Journal of Young Pharmacists, 2026; 18(2):399-408.
https://www.jyoungpharm.org

Original Article

Development and Optimization of a Nasal *in situ* Gel for Enhanced Brain Delivery of Safinamide in Parkinson's Disease

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ABSTRACT

Background: Parkinson's Disease (PD) is the second most prevalent neurodegenerative disorder. Currently levodopa along with MAO-B inhibitors remains first line therapy for the management of motor complications. However, its conventional oral dosage forms face significant challenges in achieving effective drug delivery to the target site (the brain) due to the restrictive nature of the blood brain barrier. Strategy involves developing an optimized nasal *in situ* gel formulation for safinamide to enhance its delivery to the brain. **Materials and Methods:** Factorial design was adopted to develop and optimize Safinamide nasal *in situ* gel. Poloxamer 188 (A: 17.5-30%) and oleic acid (B: 1.25-1.5%) were chosen as the independent variables, while gelling time, mucoadhesive strength, and partition coefficient were designated as the dependent variables. **Results:** The formulations were evaluated for various parameters, such as drug content, pH, gelling temperature, viscosity, and *in vivo* properties. The optimal formulation, S1 (17.5%, 1.25%), achieved a body-temperature-appropriate gelation point of 37.8°C, while a higher polymer concentration (S9:30% w/w) increased it to 39.3°C. All gels exhibited a nasal-friendly pH range (7.1-7.5) and high drug content (96.4-99.4). **Conclusion:** The results demonstrate that an optimized *in situ* gelling system shows efficient patient friendly platform and facilitate direct nose-to-brain transport, offering a promising noninvasive strategy for improving safinamide delivery in PD management.

Keywords: Gelling temperature, *In situ* gel, *In vivo* drug release, Oleic acid, Parkinson's disease, Poloxamer 188, Viscosity.

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Received: 02-12-2025;
Revised: 16-01-2026;
Accepted: 25-03-2026.

INTRODUCTION

PD is a progressive neurodegenerative disorder with an estimated prevalence of 1-3% among adults aged over 60 years of age and 4% over 80 years of age. The average age at onset is 58-62 years, with most cases occurring at 60-79 years of age (Kouli *et al*., 2018). In India, increasing life expectancy has raised age-related disorders, such as Parkinson's disease, with a prevalence expected to grow by 50% by 2030. While levodopa with carbidopa is the standard therapy, prolonged treatment leads to reduced response and motor fluctuations, necessitating adjunct therapies such as safinamide (Ahmad Al-Sabbagh *et al*., 2024).

Safinamide (Xadago®) is an orally active, 50 mg and 100 mg are FDA approved strengths which is a selective (USFDA, 2017; Marika *et al*., 2024). and reversible MOA-B inhibitor, used as an adjunct treatment in PD (Blair *et al*., 2017).

DOI: 10.5530/jyp.20260307

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Nasal route is expedited route over other routes of administration where the absorption limitations and drug targeting issues. The nasal route effectively bypasses the blood-brain barrier to deliver drugs to the Central Nervous System (CNS). *In situ* system converts solution to gel once administered in the body (Sabale *et al*., 2020). *In situ* gelling systems are popular because of their advantages over conventional drug delivery systems, including sustained drug release, reduced administration frequency, and improved patient compliance and comfort (Vigani *et al*., 2020).

Physiological barriers such as the Blood-Brain Barrier (BBB) and Blood-Cerebrospinal Fluid (CSF) barrier limit drug delivery for neurological disorders, including Parkinson's disease. Nose-to-brain delivery offers a promising alternative by using the direct connection between the nasal cavity and the CNS through the olfactory and trigeminal pathways, enabling rapid brain transport while bypassing hepatic first-pass metabolism and reducing systemic exposure (Achar *et al*., 2021 and Drath *et al*., 2025).

Conventional intranasal liquids, however, suffer from rapid mucociliary clearance and short residence time. To overcome this, thermosensitive *in situ* gels have been developed. These systems remain fluid at room temperature but gel at nasal temperature, improving retention and enabling sustained release, thereby enhancing intranasal delivery efficiency (Pires *et al.*, 2022). The aim of the study was to facilitate targeted delivery of safinamide to its therapeutic site of action (brain), thereby circumventing first-pass hepatic metabolism and reducing the need for concomitant adjuvant therapy.

MATERIALS AND METHODS

Materials

Safinamide was obtained from MSN Life Sciences, Poloxamer-188 and Oleic acid were obtained from Sigma-Aldrich, HPMC K 100 M samples obtained from BASF and Ethanol from Merck. All materials used in the research work were analytical grades.

Formulation of Safinamide *in situ* gel

A full factorial experimental design was employed to develop a safinamide-loaded nasal *in situ* gel. The drug was gradually dissolved in an ethanol-distilled water mixture (1:1, v/v) under continuous stirring. Poloxamer solution: Poloxamer 188 was slowly added in purified water (part I) to which oleic acid is added under continuous mixing. Polymeric solution: Part II of water (preheated at 40°C) HPMC K100 M is added under continues stirring, cool down to room temperature. Polymeric solution is added to the poloxamer solution followed by drug solution incorporated into the polymeric dispersion, and the resulting formulation was stirred for 15 min using a stirrer to ensure homogeneity. Finally, the volume was adjusted to the required level using distilled water (Sherafudeen *et al.*, 2015 and Agrawal *et al.*, 2011).

Evaluation of Safinamide *in situ* Gel

Ternary Phase Diagram

Ternary phase diagram is a triangular graphical representation used to illustrate the phase behavior of three-component (ternary) systems in equilibrium (Dhoot *et al.*, 2018). This helps visualize how the composition of a mixture affects gel formation.

Gelling time

Gelling time was defined as time required for the transformation of the sol into a gel. The gelation time was monitored by placing a small amount of solution in a test tube and adding a small amount of simulated nasal fluid, maintaining the temperature at 37°C, and visually observing the gel (the test tube was placed horizontally to observe the state of the sample and examine the gelation) formation. The gelation onset time recorded as the gelling time in seconds (Ann Rose Augusthy *et al.*, 2017).

Mucoadhesive strength

The force required to detach the *in situ* gel between the two nasal mucosae was determined using a specialized chemical balance. One nasal mucosa was tied to a glass surface with a rubber band, while the other was placed in an inverted position so that both mucosal surfaces faced each other (Paul *et al.*, 2017). The prepared *in situ* gel was placed between the mucosa and left in contact for a few minutes. Different mucosae were used for each formulation. The weight was increased on the other pan until the mucosa detached. Mucoadhesive strength was expressed as force detachment per cm² of the mucosa area.

Measurement of transition temperature ($T_{\text{sol-gel}}$)

The gelling temperature refers to the temperature at which the meniscus of the formulation does not move when the test tube is slanted at 90 °C. The gelling temperature was determined by placing a test tube containing a sufficient quantity of the prepared solution in a water bath at 30°C. The temperature of the water bath was increased slowly at a constant rate of 1°C every 2 min (Agrawal *et al.*, 2011).

Measurement of *in situ* gel Rheology

A Brookfield viscometer (DV-II+Pro, USA) was used to measure the viscosities of the prepared formulation. Spindle No. 64 was used for this purpose. The viscosity was recorded by rotating the spindle at 50 rpm (Ashutosh *et al.*, 2014).

Determination of pH

1 mL of the prepared gel was transferred to a 10 mL volumetric flask, and the solution was diluted with distilled water. The pH of the resulting solution was determined using a digital pH meter that was previously calibrated using phosphate buffers at pH 4 and 7 (Garala *et al.*, 2013).

Drug content

1 mL of the prepared formulation was dispersed in 10 mL of distilled water with occasional shaking. The resulting solution was filtered through a 0.45 µm filter paper (Girase *et al.*, 2021; Rushikesh Ugale *et al.*, 2025). The amount of safinamide mesylate in the formulation was determined spectrophotometrically at 225 nm.

Ex vivo permeation study

Fresh goat nasal mucosa was collected from the slaughterhouse. The skin hair was shaved, and the skin washed with normal saline. The skin was dried between two filter papers and used directly without storage for further analysis. The dried mucosa was placed between the donor and receptor compartments in the Franz diffusion cell, approximately 5 mL of solution was placed in the donor compartment, and the receptor compartment containing pH 6.8 buffer acted as the dissolution media. The study was conducted using a magnetic stirrer (50 rpm), and the temperature was maintained at 37±0.5°C (Basu *et al.*, 2012). At a predetermined time, a 2 mL sample was taken up to 6 hr, and drug permeation was analyzed using UV-visible spectrophotometry (225 nm).

Droplet size distribution

The droplet size distribution of the nasal spray was evaluated using laser diffraction (Malvern Spraytec). Laser diffraction measures the droplet size distribution based on the angular variation of light scattered by droplets passing through a laser beam. Larger droplets scatter light at small angles, whereas smaller droplets scatter light at wider angles. The scattered light pattern was analyzed using Mie theory to calculate the droplet size distribution. The formulations were analyzed in triplicate, and the droplet size distribution was expressed in terms of D10, D50, D90, and Span (Strien *et al.*, 2024).

$$\text{Span} = \frac{D90 - D10}{D50}$$

RESULTS

Ternary Phase System

The ternary phase system prepared with varying concentrations of poloxamer 188, oleic acid, and water (Table 1) was used to construct the phase diagram (Figure 1), which provides essential insights into the formulation variables governing the performance of nasal *in situ* gel systems. The red-highlighted region in the diagram corresponds to formulations that successfully formed thermoresponsive gels at physiological temperature, whereas the rest were either unstable or failed to gel appropriately at physiological temperature.

In summary, the optimal gelation zone in the ternary diagram was associated with Poloxamer 188:15-30%, Oleic Acid: 2-8%, and water: 62-80%.

Experimental Design

A full factorial design was opted to evaluate the effects of independent formulation variables on gelling time, mucoadhesive strength, and permeability coefficient. Mathematical fitting and analysis were performed using a polynomial equation. Table 2 represents the different trails proposed by the software and tested responses.

Optimization of Dependent Variables

Response A (Gelling Time Analysis)

Gelling time was predominantly influenced by Poloxamer 188 concentration, with formulations gelling between 22.9 to 47.9 sec. The quadratic model showed strong fit (p=0.0002, r^2=0.984) and predictive adequacy which was represented using 3D response surface plot (Figure 2A) and Contour plot (Figure 2B).

Response B (Mucoadhesive Strength Analysis)

Mucoadhesive strength results ranged from 1561.1 to 2783.8 g/cm^2. The quadratic model was highly significant (p: 0.0001 and r^2: 0.972). 3D response surface plot (Figure 3A) and Contour plot (Figure 3B) indicate that the mucoadhesive strength is majorly impacted by Poloxamer 188 concentration.

Response C (Permeability Coefficient Analysis)

Permeability coefficient results of runs ranging from 0.0013 to 0.00339 cm/s. The quadratic model was statistically significant with (p value: 0.0023 and r^2: 0.898). Figures 4A, 4B represents the 3D response plots and 2D contour plots respectively which

Table 1: Ternary phase composition.

Formulation	Poloxamer 188 (%)	Oleic acid (%)	Water (%)	Formation of a Successful Gel
TG1	15	5	80	Yes
TG2	20	4	76	Yes
TG3	25	5	70	Yes
TG4	30	8	62	Yes
TG5	25	16	59	No
TG6	20	8	72	Yes
TG7	18	11	71	No
TG8	15	10	75	Yes
TG9	10	15	75	No
TG10	15	15	70	No
TG11	20	16	64	No
TG12	30	20	50	No
TG13	40	5	55	No

indicates, poloxamer 188 and oleic acid showed significant individual effects, while their interaction was not significant.

The model's suitability for prediction and optimization of all responses was affirmed by the non-significant lack-of-fit, confirming its adequacy.

Optimization of Formulation

To optimize the composition of independent variables, target ranges of responses were freeze i.e., gelling time (35-45 sec), mucoadhesive strength (2000 mg/cm²) and permeation coefficient (0.002 cm/s). The objective is to formulate the composition which can result in targeted response results. With poloxamer 188 at 17.5% and Oleic acid at 1.25% the target results were achieved, the same obtained from overlay plot (Figure 5) and point predication table is represented (Table 3) and reproducibility was observed in trials S2 and S8 at same concentrations.

Transition Temperature ($T_{sol-gel}$)

The gelling temperature of all the formulations were in the range of 32.4 to 40.6°C. Concentration of poloxamer 188 predominately impacted the gelling temperature. Target Nasal gelation is 34-37°C.

Rheological parameters of *in situ* gel

Viscosity increased significantly with increasing poloxamer 188 concentrations, which is reflected in the results (Table 4). Viscosity results of all the runs were in the range of 424. 2 cP to 727.9 cP.

pH

The pH of the formulation was found to be between 7.1-7.5, which is optimal.

Drug Content

The drug content of all formulations was within the target specifications, i.e., 96.41-99.44% w/w.

Ex vivo permeation results

Ex vivo permeation of all the formulations was evaluated, and results are represented in Table 5 and Figure 6. The impact of dependent variables concentrations on the drug release was clearly demonstrated.

Table 2: Formulation of *in situ* gels as suggested by factorial design.

	Factor A	Factor B	Response A	Response B	Response C
Run	Poloxamer 188	Oleic acid	Gelling time	Mucoadhesive strength	Permeability coefficient
	%	%	s	mg/cm²	cm/s
S1	17.5	1.25	38.6	2109.4	0.00203
S2	17.5	1.25	38.4	2008.8	0.00156
S3	17.5	0.5	32.1	1895.1	0.00144
S4	5.0	2.0	22.9	2674.1	0.00334
S5	5.0	0.5	28.4	2783.8	0.00167
S6	5.0	1.25	27.3	2613.9	0.00174
S7	17.5	2.0	29.7	1785.3	0.00339
S8	17.5	1.25	38.6	2004.7	0.00199
S9	30	2.0	42.1	1561.1	0.00197
S10	30	1.25	45.3	1603.7	0.00152
S11	30	0.5	47.9	1658.6	0.0013

Table 3: Point Prediction of optimized formulation.

Response	Predicted Mean	Predicted Median	Observed	Std Dev	SE Mean	95% CI low for Mean	95% CI high for Mean	95% TI low for 99% Pop	95% TI high for 99% Pop
Gelling time	37.4483	37.4483	39.11	2.2073	0.916533	35.281	39.6155	25.4939	49.4027
Mucoadhesive strength	1990.76	1990.76	1935.38	88.1783	36.614	1904.18	2077.33	1513.2	2468.31
Permeability coefficient	0.00193448	0.00193448	0.00199	0.000273975	0.000113762	0.00166548	0.00220349	0.000450679	0.00341829

Droplet Size Distribution

The droplet size distribution of the optimized formula is shown in Figure 7. The span of the formulation was 1.944, indicating a moderately broad droplet size distribution, suggesting acceptable uniformity of atomized droplets suitable for nasal administration, with minimal risk of excessive fine or oversized droplets.

DISCUSSION

Safinamide nasal *in situ* gel was successfully formulated using a simple solution method and optimized through a full factorial design (Design Expert software version 11.03) by varying Poloxamer 188 (5-30% w/w) and oleic acid (0.5-2% w/w) concentration. Initial concentration ranges of Poloxamer 188 and oleic acid were established based on the ternary phase diagram, ensuring selection within the gel-forming domain (Dhoot *et al*., 2018). The formulations were evaluated for critical quality attributes including gelling time, mucoadhesive strength, and permeation coefficient.

Gelling time was significantly influenced by Poloxamer 188 concentrations. Higher polymer concentrations, i.e., 30% w/w, exhibited prolonged gelation (more than 40 S) due to increased viscosity and formation of a denser micellar network, which delays sol-gel transition. Oleic acid concentration showed no significant influence on gelling time which was observed in S4

Table 4: Evaluation tests for the Safinamide *in situ* gel.

Run	Gelling temperature	Viscosity	pH	Drug content
Units	ºC	Cp		%
S1	37.8	554.6±4.1	7.4±0.4	98.52±7.8
S2	37.6	543.2±6.8	7.2±0.2	98.97±3.6
S3	32.4	503.9±5.3	7.1±0.3	97.44±4.1
S4	35.9	424.2±6.1	7.5±0.3	97.72±3.8
S5	36.3	478.4±9.3	7.2±0.5	98.85±7.8
S6	36.7	466.8±1.8	7.2±0.2	98.26±6.6
S7	38.8	612.7±3.6	7.5±0.5	96.41±4.1
S8	37.6	555.1±7.1	7.2±0.5	97.26±5.2
S9	40.6	688.3±14.7	7.4±0.6	98.83±4.3
S10	39.3	701.6±11.6	7.1±0.3	99.12±8.3
S11	39.4	727.9±8.3	7.4±0.7	99.44±6.7

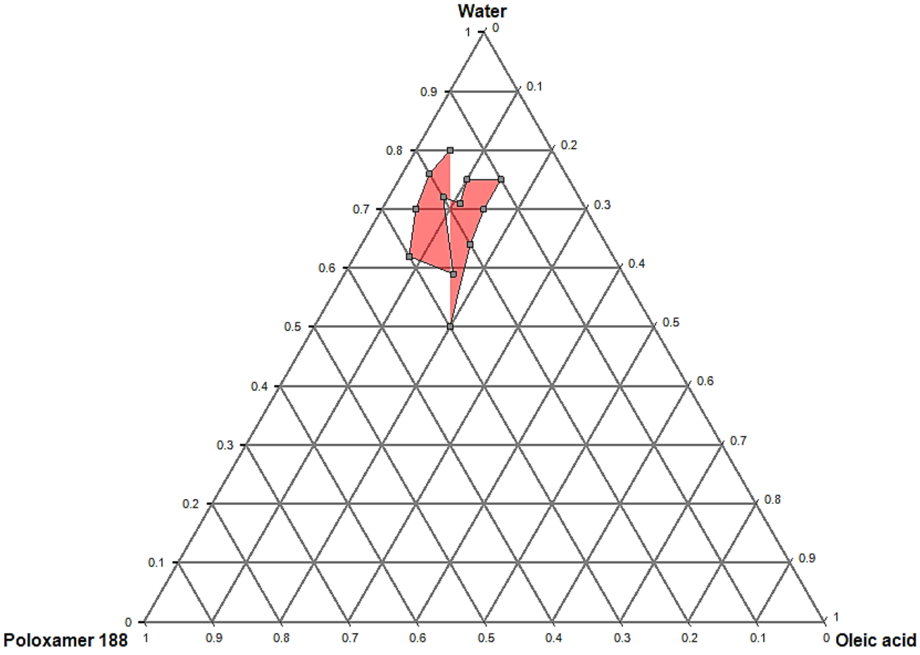

Figure 1: Ternary phase diagram including poloxamer 188, oleic acid, and water. The highlighted (red) indicates the successful formation of an *in situ* gel.

Table 5: ***Ex vivo*** **permeation results of all the formulations (mean±SD, *n*=3).**

Time (h)	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11
0	0	0	0	0	0	0	0	0	0	0	0
0.5	36.09±3.4	36.51±1.5	26.09±3.7	43.36±4.5	28.75±3.2	30.18±4.1	40.37±3.8	35.37±3.7	38.73±3.1	32.65±1.8	24.21±2.8
1	43.25±5.2	43.85±3.7	33.07±5.1	55.59±5.1	36.27±4.4	39.66±4.3	50.68±2.9	44.28±4.1	47.17±2.7	41.73±6.2	31.44±3.8
2	68.48±1.8	70.77±2.9	50.12±4.6	78.15±6.7	51.94±5.5	54.34±2.7	76.91±5.6	68.79±3.9	71.95±5.8	58.11±3.6	48.81±1.9
4	69.27±5.3	72.28±5.7	57.49±2.8	81.86±3.5	62.61±3.2	65.38±6.1	78.38±2.2	71.15±6.2	74.15±5.2	70.95±5.2	53.59±5.3
6	82.65±6.2	78.34±2.6	64.13±4.7	99.87±5.9	68.49±1.9	71.75±4.8	99.61±6.7	76.26±5.7	86.88±4.5	74.37±4.4	60.18±4.7
8	94.39±4.4	96.18±4.8	70.85±6.2		75.18±4.3	84.86±3.7		94.73±2.9	99.17±6.1	88.21±3.8	68.26±1.8
10	99.14±5.2	99.44±3.3	79.33±1.3		86.38±6.8	94.27±2.9		98.83±4.1		99.11±1.9	71.85±6.4
12			88.01±5.2		99.92±4.4	99.34±5.1					84.22±2.9
14			99.67±4.8								95.61±5.3
16											99.84±3.6

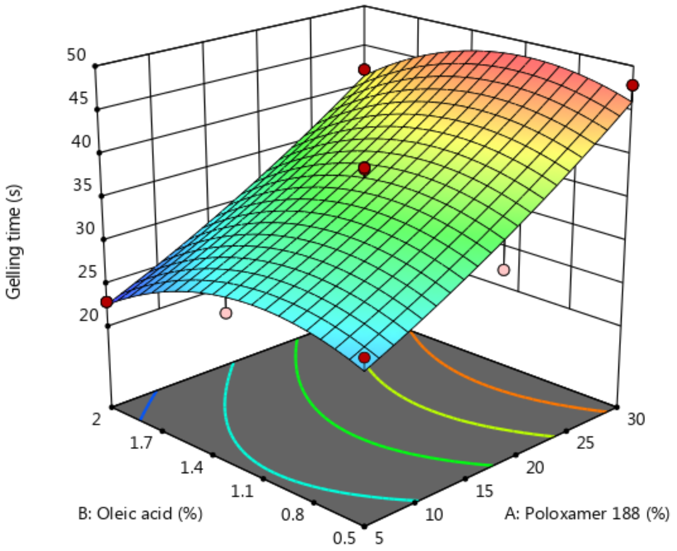

Figure 2A: 3D response surface plot of Response A.

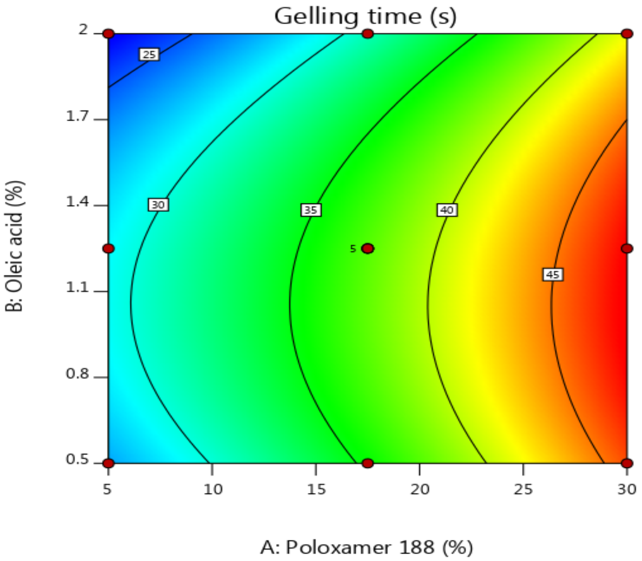

Figure 2B: 2D Contour plot of Response A.

and S7 trials where the oleic acid concentration is 2% w/w whereas the observed gelling time was 22.9 S and 29.7 S respectively.

Mucoadhesive strength exhibited an inverse relationship with Poloxamer 188 concentration. Lower polymer concentrations (5% w/w) showed higher mucoadhesive strength (S4: 2674.1; S5: 2783.8), whereas higher concentrations (S9: 1561.1; S10: 1658.6) demonstrated reduced adhesion. This behavior may be attributed to increased flexibility and chain mobility of the polymer network at lower concentrations, allowing greater interpenetration with nasal mucin (Paul *et al*., 2017).

Permeation studies demonstrated that increasing the concentration of Poloxamer 188 significantly decreased drug permeation. Formulations with higher polymer content exhibited lower permeability coefficients (S9: 0.00197 cm/s; S10: 0.00152 cm/s), whereas those with lower concentrations showed enhanced drug transport (S4: 0.00334 cm/s; S6: 0.00339 cm/s). This reduction in permeation at elevated polymer levels is attributed to increased viscosity and the formation of a dense gel network that restricts drug diffusion. Oleic acid contributed to a modest enhancement in drug permeation owing to its penetration-enhancing properties, which facilitate diffusion by disrupting lipid bilayers. Formulations containing higher oleic acid levels (2% w/w), such as S4 and S7, exhibited increased permeability coefficients (0.00334 cm/s and 0.00339 cm/s, respectively). However, formulation S9, despite having elevated oleic acid content, showed reduced permeation (0.00197 cm/s) due to the dominant diffusion-retarding effect of the high Poloxamer 188 concentration.

The study further demonstrated that Poloxamer 188 and oleic acid significantly influence the physicochemical properties of the formulation, including gelation temperature, viscosity, and drug release behavior. Poloxamer 188 exhibited concentration-dependent thermoresponsive behavior, with higher concentrations (30% w/w) showing elevated gelation temperatures (≈39-41°C), while lower concentrations (5-17.5%

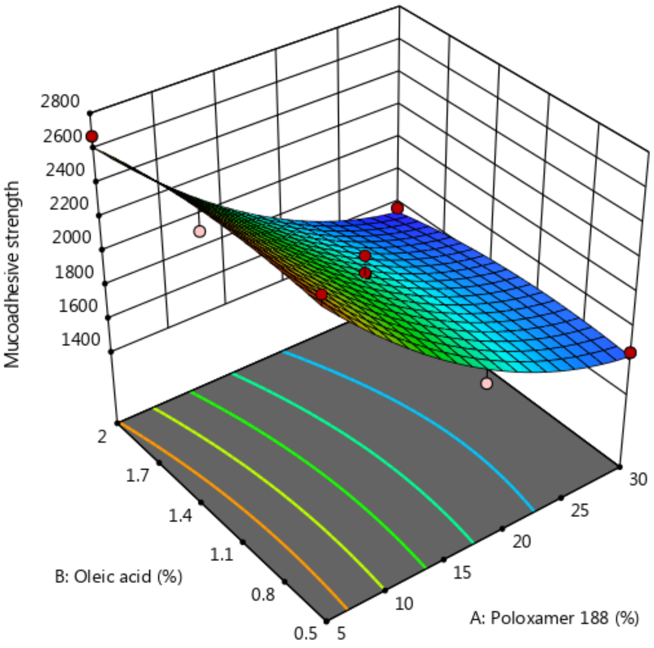

Figure 3A: 3D response surface plot of Response B.

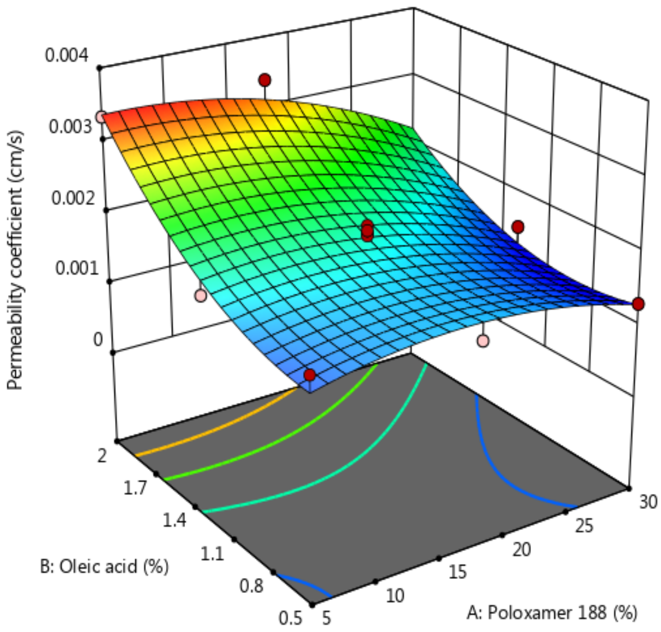

Figure 4A: 3D response surface plot of Response C.

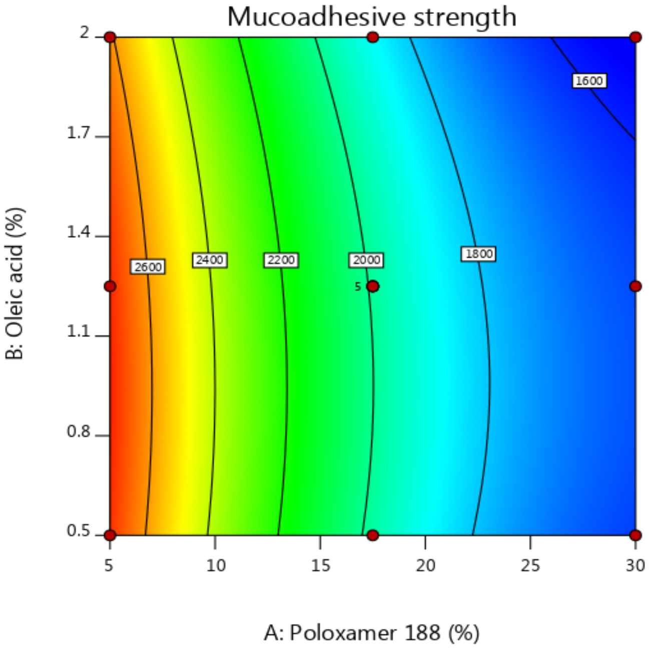

Figure 3B: 2D Contour plot of Response B.

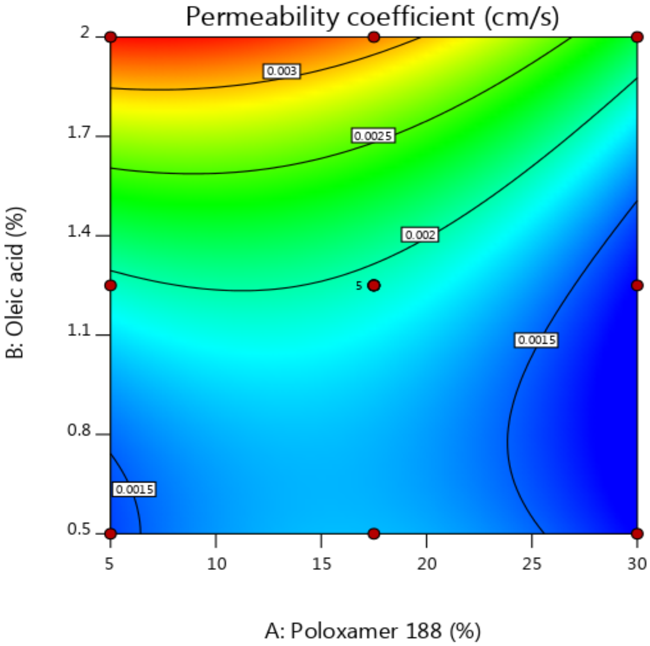

Figure 4B: 2D Contour plot of Response C.

w/w) gelled near physiological temperature. Oleic acid reduced gelation temperature by interfering with micellar organization, with more pronounced effects at higher concentrations (Agrawal *et al.*, 2011; Ashutosh *et al.*, 2014).

Viscosity increased with increasing Poloxamer 188 concentration due to enhanced micellar entanglement, while oleic acid modulated rheology through hydrophobic interactions. All formulations are maintained in a pH range of 7.1-7.5, indicating suitability for nasal administration and formulation stability. Drug content ranged from 96.41-99.44%, confirming uniform drug distribution in all formulations.

Drug permeation followed a concentration-dependent pattern, where formulations with lower Poloxamer 188 content (S4-S7) showed faster initial release due to a looser gel network (6 H), whereas higher polymer concentrations (S9-S11) provided sustained drug release up to 16 hr. Oleic acid further enhanced drug permeation due to its lipid-disrupting properties (Basu *et al.*, 2012).

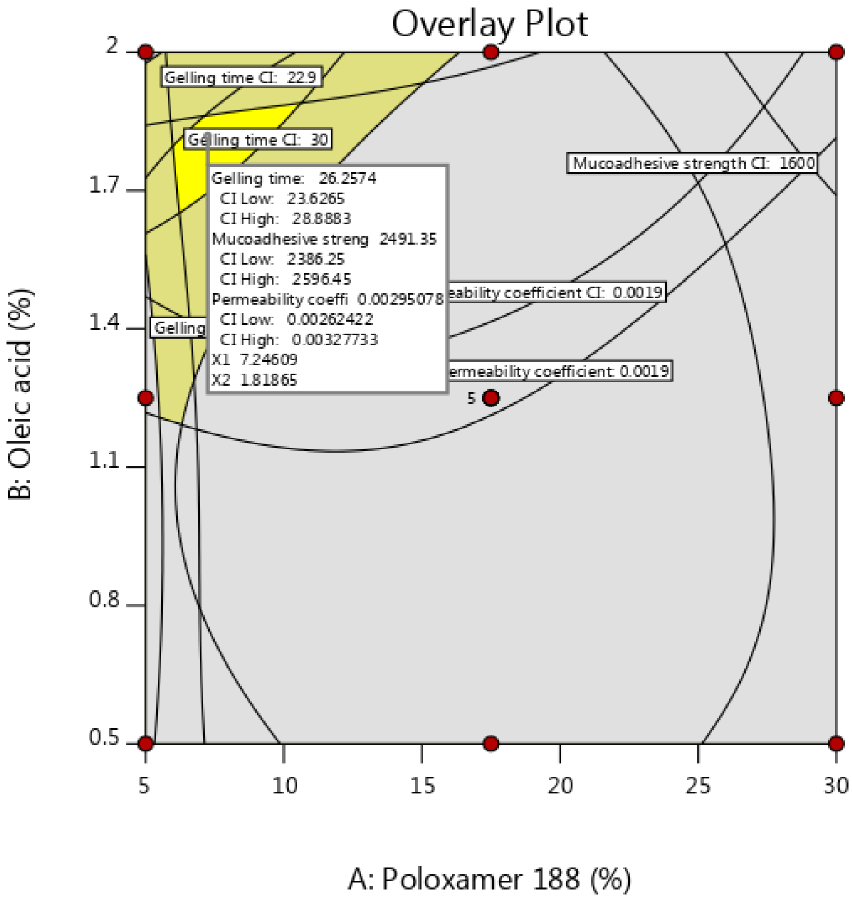

Figure 5: Overlay plot of region highlighting the optimized space and values.

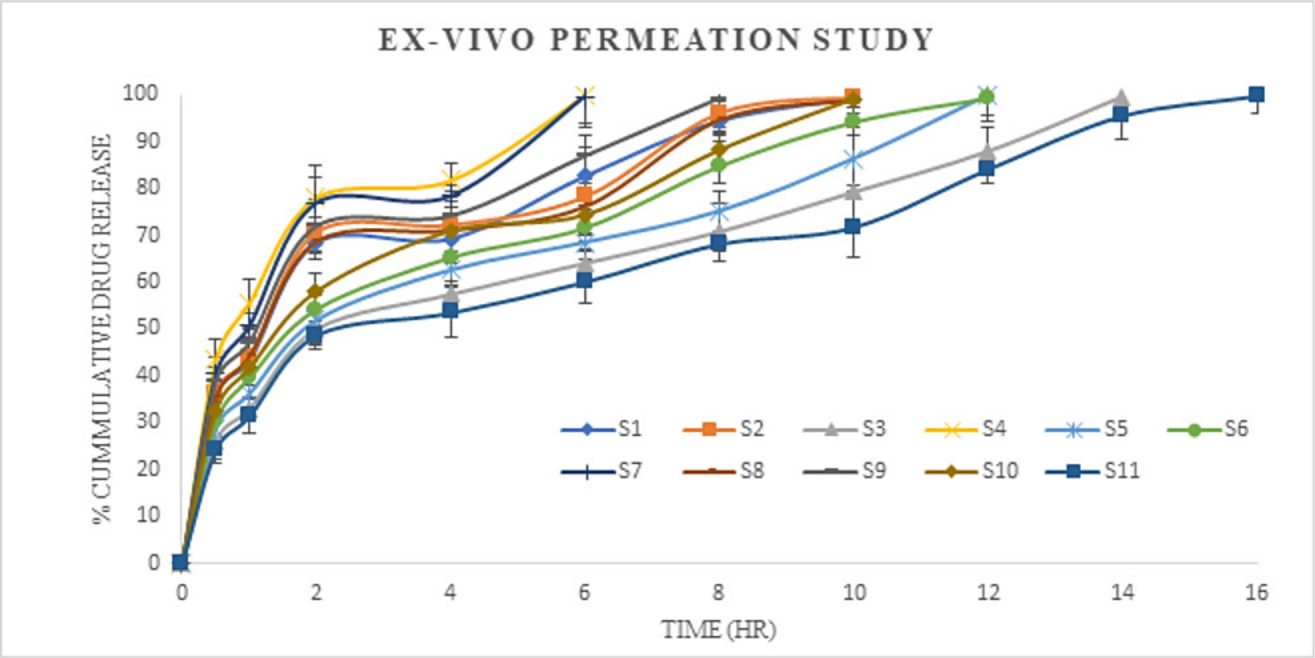

Figure 6: Time vs Cumulative drug release of all the trail runs (mean±SD, n=3).

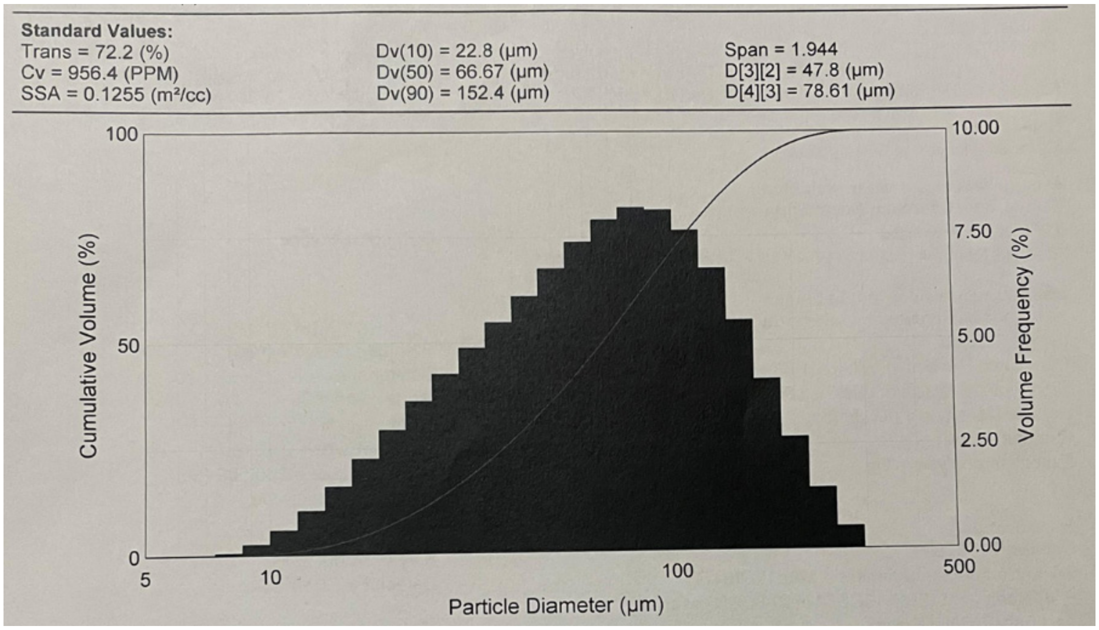

Figure 7: Droplet size distribution of Nasal Spray.

To validate the results, two additional trials were conducted at the optimized concentration, and the outcomes demonstrated good reproducibility.

The mean droplet size of 47.8 μm and a span value of 1.944 indicate a narrow particle size distribution, reflecting good formulation homogeneity and controlled processing. A span value below 2 is generally considered indicative of uniform particle distribution suitable for nasal delivery systems.

CONCLUSION

The present study successfully developed and optimized a safinamide-loaded nasal *in situ* gel using a factorial design approach. Poloxamer 188 and oleic acid were identified as critical formulation variables governing the physicochemical properties and performance of the system. Poloxamer 188 predominantly influenced gelling behavior, viscosity, mucoadhesion, and drug permeation, exhibiting concentration-dependent thermoresponsive characteristics. Higher polymer concentrations resulted in increased viscosity, prolonged gelation time, reduced mucoadhesive strength, and sustained drug release due to the formation of a dense gel matrix. In contrast, lower polymer concentrations favored faster drug permeation and enhanced mucoadhesion.

Oleic acid acted as an effective permeation enhancer and gel modifier, improving drug transport across the membrane without significantly affecting pH or formulation stability. The optimized formulations demonstrated suitable pH values, high drug content uniformity, controlled drug release profiles, and desirable rheological properties. Particle size analysis further confirmed a narrow size distribution and good homogeneity, supporting improved dissolution and bioavailability. The present study was limited to *in vitro* and *ex vivo* evaluations using nasal mucosa as a surrogate for clinical conditions. Therefore, further investigations employing appropriate animal models are planned to comprehensively assess the *in vivo* performance of the optimized formulation.

Overall, the study establishes that a rational balance between Poloxamer 188 and oleic acid concentrations is essential for achieving optimal gelation, permeability, and drug release behavior. Optimized formulation of nasal *in situ* gel system shows strong potential as an efficient and patient-friendly platform for brain targeted delivery of Safinamide.

ABBREVIATIONS

PD: Parkinson's Disease; **MAO-B:** Monoamine Oxidase-B; **FDA:** Food and Drug Administration; **USFDA:** United States Food and Drug Administration; **CNS:** Central Nervous System; **BBB:** Blood-Brain Barrier; **CSF:** Cerebrospinal Fluid; **HPMC:** Hydroxypropyl Methylcellulose; **UV:** Ultraviolet; **RP-HPLC:** Reverse Phase High-Performance Liquid Chromatography; **SD:** Standard Deviation; **ANOVA:** Analysis of Variance; **w/w:** Weight by Weight; **v/v:** Volume by Volume; **rpm:** Revolutions Per Minute; **CI:** Confidence Interval; **SE:** Standard Error; **Span:** Particle Size Distribution Width Parameter; **$T_{sol-gel}$:** Sol-to-Gel Transition Temperature.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Reddy DRK, Chappidi SR. Development and Optimization of a Nasal *in situ* Gel for Enhanced Brain Delivery of Safinamide in Parkinson's Disease. J Young Pharm. 2026;18(2):399-408.