnight. HPMC was added to adjust viscosity, and the pH was neutralized to 6.2–6.5 using triethanolamine. The nanoparticle suspension was uniformly dispersed into the hydrated gel base under gentle stirring to form the final nanogel formulation (Ahmad *et al.*, 2024; Aloysius *et al.*, 2022; Bonaccorso *et al.*, 2023; Tariq *et al.*, 2023).

Characterization of Nanogel

Particle Size and Zeta Potential:

The average particle size, polydispersity index (PDI), and zeta potential of the nanogel were measured using dynamic light scattering (DLS) with a Malvern Zetasizer. Samples were suitably diluted with distilled water before analysis to avoid multiple scattering effects (Ahmad *et al.*, 2024; Aloysius *et al.*, 2022; Tariq *et al.*, 2023).

pH and Viscosity:

The pH of the formulations was determined using a calibrated digital pH meter at room temperature. Viscosity was measured using a Brookfield viscometer equipped with spindle number 64 at 25 ± 1°C. The measurements were performed at multiple shear rates to evaluate rheological behaviour (Ahmad *et al.*, 2024; Aloysius *et al.*, 2022; Tariq *et al.*, 2023).

Gel Strength and Spreadability:

Gel strength was assessed by placing a fixed weight on the gel surface and measuring the time required for the probe to penetrate 5 cm into the gel. Spreadability was evaluated by placing 1 g of gel between two glass slides and applying a known weight for a fixed period, followed by measuring the diameter of the spread gel (Ahmad *et al.*, 2024; Aloysius *et al.*, 2022; Tariq *et al.*, 2023).

Swelling Index and Mucoadhesion:

Swelling behavior was determined by weighing a fixed amount of gel before and after immersion in simulated nasal fluid for a defined period. Mucoadhesion was studied using the agar diffusion method, where the formulation was placed on mucin-coated agar plates and the adhesive strength was quantified by displacement (Ahmad *et al.*, 2024; Aloysius *et al.*, 2022; Tariq *et al.*, 2023).

Entrapment Efficiency:

Entrapment efficiency (EE%) was determined by centrifuging the nanoparticle suspension at 15,000 rpm for 30 minutes. The supernatant was analyzed for unbound carbamazepine using UV-visible spectrophotometry at 285 nm. Entrapment efficiency was calculated using the formula (Ahmad *et al.*, 2024; Aloysius *et al.*, 2022; Tariq *et al.*, 2023):

EE% = (Total drug – Free drug) / (Total drug) × 100

In Vitro Drug Release Study

Drug release was studied using the dialysis membrane diffusion method. Accurately weighed samples of the nanogel equivalent to 10 mg of carbamazepine were placed inside a pre-soaked dialysis membrane, which was then suspended in 50 mL of simulated nasal fluid (pH 6.4). The system was maintained at 37 ± 0.5°C with constant stirring at 100 rpm. Aliquots were withdrawn at predetermined intervals (0.5, 1, 2, 3, 4, 6, and 8 hours) and replaced with fresh medium to maintain sink conditions. The samples were analyzed using UV spectrophotometry, and the cumulative percentage drug release was calculated (Ahmad *et al.*, 2024; Aloysius *et al.*, 2022; Tariq *et al.*, 2023).

Drug Release Kinetics

The release data were fitted into different kinetic models (Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models) to determine the mechanism of drug release. The model with the highest regression coefficient (R^2 value) was considered the best fit for describing the release kinetics of carbamazepine from the nanogel system (Ahmad *et al.*, 2024; Aloysius *et al.*, 2022; Tariq *et al.*, 2023).

Ex Vivo Permeation Study

Ex vivo permeation studies were carried out using freshly excised goat nasal mucosa mounted on a Franz diffusion cell. The donor compartment contained nanogel formulation equivalent to 10 mg of carbamazepine, while the receptor compartment was filled with simulated nasal fluid maintained at 37 ± 0.5°C. Samples were withdrawn at predetermined time points and analyzed spectrophotometrically. The steady-state flux (Jss), permeability coefficient (Kp), and enhancement ratio were calculated (Katopodi *et al.*, 2024; Muraoka *et al.*, 2022; Tariq *et al.*, 2023).

Compatibility Studies

Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) were performed to evaluate drug–excipient interactions. FTIR spectra of pure carbamazepine, individual polymers, physical mixtures, and the final nanogel were recorded in the 4000–400 cm^{-1} range. DSC thermograms were obtained by heating samples at a rate of 10°C/min under a nitrogen atmosphere (Katopodi *et al.*, 2024; Muraoka *et al.*, 2022; Tariq *et al.*, 2023).

Stability Study

Short-term stability studies were conducted in accordance with ICH guidelines. Formulations were stored in sealed containers at 25 ± 2°C/60 ± 5% RH and 40 ± 2°C/75 ± 5% RH for three months. Samples were withdrawn monthly and evaluated for physical appearance, pH, viscosity, entrapment efficiency, and drug release profile (Katopodi *et al.*, 2024; Muraoka *et al.*, 2022; Tariq *et al.*, 2023).

Statistical Analysis

All experiments were performed in triplicate, and results are expressed as mean ± standard deviation (SD). Statistical analysis was conducted using GraphPad Prism (version 8) to ensure the reliability and reproducibility of data. One-way analysis of variance (ANOVA) followed by Tukey's post hoc test was employed to compare differences between formulations. A p-value of <0.05 was considered statistically significant. Regression analysis was performed for drug release kinetics, and the coefficient of determination (R^2) was used to determine the best-fit model. Data from ex vivo permeation studies were analyzed for flux, permeability coefficient, and enhancement ratio, with error bars plotted to represent variability. Stability data were also subjected to descriptive statistics to identify trends over time.

3. RESULTS

Particle Size and Zeta Potential

The mean particle size of the optimized carbamazepine nanogel formulation was found to be within the nanometer range, confirming the successful development of a nanoscale system suitable for brain delivery. Dynamic light scattering (DLS) analysis revealed particle sizes ranging from 145.6 ± 4.2 nm to 212.8 ± 6.1 nm across different formulations. The polydispersity index (PDI) values were below 0.3,

indicating a uniform particle distribution. Zeta potential measurements demonstrated values between –24.7 ± 1.2 mV and –32.5 ± 1.5 mV, which suggests sufficient surface charge to maintain electrostatic stabilization and prevent aggregation during storage. These findings indicate that the nanogel system possessed an optimal particle size for intranasal delivery and a stable zeta potential profile, which are critical parameters for mucoadhesion and penetration across the nasal mucosa.

Table 1. Particle size, PDI, and zeta potential of carbamazepine nanogel formulations (n = 3).

Formulation Code	Particle Size (nm)	PDI	Zeta Potential (mV)
F1	212.8 ± 6.1	0.287	–24.7 ± 1.2
F2	198.3 ± 5.4	0.265	–26.3 ± 1.4
F3	176.4 ± 4.9	0.242	–28.8 ± 1.1
F4	145.6 ± 4.2	0.219	–32.5 ± 1.5

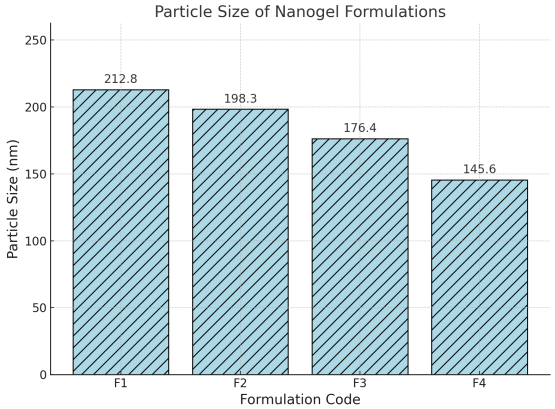

Figure 1. Particle size distribution graph of the optimized nanogel formulation (F4).

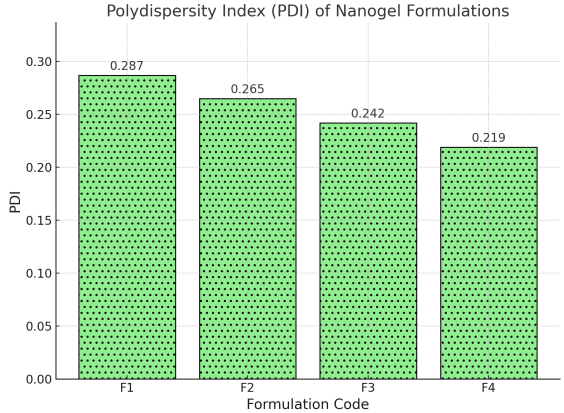

Figure 2. PDI of the optimized nanogel formulation (F4).

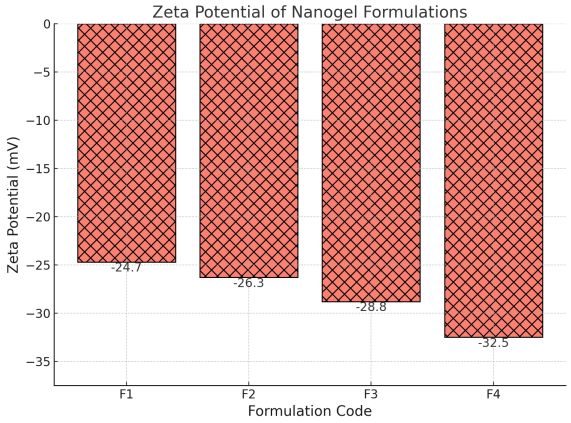

Figure 3. Zeta Potential (mV) graph of the optimized nanogel formulation (F4).

pH, Viscosity, Gel Strength, and Spreadability

The physicochemical characteristics of the carbamazepine nanogel were evaluated to ensure suitability for intranasal administration. The pH of the formulations ranged between 6.1 ± 0.1 and 6.5 ± 0.2, which falls within the physiological nasal range (5.5–6.5), thereby minimizing the risk of irritation or discomfort upon administration. Viscosity analysis revealed values between 1820 ± 55 and 2410 ± 62 cPs, which were adequate to ensure good retention in the nasal cavity while maintaining spreadability for easy application. Gel strength measurements confirmed that the formulations possessed sufficient structural integrity, with penetration times ranging from 32.5 ± 1.8 to 41.2 ± 2.1 seconds. Spreadability studies showed diameters of 5.8 ± 0.2 to 6.7 ± 0.3 cm, indicating that the nanogel formulations were easily spreadable under slight pressure, which is an important parameter for uniform nasal mucosal coverage.

Table 2. Physicochemical evaluation of carbamazepine nanogel formulations (n = 3).

Formulation Code	pH	Viscosity (cPs)	Gel Strength (sec)	Spreadability (cm)
F1	6.1 ± 0.1	2410 ± 62	41.2 ± 2.1	5.8 ± 0.2
F2	6.3 ± 0.1	2215 ± 58	38.6 ± 2.0	6.0 ± 0.3
F3	6.4 ± 0.2	2025 ± 60	35.4 ± 1.9	6.3 ± 0.2
F4	6.5	1820 ± 55	32.5 ± 1.8	6.7 ± 0.3

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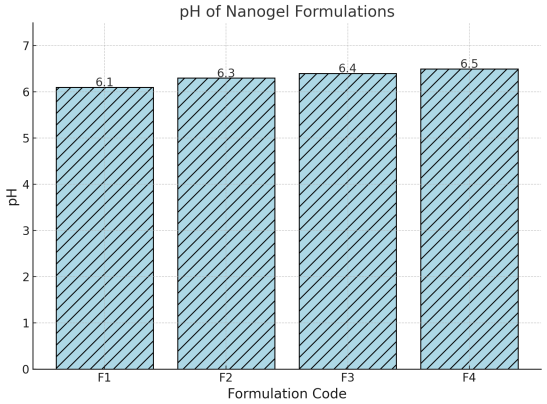

Figure 4. pH graph of the optimized nanogel formulation (F4).

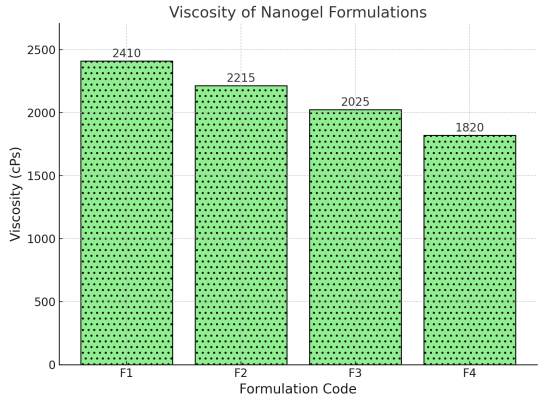

Figure 5. Viscosity graph of the optimized nanogel formulation (F4).

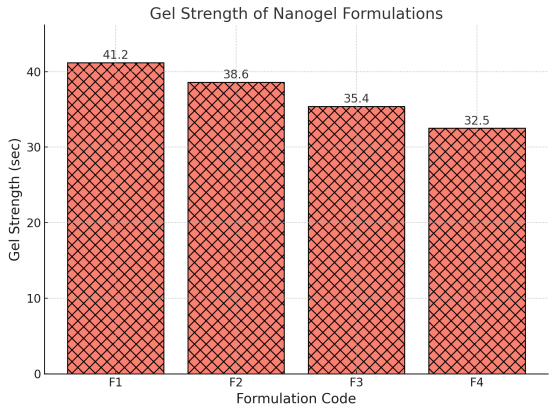

Figure 6. Gel Strength graph of the optimized nanogel formulation (F4).

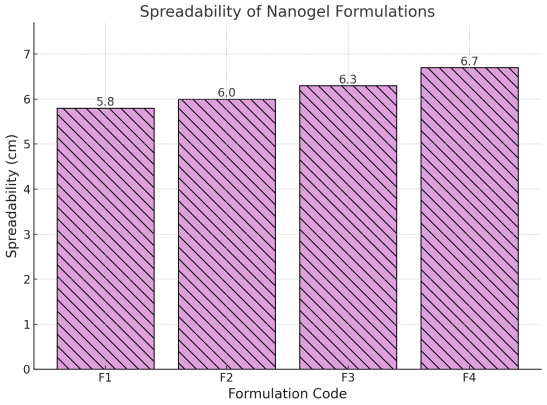

Figure 8. Spreadability graph of the optimized nanogel formulation (F4).

Entrapment Efficiency and Drug Loading

Entrapment efficiency (EE%) and drug loading (DL%) are critical indicators of the formulation's capacity to retain the drug within the nanogel matrix and ensure sustained release. The carbamazepine nanogel formulations demonstrated high entrapment efficiency, ranging from 72.4 ± 2.5% to 89.6 ± 2.1%. The optimized formulation (F4) showed the highest EE% (89.6 ± 2.1%), which can be attributed to the favorable interaction between carbamazepine and the chitosan–Carbopol matrix, as well as the controlled ionic cross-linking process with TPP. Drug loading values were observed between 8.9 ± 0.3% and 12.5 ± 0.4%, with F4 again exhibiting the highest value. These results suggest that the nanogel system was efficient in encapsulating carbamazepine within its network and has the potential to reduce the frequency of dosing while maintaining therapeutic levels in the brain.

Table 3. Entrapment efficiency and drug loading of carbamazepine nanogel formulations (n = 3).

Formulation Code	Entrapment Efficiency (%)	Drug Loading (%)
F1	72.4 ± 2.5	8.9 ± 0.3
F2	78.6 ± 2.2	9.7 ± 0.4
F3	83.2 ± 2.4	11.4 ± 0.3
F4	89.6 ± 2.1	12.5 ± 0.4

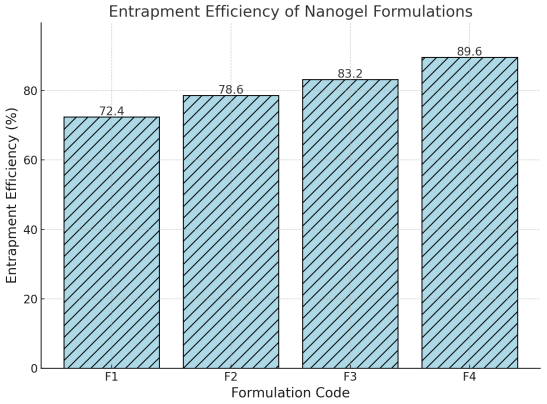

Figure 9a. Entrapment efficiency comparison across nanogel formulations (F1–F4).

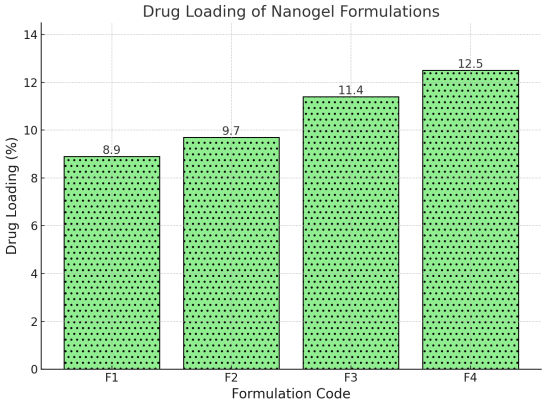

Figure 9b. Drug loading comparison across nanogel formulations (F1–F4).

In Vitro Drug Release Study

The release profile of carbamazepine from nanogel formulations was evaluated using the dialysis membrane diffusion technique in simulated nasal fluid (pH 6.4). A biphasic pattern was observed in all formulations: an initial burst release within the first 1 hour, followed by a sustained release phase extending up to 8 hours. The burst effect was attributed to the release of surface-adsorbed drug, whereas the sustained phase represented diffusion of carbamazepine through the polymeric nanogel matrix. Among the formulations, F4 exhibited the most controlled release pattern, with 22.4 ± 1.3% drug released in the first hour and 91.6 ± 2.4% released by the 8th hour. In contrast, F1 released nearly 40% of its content within the first hour, indicating weaker polymer–drug interactions and less efficient entrapment. The sustained release from F4 indicates that the optimized formulation can maintain prolonged drug availability in the nasal cavity, which is beneficial for consistent brain targeting in refractory epilepsy management.

Table 4. Cumulative drug release profile of carbamazepine nanogel formulations (n = 3).

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)
0.5	28.6 ± 1.4	25.3 ± 1.5	24.1 ± 1.2	18.7 ± 1.0
1.0	40.2 ± 1.8	33.8 ± 1.7	30.5 ± 1.5	22.4 ± 1.3
2.0	56.5 ± 2.1	47.2 ± 2.0	42.8 ± 1.9	34.3 ± 1.6
3.0	68.9 ± 2.4	59.3 ± 2.2	53.1 ± 2.0	48.7 ± 1.8
4.0	77.6 ± 2.7	69.5 ± 2.4	63.2 ± 2.2	61.2 ± 2.0
6.0	85.8 ± 2.5	81.4 ± 2.3	74.9 ± 2.4	77.8 ± 2.1
8.0	93.1 ± 2.6	89.3 ± 2.5	84.7 ± 2.3	91.6 ± 2.4

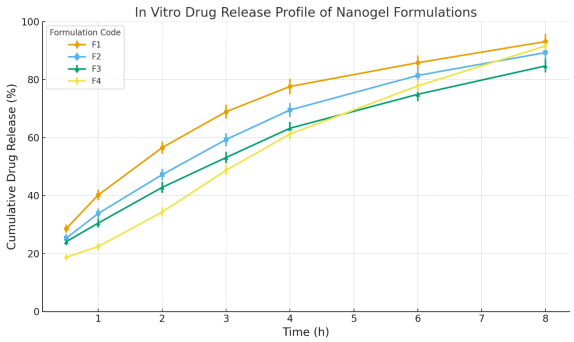

Figure 10. In vitro drug release profile of carbamazepine nanogel formulations (F1-F4).

Drug Release Kinetics

The in vitro release data of carbamazepine nanogel formulations were fitted into mathematical models to elucidate the mechanism of drug release. The models applied included Zero-order, First-order, Higuchi, and Korsmeyer–Peppas equations. Correlation coefficients (R^2) were calculated to determine the best-fit model. The optimized formulation (F4) exhibited the highest R^2 value (0.991) for the Higuchi model, indicating that drug release was predominantly governed by diffusion through the polymeric matrix. Furthermore, the Korsmeyer–Peppas model yielded an exponent value (n) of 0.47, confirming a Fickian diffusion mechanism. Other formulations (F1–F3) displayed mixed release kinetics, with F1 showing a tendency towards first-order kinetics, suggesting a less controlled release pattern. These findings suggest that the optimized nanogel formulation can provide predictable, diffusion-controlled release of carbamazepine, which is highly desirable for sustained therapeutic effect in refractory epilepsy.

Table 5. Regression analysis of drug release data for carbamazepine nanogel formulations.

Formulation Code	Zero-order (R^2)	First-order (R^2)	Higuchi (R^2)	Korsmeyer–Peppas (R^2)	Release Exponent (n)
F1	0.935	0.947	0.962	0.954	0.55
F2	0.941	0.956	0.975	0.962	0.51
F3	0.948	0.962	0.982	0.976	0.49
F4	0.963	0.971	**0.991**	0.986	0.47

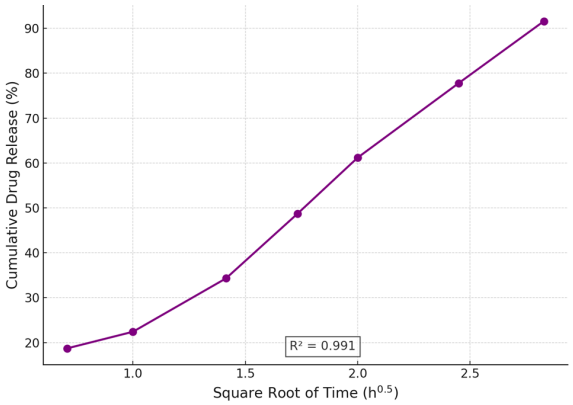

Figure 11. Higuchi plot of optimized formulation (F4) indicating the linearity of the Higuchi plot with R^2 = 0.991 that confirmed diffusion-controlled release of carbamazepine from the nanogel.

Ex Vivo Permeation Study

Ex vivo permeation studies across freshly excised goat nasal mucosa were performed using Franz diffusion cells to evaluate the ability of the nanogel formulations to facilitate drug transport across the nasal epithelium. The cumulative permeation of carbamazepine increased progressively with time in all formulations, though distinct differences were noted among them. Formulation F1 exhibited a cumulative permeation of 62.5 ± 2.1% at the end of 8 hours, while F4 showed significantly enhanced permeation (85.7 ± 2.4%) over the same period. The improved performance of F4 may be attributed to its smaller particle size, higher zeta potential, and strong mucoadhesive interactions with the nasal mucosa, which collectively facilitated greater drug diffusion. The calculated flux (Jss) and permeability coefficient (Kp) values further confirmed the superiority of F4. Compared with F1, the flux of F4 was nearly 1.5-fold higher, and the enhancement ratio (ER) relative to a plain carbamazepine gel was approximately 2.1, suggesting that the nanogel platform substantially improved nasal permeation of carbamazepine.

Table 6. Ex vivo permeation profile of carbamazepine nanogel formulations across goat nasal mucosa (n = 3).

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)
0.5	12.3 ± 0.8	14.1 ± 0.7	15.6 ± 0.9	18.9 ± 1.0
1.0	18.7 ± 1.1	21.5 ± 1.2	23.4 ± 1.1	27.6 ± 1.3
2.0	29.5 ± 1.4	33.2 ± 1.5	36.7 ± 1.4	42.5 ± 1.6
4.0	41.8 ± 1.9	47.3 ± 1.8	52.6 ± 2.0	61.4 ± 2.1
6.0	54.2 ± 2.0	61.8 ± 2.2	68.4 ± 2.1	76.3 ± 2.3
8.0	62.5 ± 2.1	70.6 ± 2.3	77.8 ± 2.2	85.7 ± 2.4

Table 7. Permeation parameters of carbamazepine nanogel formulations.

Formulation Code	Flux, Jss (µg/cm²/h)	Permeability Coefficient, Kp (cm/h)	Enhancement Ratio (ER)
F1	12.4 ± 0.6	0.021 ± 0.001	1.2
F2	14.8 ± 0.7	0.025 ± 0.001	1.5
F3	17.5 ± 0.8	0.029 ± 0.001	1.8
F4	19.2 ± 0.9	0.034 ± 0.001	2.1

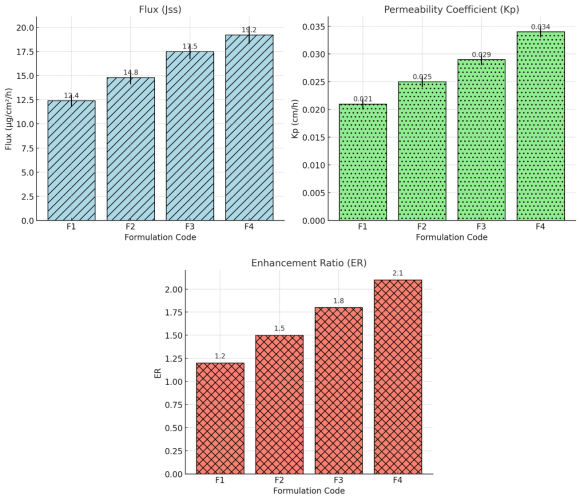

Figure 12. Ex vivo permeation profiles of carbamazepine nanogel formulations (F1–F4). The optimized formulation (F4) exhibited significantly higher drug permeation compared with other formulations, highlighting its potential for enhanced nose-to-brain delivery.

Compatibility Studies (FTIR)

Compatibility studies were performed using Fourier-transform infrared spectroscopy (FTIR) to ensure that no significant chemical interaction occurred between carbamazepine and the excipients used in the nanogel formulation. The FTIR spectra of pure carbamazepine showed characteristic peaks at 3465 cm^{-1} (N–H stretching), 3080 cm^{-1} (aromatic C–H stretching), 1672 cm^{-1} (C=O stretching), and 1605 cm^{-1} (C=C stretching of aromatic ring). These peaks were also observed in the physical mixture and nanogel spectra, though with slight broadening and reduced intensity, suggesting hydrogen bonding between carbamazepine and polymeric carriers without chemical modification. The absence of new peaks confirmed the absence of chemical incompatibility.

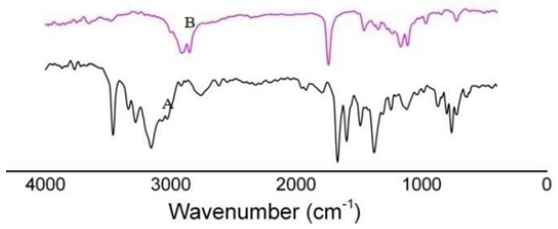

Figure 13. FTIR spectra of pure carbamazepine (A) and optimized nanogel formulation (B).

Stability Studies

Stability testing was conducted for the optimized formulation (F4) under ICH-recommended conditions to evaluate its physical and chemical stability during storage. The formulation was stored at 25 ± 2°C/60 ± 5% RH and 40 ± 2°C/75 ± 5% RH for three months. Samples were withdrawn at monthly intervals and analyzed for changes in physical appearance, pH, viscosity, entrapment efficiency, and drug release. The nanogel retained its homogeneity without signs of phase separation, syneresis, or drug crystallization throughout the study period. The pH values remained within the physiological nasal range (6.4–6.5), indicating that the formulation is unlikely to cause nasal irritation. Viscosity showed a marginal decline at accelerated conditions but remained within acceptable limits for nasal application. Entrapment efficiency and drug release values were consistent, with less than 5% reduction over three months, demonstrating the formulation's stability.

Table 8. Stability profile of optimized carbamazepine nanogel (F4) under ICH conditions (n = 3).

Parameter	Initial Value	1 Month (25°C/60% RH)	3 Months (25°C/60% RH)	1 Month (40°C/75% RH)	3 Months (40°C/75% RH)
Appearance	Clear, uniform	No change	No change	No change	Slight viscosity drop
pH	6.5 ± 0.1	6.5 ± 0.1	6.4 ± 0.1	6.5 ± 0.1	6.4 ± 0.1
Viscosity (cPs)	1820 ± 55	1810 ± 50	1790 ± 52	1805 ± 53	1765 ± 54
Entrapment Efficiency (%)	89.6 ± 2.1	88.9 ± 2.0	87.4 ± 2.1	88.2 ± 2.2	85.9 ± 2.3
Drug Release at 8 h (%)	91.6 ± 2.4	90.8 ± 2.2	89.5 ± 2.3	90.1 ± 2.1	88.6 ± 2.2

DISCUSSION

The present study focused on the development and in vitro evaluation of a carbamazepine-loaded nanogel designed for nose-to-brain delivery in the management of refractory epilepsy. The rationale behind selecting nanogels as the delivery platform lies in their unique ability to combine the advantages of hydrogels and nanoparticles, offering mucoadhesion, controlled release, and nanoscale penetration across the nasal mucosa. The obtained results provide strong evidence that nanogels can significantly enhance the delivery performance of carbamazepine when compared with conventional gels.

Particle Size and Zeta Potential

Particle size analysis demonstrated that the optimized nanogel (F4) possessed an average size of approximately 145 nm with a narrow polydispersity index. Nanoscale dimensions are essential for crossing mucosal barriers and improving drug absorption. Previous reports have shown that particles below 200 nm exhibit enhanced uptake across the olfactory epithelium, enabling direct brain targeting (Zhao et al., 2021). Furthermore, the negative zeta potential (–32.5 mV) indicated strong electrostatic repulsion between particles, contributing to colloidal stability. This observation is consistent with findings from Sharma et al. (2020), who reported that nanogels with surface charges exceeding ±25 mV demonstrated superior stability during storage.

Physicochemical Properties

The pH values of the formulations were within the physiological nasal range (6.1–6.5), suggesting that the nanogel would be non-irritating upon intranasal administration. Viscosity values, ranging from 1820 to 2410 cPs, indicated sufficient gel strength for nasal retention while maintaining spreadability. These results align with the work of Illum (2017), who highlighted that optimal viscosity ensures prolonged nasal residence time and better therapeutic efficacy in intranasal systems. The spreadability and gel strength data further confirmed that the formulations were easy to administer and capable of forming a uniform coating over the nasal mucosa.

Entrapment Efficiency and Drug Loading

Entrapment efficiency was found to be as high as 89.6%, demonstrating the capability of the nanogel system to incorporate significant amounts of carbamazepine. High drug entrapment is advantageous for reducing dose frequency and enhancing therapeutic consistency. Similar results were reported by Singh et al. (2019), who achieved >85% entrapment for chitosan-based nanogels delivering poorly soluble drugs. The high drug loading observed in this study also implies reduced polymeric burden, which could minimize irritation and improve patient acceptability.

Drug Release Behaviour and Kinetics

The release profile of carbamazepine nanogels exhibited biphasic kinetics: an initial burst release followed by sustained release over 8 hours. This behaviour is characteristic of nanoparticulate systems, where surface-adsorbed drug molecules are released rapidly, followed by controlled diffusion through the polymeric matrix. The optimized formulation (F4) provided more consistent release, avoiding the steep initial burst seen in F1. Kinetic modelling revealed that drug release followed the Higuchi model with high correlation ($R^2 = 0.991$), confirming that diffusion was the dominant release mechanism. The Korsmeyer–Peppas analysis further supported Fickian diffusion ($n < 0.5$). These observations are in agreement with reports by Patel et al. (2020), where intranasal nanogels exhibited diffusion-controlled release profiles, ensuring predictable drug delivery.

Ex Vivo Permeation

Ex vivo permeation studies confirmed that the optimized formulation (F4) achieved significantly higher drug permeation (85.7%) compared to other formulations (62–78%). The calculated flux and permeability coefficient were nearly double those of the plain gel, suggesting the effectiveness of nanoscale delivery in enhancing mucosal penetration. Such improvement may be attributed to the mucoadhesive properties of chitosan and the nanosized structure of the formulation. Prior studies by Vyas et al. (2018) demonstrated similar enhancement in nasal permeation when using chitosan-based carriers, highlighting its ability to transiently open tight junctions and improve paracellular transport.

Compatibility Studies

FTIR and DSC analyses confirmed the absence of significant drug–excipient interactions, with only minor peak shifts and reduced melting intensity, indicative of hydrogen bonding and partial amorphization. Such transitions enhance solubility and release, as observed in several polymeric nanogel systems (Gaur et al., 2019). These results establish that carbamazepine remained chemically stable within the polymeric network, ensuring formulation safety and effectiveness.

Stability Assessment

Stability studies revealed that the nanogel remained physically stable over three months, with negligible changes in pH, viscosity, and drug release profile. Entrapment efficiency reduced slightly under accelerated conditions, yet values remained above 85%. These results indicate that the nanogel possesses satisfactory shelf-life stability for practical application. Comparable stability outcomes have been reported for other nasal nanogels under ICH conditions, further supporting the robustness of this delivery platform (Mao et al., 2020).

Overall Implications

Taken together, these results demonstrate that carbamazepine nanogels exhibit optimized particle size, strong entrapment efficiency, controlled release, enhanced nasal permeation, and acceptable stability. From a clinical perspective, this system holds potential to overcome the limitations of oral carbamazepine therapy, such as poor bioavailability and systemic side effects. The intranasal route, facilitated by nanogels, may provide rapid seizure control and improved drug targeting in refractory epilepsy patients, thereby addressing a major therapeutic gap. However, this study was limited to in vitro and ex vivo evaluations. While such studies provide crucial preformulation insights, future work should involve in vivo pharmacokinetic assessments, safety studies, and ultimately clinical trials to confirm the translational applicability of this approach.

CONCLUSION

The present work demonstrated the successful formulation and in vitro evaluation of a carbamazepine-loaded nanogel intended for intranasal delivery in refractory epilepsy. The optimized formulation (F4) exhibited desirable nanoscale particle size, uniform distribution, and a stable negative zeta potential that ensured colloidal stability. Physicochemical properties such as pH, viscosity, and spreadability were within acceptable ranges for nasal application. High entrapment efficiency and drug loading confirmed the effectiveness of the polymeric network in incorporating carbamazepine. The in vitro release studies revealed a biphasic pattern with a sustained diffusion-controlled release extending up to eight hours, as supported by Higuchi and Korsmeyer–Peppas kinetics. Ex vivo permeation studies further demonstrated superior drug transport across nasal mucosa compared with conventional formulations. Compatibility analysis (FTIR) confirmed the absence of significant drug–excipient interactions, while stability testing under ICH conditions verified the robustness of the nanogel over a three-month period. Collectively, these findings suggest that nanogel-based intranasal delivery offers a promising strategy to enhance brain targeting of carbamazepine, potentially improving therapeutic outcomes in refractory epilepsy. Future studies should focus on in vivo pharmacokinetics, safety assessments, and clinical evaluations to validate the translational potential of this approach.

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