

Design, Characterization, and Evaluation of a Thermogelling Intranasal Delivery System of Rasagiline Mesylate for Brain Targeting

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Research Article

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Abstract

Background: Parkinson's Disease is the second most common neurodegenerative disorder worldwide. Although levodopa and monoamine oxidase-B (MAO-B) inhibitors remain the cornerstone of symptomatic management, oral administration is often limited by poor brain targeting and restricted penetration across the blood–brain barrier. The present study aimed to develop and optimize a thermoresponsive nasal in situ gel of Rasagiline Mesylate to facilitate direct nose-to-brain delivery.

Materials and Methods: A Central Composite Design (CCD) was employed to optimize the formulation. Poloxamer 407 (A: 15–30%, including axial points of 11.89 and 33.11%) and dodecyl maltoside (B: 1.0–2.0%, including axial points of 0.79 and 2.21%) were selected as independent variables, while gelation time, mucoadhesive strength, and permeation coefficient were considered response variables. The developed formulations were characterized for gelation time, mucoadhesive strength, drug content, pH, gelation temperature, viscosity, in vitro permeation, droplet size distribution, and plume geometry.

Results: The optimized formulation (RM1; 22.5% Poloxamer 407 and 1.5% dodecyl maltoside) demonstrated rapid thermogelation at physiological temperature (36–37 s), favourable mucoadhesive strength (~2000 dyne/cm²), and an enhanced permeation coefficient (0.00203 cm/s). In contrast, formulations containing higher polymer concentrations (RM10; 30% Poloxamer 407 and 2% dodecyl maltoside) exhibited prolonged gelation and reduced permeation performance. All formulations maintained a pH of approximately 7.3, indicating suitability for nasal administration. The optimized gel also exhibited acceptable spray characteristics, viscosity, and drug content uniformity.

Conclusion:

The optimized thermosensitive nasal in situ gel of rasagiline mesylate demonstrated desirable physicochemical properties, mucoadhesion, and permeation behavior, supporting its potential as a non-invasive nose-to-brain delivery platform. This approach may enhance central nervous system targeting of MAO-B inhibitors and represents a promising strategy for improving therapeutic outcomes in Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by the gradual degeneration of dopaminergic neurons in the substantia nigra region of the brain, resulting in impaired motor and non-motor functions. Clinically, PD is associated with symptoms such as tremors, rigidity, bradykinesia, postural instability, cognitive impairment, and sleep disturbances. It is recognized as the second most prevalent neurodegenerative disorder globally, following Alzheimer's disease. Worldwide, PD affects approximately 1–3% of individuals over the age of 60, with its prevalence increasing significantly with advancing age. Recent epidemiological studies estimate that over 10 million individuals are currently living with Parkinson's disease globally, with incidence and mortality rates steadily rising due to increased life expectancy and aging populations. Furthermore, Parkinson's disease significantly contributes to disability and reduced quality of life, with mortality rates reported to be approximately 1.5–2 times higher in affected individuals compared to the general population. Despite the availability of conventional therapies such as levodopa, long-term treatment is often associated with motor complications and diminished therapeutic efficacy, underscoring the need for advanced and targeted drug delivery strategies [1, 2, 3].

Rasagiline Mesylate (Azilect) is an orally active medication available in 0.50 mg and 1 mg FDA-approved oral tablets, indicated for the treatment of idiopathic Parkinson's disease both as initial monotherapy and as an adjunct to levodopa. The oral bioavailability of Rasagiline Mesylate is 35–36%, and it is rapidly absorbed and extensively metabolized in the liver. The present study aims to formulate a nasal in situ gel, although the drug belongs to BCS Class III, indicating low permeability [5, 6]. To enhance the permeability of the Rasagiline Mesylate in situ gel, DDM, a non-ionic alkyl maltoside surfactant, is employed as a permeation enhancer in intranasal drug delivery systems. DDM primarily acts by transiently modulating the integrity of epithelial cell membranes and tight junctions within the nasal mucosa [7].

To circumvent first-pass metabolism and target the brain, the nasal route is preferred. Nasal in situ gel formulations are gaining importance in the development of dosage forms, particularly for brain-related disorders such as Parkinson's disease. The in situ gel formulation offers advantages such as prolonged residence time and controlled drug release, thereby

enhancing therapeutic efficacy. Incorporating DDM in the formulation facilitates improved drug permeation through the nasal mucosa, potentially increasing bioavailability. This approach aims to provide a non-invasive, effective delivery system for Rasagiline Mesylate, targeting the central nervous system while minimizing systemic side effects [8, 9].

MATERIALS AND METHODS

Materials

RM was obtained from Optimus as free sample, Poloxamer-407 (Colorcon), HPMC E50 LV (Colorcon), DDM (Jiangsu Sinopep Allsino Biopharmaceutical) & Ethanol (Merck). All materials used in the research work were analytical grades.

Methods

Design of RM In Situ Gel:

A Central Composite Design was employed to formulate an RM in situ gel. The drug was incrementally dissolved in an ethanol–distilled water mixture (1:1, v/v) under continuous agitation. For the poloxamer solution, Poloxamer 407 was gradually introduced into purified water (Part I), to which DDM was added with constant mixing. For the polymeric solution, Part II of water containing HPMC E50LV was incorporated under continuous stirring and subsequently cooled to ambient temperature. The polymeric solution was then combined with the poloxamer solution, followed by the integration of the drug solution into the polymeric dispersion. The resultant formulation was stirred for 15 minutes using a stirrer to ensure uniformity. Finally, the volume was adjusted to the desired level using distilled water [10]. Detailed process flow is captured in Fig. 1.

IN VITRO TESTING OF RM:

Gelling time:

The gelling time is defined as the duration required for the conversion of a sol into a gel. This gelation time was assessed by introducing a small quantity of the solution into a test tube, followed by the addition of a small amount of simulated nasal fluid, while maintaining the temperature at 37°C. The formation of the gel was visually observed, with the test tube positioned horizontally to facilitate the examination of the sample's state and the gelation process. The onset of gelation was recorded as the gelling time, measured in seconds [11].

Mucoadhesive strength

The force necessary to separate the in-situ gel from between the two nasal mucosae was measured using a specialized chemical balance. One nasal mucosa was secured to a glass surface with a rubber band, while the other was positioned inversely so that both mucosal surfaces were in contact. The prepared in-situ gel was placed between the mucosae and allowed to remain in contact for several minutes. Different mucosae were employed for each formulation. The weight on the opposite pan was incrementally increased until the mucosae detached. Mucoadhesive strength was quantified as the force of detachment per cm² of the mucosal area [12, 13].

Gelling Temperature (T):

The gelling temperature is defined as the temperature at which the meniscus of the formulation remains stationary when the test tube is inclined at an angle of 90°. To determine the gelling temperature, a test tube containing an adequate amount of the prepared solution was placed in a water bath maintained at 30°C. The temperature of the water bath was then gradually increased at a constant rate of 1°C every 2 minutes [14].

Viscosity:

The viscosities of the prepared formulation were measured using a Brookfield viscometer (DV-II + Pro, USA). For this measurement, Spindle No. 64 was employed. The viscosity was determined by rotating the spindle at a speed of 50 rpm [15].

pH:

The pH level is a crucial parameter in nasal formulations, as extreme pH values can result in nasal irritation. The pH of the prepared formulations was assessed using a dilution method, wherein 1 mL of the gel was placed in a 10 mL volumetric flask and diluted with distilled water. The pH of the resulting solution was measured using a digital pH meter, which had been previously calibrated with phosphate buffers at pH levels of 1.2, 4, 7, and 9 [16, 17].

Drug content:

1 mL of the prepared formulation was dispersed in 10 mL of methanol for a duration of 2–3 minutes with intermittent shaking. The resultant solution was filtered through a 0.45 µm filter paper and subsequently diluted with methanol. The quantity of RM in the formulation was quantified using a Shimadzu 1800 spectrophotometer at a wavelength of 264 nm. The absorbance of the solution was recorded, and the concentration of RM was determined utilizing a previously established calibration curve. All measurements were conducted in triplicate to ensure accuracy and reproducibility. The results were expressed as the mean ± SD [18].

In vitro permeation study:

Permeation studies were conducted utilizing a Franz diffusion cell apparatus with goat nasal mucosa. The tissue was cleansed with a pH 6.8 phosphate buffer and subsequently positioned between the donor and receptor compartments. A volume of 5 mL of the formulation was introduced into the donor compartment, while the receptor compartment was filled with a pH 6.8 phosphate buffer. The temperature was consistently maintained at $37 \pm 0.5^\circ\text{C}$ throughout the study, facilitated by a 500 rpm magnetic stirrer. At predetermined intervals, 2 mL samples were collected up to 6 hours, and drug permeation was analyzed using UV-visible spectrophotometry at 272 nm [19, 20].

Droplet size distribution

The particle size distribution of the nasal spray formulation was assessed using a Malvern laser diffraction particle size analyzer to evaluate aerosol droplet size for intranasal delivery. The instrument was calibrated per manufacturer's guidelines. The formulation was loaded into the nasal spray device, primed for consistent delivery, and positioned in the laser beam path. The formulation was actuated manually or with an automated actuator to produce aerosolized droplets within the detection zone. The laser diffraction principle measured particle size distribution based on the scattering pattern. Measurements were conducted under ambient conditions, with each sample analyzed in triplicate for reproducibility. Data were processed using Malvern software to determine particle size distribution parameters, including VMD, D10, D50, D90 values, and span index. The results assessed the dispersion efficiency and droplet size uniformity of the nasal spray formulation, critical for nasal deposition and intranasal drug delivery performance [21, 22].

$$\text{Span} = \frac{D_{90} - D_{10}}{D_{50}}$$

Plume Geometry:

The analysis of plume geometry for the nasal spray formulation was performed utilizing the SprayVIEW NSP system to evaluate the spray pattern, plume angle, and aerosolization characteristics. The study was conducted under controlled conditions to ensure reproducibility and accuracy. The nasal spray device was primed according to the manufacturer's instructions to achieve consistent spray output. The formulation-filled container was mounted vertically on the SprayVIEW NSP

actuator and positioned 60 mm from the laser imaging zone. An automated mechanism was employed to minimize operator variability during actuation, with high-speed digital imaging capturing the spray plume post-aerosolization. Integrated software analyzed plume geometry parameters, including left and right plume arm angles, overall plume angle, plume width, and spray symmetry. Each formulation was evaluated in triplicate, with average values recorded. The plume geometry was deemed acceptable, exhibiting a symmetrical pattern and consistent plume angle, indicating the formulation's suitability for effective intranasal drug delivery [23, 24, 25, 26].

RESULTS

Experimental Design

Central Composite Design (CCD) 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 1 represents the different trails proposed by the software and tested responses.

Table 1
Central Composite Design: Formulation composition and Measured Responses

Run	Factor A	Factor B	Response A	Response B	Response C
	Poloxamer 407	DDM	Gelling time	Mucoadhesive strength	Permeability coefficient
%	%	s	mg/cm ²	cm/s	
RM1	22.5	2.2	38.5	1765.19	0.00241
RM2	22.5	1.5	37.1	2026.33	0.00203
RM3	30.0	1.0	41.6	2451.66	0.00169
RM4	15.0	2.0	29.7	1557.13	0.00284
RM5	11.9	1.5	26.1	1276.79	0.0034
RM6	22.5	0.8	37.5	1716.16	0.00169
RM7	22.5	1.5	36.9	1961.33	0.00201
RM8	22.5	1.5	36.7	2157.46	0.00205
RM9	33.1	1.5	45.4	2745.86	0.00156
RM10	30.0	2.0	43.9	2353.59	0.00168
RM11	15.0	1.0	31.2	1470.99	0.0024

Optimization of Dependent Variables

Response A (Gelling Time)

Analysis of variance (ANOVA) revealed that the quadratic model was highly significant ($F = 291.75$, $p < 0.0001$). Poloxamer 407 (A) exerted a significant influence on the response ($p < 0.0001$), whereas DDM (B) did not demonstrate a significant effect ($p = 0.1689$). The interaction term (AB) and the quadratic term (A^2) were significant ($p = 0.0114$ and $p = 0.0256$, respectively), while B^2 did not exhibit a significant effect ($p = 0.0657$). The non-significant lack-of-fit ($p = 0.0995$) confirmed the model's adequacy and its strong concordance with the experimental data which was represented using 3D response surface plot (Fig. 2A) and Contour plot (Fig. 2B)

Response B (Mucoadhesive Strength Analysis):

Analysis of variance (ANOVA) confirmed the significance of the quadratic model, with an F-value of 43.33 and a p-value of 0.0004. Poloxamer 407 (A) exhibited a significant effect on the response ($p < 0.0001$), whereas DDM (B), the interaction between A and B, and the A^2 terms were not significant ($p > 0.05$). The B^2 term was significant ($p = 0.0211$), indicating a nonlinear effect of DDM. The non-significant lack-of-fit ($p = 0.5781$) verified the model's adequacy and predictive reliability. 3D response surface plot and Contour plot are represented in Fig. 3A & 3B.

Response C (Permeability Coefficient Analysis):

Analysis of variance (ANOVA) revealed that the quadratic model was statistically significant ($F = 22.49$, $p = 0.0019$). Both Poloxamer 407 (A) and DDM (B) exerted a significant influence on the response ($p = 0.0002$ and $p = 0.0268$, respectively), whereas the interaction term (AB) did not demonstrate significance ($p = 0.2312$) which was represented using 3D response surface plot (Fig. 4A) and Contour plot (Fig. 4B).

Optimization of Formulation:

To optimize the composition of independent variables, specific target ranges for responses were established, namely gelling time (35–45 s), mucoadhesive strength (≈ 2000 mg/cm²), and permeation coefficient (≈ 0.002 cm/s). The objective was to formulate a composition capable of achieving these targeted response outcomes. With poloxamer 407 at a concentration of 22.5% and DDM at 1.50%, the desired results were attained, as corroborated by the overlay plot (Fig. 5) and the point prediction Table 2. Reproducibility was observed in trials RM2, RM7, and RM8 at these same concentrations.

Table 2
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	31.016	31.016	30.21	0.49	0.264	30.34	31.69	27.864	34.168
Mucoadhesive strength	1586.36	1586.36	1615.8	95.53	51.71	1453.43	1719.3	968.044	2204.68
Permeability coefficient	0.0026	0.0026	0.0029	0.0002	8.93984E-05	0.0023	0.0028	0.0015	0.0036

Diagnostic plots of externally studentized residuals and Cook's distance confirmed the suitability of the developed response surface models (Fig. 6) for (A) gelation time, (B) mucoadhesive strength, and (C) permeation coefficient. Residuals were randomly distributed around zero and remained within the acceptable limits (± 5.75), indicating the absence of significant outliers and model bias. Cook's distance analysis revealed that most experimental runs had negligible influence on model predictions, with only a few observations showing moderate influence. Overall, the results demonstrate the robustness, adequacy, and predictive reliability of the quadratic models used for formulation optimization.

Transition Temperature (T_{sol-gel}):

The gelling temperature of all formulations ranged from 29.7 to 40.3°C. The concentration of poloxamer 407 predominantly influenced the gelling temperature. The target nasal gelation temperature is 34–37°C.

Rheological parameters of in situ gel:

Viscosity increased significantly with increasing poloxamer 407 concentrations, which is reflected in the results (Table 3). Viscosity results of all the runs were in the range of 418.6 cP to 745.2 cP.

Table 3
Evaluation tests for the RM in situ gel.

Run	Gelling temperature	Viscosity	pH	Drug content
Units	°C	Cp		%
RM1	34.5	512.5 ± 3.7	7.2 ± 0.1	97.54 ± 2.1
RM2	35.7	508.1 ± 4.1	7.3 ± 0.1	97.86 ± 1.9
RM3	32.4	645.2 ± 6.9	7.2 ± 0.2	96.39 ± 3.2
RM4	37.2	477.4 ± 4.6	7.3 ± 0.2	98.22 ± 1.5
RM5	40.3	418.6 ± 11.5	7.2 ± 0.1	97.95 ± 4.6
RM6	34.9	501.3 ± 7.5	7.4 ± 0.3	98.15 ± 2.9
RM7	35.8	509.4 ± 8.4	7.1 ± 0.2	98.07 ± 3.6
RM8	35.9	503.8 ± 9.3	7.2 ± 0.1	98.31 ± 4.5
RM9	29.7	745.2 ± 10.2	7.3 ± 0.2	97.85 ± 1.8
RM10	31.8	651.7 ± 12.5	7.2 ± 0.1	98.06 ± 2.7
RM11	37.6	468.4 ± 8.5	7.4 ± 0.1	97.93 ± 5.2

pH:

The pH of the trials was found to be between 7.1–7.4, Although the physiological pH of the nasal cavity is commonly reported between 4.5–6.5, the optimized RM formulation exhibited pH of 7.3 which is close to physiological blood pH and was found to be non irritating to the nasal mucosa.

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 4 & Fig. 7. The impact of dependent variables concentrations on the drug release was clearly demonstrated.

Table 4
Ex Vivo permeation results of all the formulations (mean $\pm$ SD, n = 3)

Time (h)	RM1	RM2	RM3	RM4	RM5	RM6	RM7	RM8	RM9	RM10	RM11
0	0	0	0	0	0	0	0	0	0	0	0
0.5	35.27 $\pm$ 3.7	32.16 $\pm$ 4.1	28.64 $\pm$ 2.8	39.35 $\pm$ 1.7	47.93 $\pm$ 1.8	31.57 $\pm$ 2.3	33.15 $\pm$ 2.5	32.41 $\pm$ 3.7	22.63 $\pm$ 2.8	26.61 $\pm$ 3.6	37.68 $\pm$ 1.9
1	48.92 $\pm$ 7.1	42.85 $\pm$ 2.8	37.11 $\pm$ 5.3	53.51 $\pm$ 4.2	63.25 $\pm$ 3.2	39.62 $\pm$ 4.1	41.29 $\pm$ 3.8	40.07 $\pm$ 1.9	32.97 $\pm$ 1.9	35.53 $\pm$ 4.1	50.41 $\pm$ 3.2
2	72.58 $\pm$ 5.5	69.48 $\pm$ 6.2	64.72 $\pm$ 4.7	72.77 $\pm$ 5.3	85.71 $\pm$ 3.8	67.95 $\pm$ 3.8	71.84 $\pm$ 5.2	70.35 $\pm$ 4.2	64.53 $\pm$ 3.7	61.08 $\pm$ 3.7	71.55 $\pm$ 4.7
4	74.11 $\pm$ 4.8	71.61 $\pm$ 5.6	68.36 $\pm$ 3.8	76.93 $\pm$ 2.7	96.31 $\pm$ 2.7	70.08 $\pm$ 4.8	73.26 $\pm$ 4.6	72.48 $\pm$ 6.3	61.27 $\pm$ 5.8	66.57 $\pm$ 4.8	73.53 $\pm$ 1.8
6	79.45 $\pm$ 1.9	80.04 $\pm$ 4.7	74.92 $\pm$ 1.7	87.16 $\pm$ 3.6	99.95 $\pm$ 3.7	78.13 $\pm$ 2.9	81.11 $\pm$ 4.1	82.13 $\pm$ 5.7	69.33 $\pm$ 4.3	70.71 $\pm$ 4.3	81.26 $\pm$ 5.2
8	99.69 $\pm$ 3.3	91.46 $\pm$ 3.9	81.55 $\pm$ 2.9	99.86 $\pm$ 4.4	99.13.9	85.74 $\pm$ 3.6	90.08 $\pm$ 5.5	91.26 $\pm$ 4.5	78.51 $\pm$ 2.9	79.05 $\pm$ 2.7	99.78 $\pm$ 1.7
10	98.21 $\pm$ 2.5	99.91 $\pm$ 5.1	92.74 $\pm$ 6.1	99.07 $\pm$ 3.1	98.66 $\pm$ 2.4	96.35 $\pm$ 1.9	99.97 $\pm$ 1.9	99.94 $\pm$ 5.6	85.84 $\pm$ 4.5	88.61 $\pm$ 5.5	98.97 $\pm$ 2.2
12	97.11 $\pm$ 2.9	98.44 $\pm$ 3.6	99.64 $\pm$ 3.8	98.672.9	98.05 $\pm$ 2.2	99.18 $\pm$ 3.2	99.02 $\pm$ 2.1	99.65 $\pm$ 3.2	92.34 $\pm$ 5.7	99.17 $\pm$ 4.2	98.22 $\pm$ 1.9

Droplet Size Distribution

The droplet size distribution of the optimized formulation is depicted in Fig. 8. The span of the formulation was 1.9, and the D90 was 198.8 μ m, indicating a moderately broad droplet size distribution. This suggests an acceptable uniformity of atomized droplets suitable for nasal administration, with minimal risk of producing excessively fine or oversized droplets.

Plume geometry:

The plume geometry evaluation performed using the SprayVIEW® NSP system demonstrated that the developed nasal formulation produced a uniform and symmetrical spray pattern (Fig. 9), reflecting efficient aerosolization characteristics and suitability for intranasal administration. The optimized formulation exhibited plume arm angles of 19.9° and 26.2°, resulting in an overall plume angle of 46.1°, which indicates appropriate spray expansion and distribution following actuation. Furthermore, the plume width was measured to be 51.27 mm at a distance of 60.0 mm from the nozzle, suggesting adequate dispersion of the formulation and reproducible spray performance. The observed spray time of 104 ms further confirmed rapid actuation and efficient aerosol generation. These plume geometry characteristics are considered favourable for achieving effective deposition within the nasal cavity, which may enhance drug residence and facilitate improved nose-to-brain delivery. The symmetrical spray profile and controlled dispersion behaviour also indicate the capability of the formulation to deliver the drug uniformly across the nasal mucosal surface, thereby supporting its potential application for efficient intranasal drug delivery.

DISCUSSION

The results show that gelling temperature decreased with higher Poloxamer 407 concentrations, highlighting its key role in gel formation. Formulations with more Poloxamer 407, like Runs 9 and 10, had lower gelling temperatures (29.7°C and 31.8°C) than those with less, such as Runs 5 and 11 (40.3°C and 37.6°C). This is due to enhanced micellar aggregation and intermolecular interactions at higher Poloxamer 407 levels, enabling gel formation at lower temperatures. DDM also influenced gelling temperature but less so than Poloxamer 407, indicating Poloxamer 407 as the main determinant of thermogelling behavior. Viscosity also increased with more Poloxamer 407, likely due to a denser micellar network enhancing rheological

properties. DDM contributed moderately to viscosity; higher DDM levels slightly increased viscosity, suggesting synergy with Poloxamer 407 to strengthen the gel matrix. Drug content analysis showed formulations with more Poloxamer 407 had slightly better drug content uniformity, likely due to better solubilization and dispersion. DDM had a minor positive effect on drug content, slightly enhancing drug incorporation. The combined effect of Poloxamer 407 and DDM indicates that while Poloxamer 407 is the primary factor in drug loading and formulation characteristics, DDM aids in viscosity and drug content modulation, enhancing the nasal in situ gel system's performance.

The droplet size distribution analysis showed satisfactory atomization for intranasal delivery, with a span of 1.9 and D90 of 198.8 μm , indicating acceptable droplet uniformity for consistent nasal deposition. The absence of excessively fine droplets may reduce pulmonary deposition, while limited oversized droplets minimize nasal runoff. Spray characteristics are suitable for effective intranasal administration. Plume geometry analysis using SprayVIEW NSP confirmed efficient aerosolization, showing a uniform, symmetrical pattern for reproducible performance and dispersion. Plume arm angles of 19.9° and 26.2° resulted in a total angle of 46.1°, indicating efficient spray expansion and nasal coverage. A plume width of 51.27 mm at 60.0 mm from the nozzle demonstrated satisfactory dispersion. The spray time of 104 ms indicated rapid actuation and generation, desirable for nasal sprays. Overall, droplet size distribution and plume geometry parameters indicate appropriate aerodynamic and spray performance for intranasal administration. The symmetrical plume profile, controlled droplet dispersion, and rapid aerosol generation are expected to enhance drug retention and nose-to-brain transport efficiency.

CONCLUSION

In conclusion, the RM thermoresponsive nasal in situ gel formulation developed exhibited favorable physicochemical and spray performance characteristics, rendering it suitable for intranasal drug delivery. Poloxamer 407 was identified as the primary determinant of gelling temperature, viscosity, and drug content, while DDM contributed synergistically to the modulation of rheological properties and drug incorporation. The optimized formulation demonstrated appropriate thermogelling behavior, satisfactory viscosity, and uniform drug distribution, thereby supporting its stability and nasal applicability. Moreover, studies on droplet size distribution and plume geometry confirmed efficient aerosolization, uniform spray dispersion, and reproducible spray performance, with minimal risk of pulmonary deposition or nasal runoff. The symmetrical plume profile, rapid spray generation, and controlled droplet distribution collectively suggest the potential of the developed formulation to achieve effective nasal deposition and enhanced nose-to-brain drug transport.

Declarations

Author Contribution

Rushi conceived the study, conducted the experiments, analyzed the data, and prepared the first draft of the manuscript. Surya supervised the research, contributed to the study design and data interpretation, and critically reviewed and revised the manuscript. Both authors read and approved the final manuscript.

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Figures

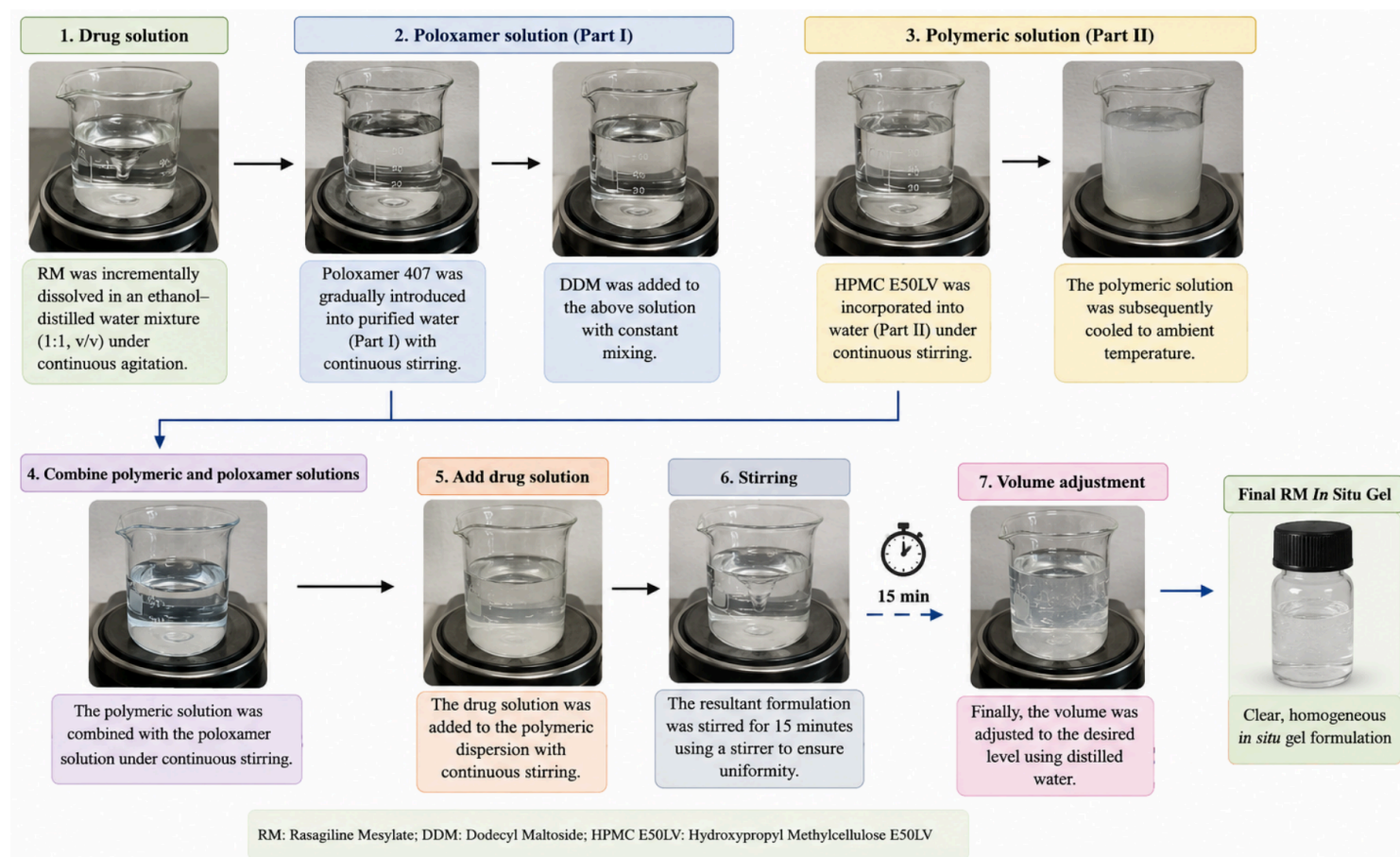


Figure 1

Rasagiline Mesylate in situ gel manufacturing process

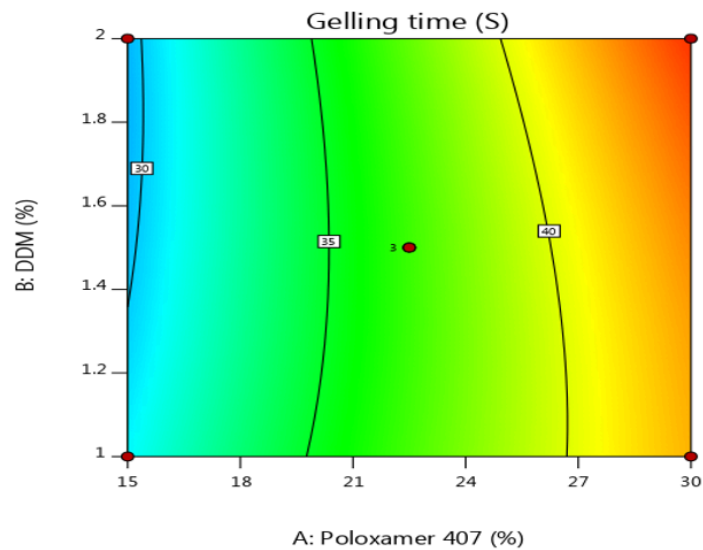
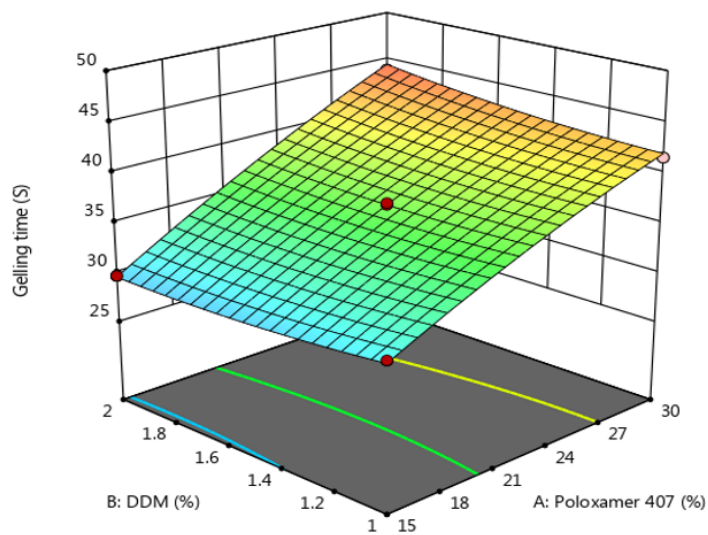


Figure 2

A 3D response surface plot of Response **A** **Figure 2B** 2D Contour plot of Response **A**

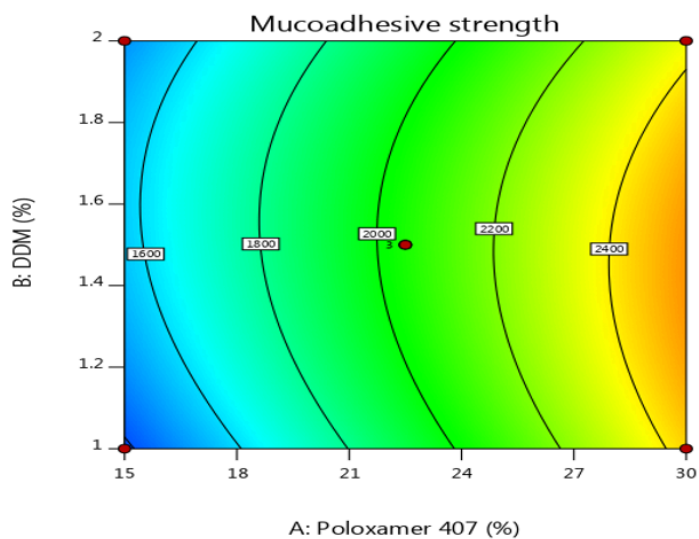
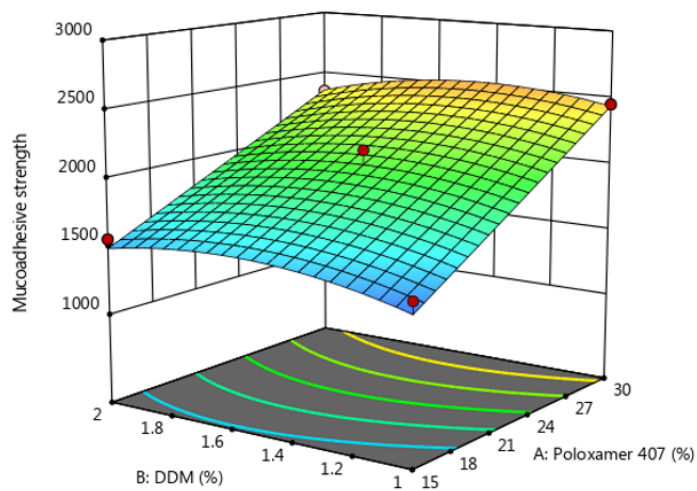


Figure 3

A: 3D response surface plot of Response **B** **Figure 3B** 2D Contour plot of Response **B**

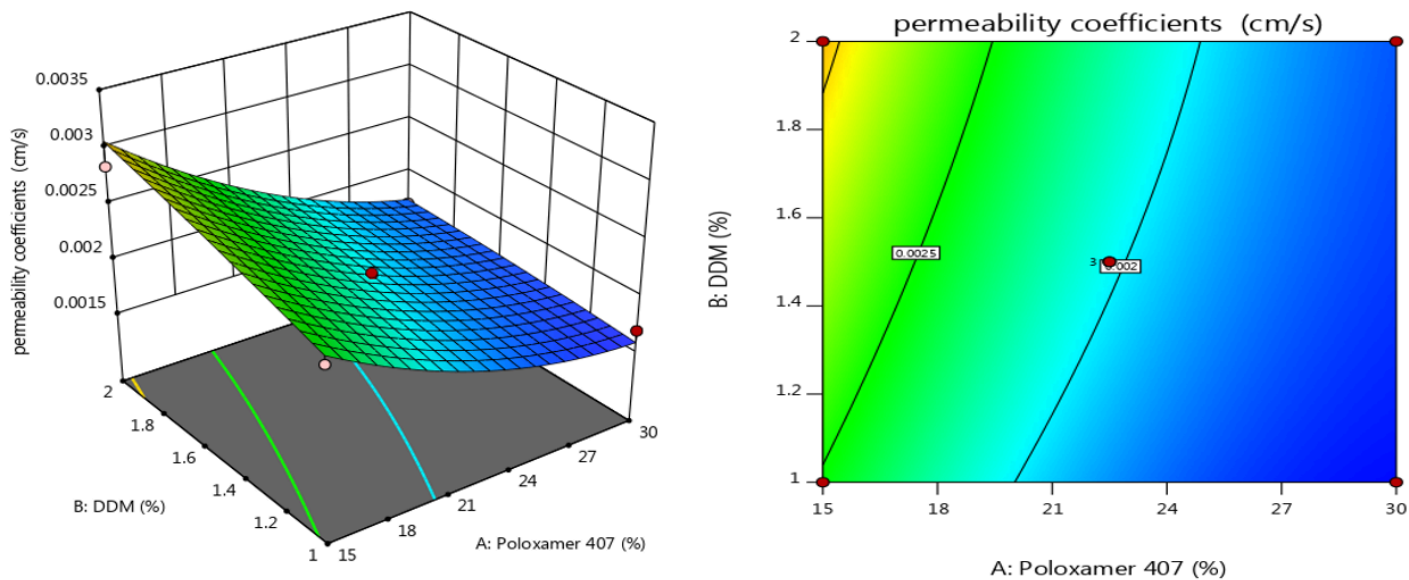


Figure 4

A: 3D response surface plot of Response C Figure 4B 2D Contour plot of Response C

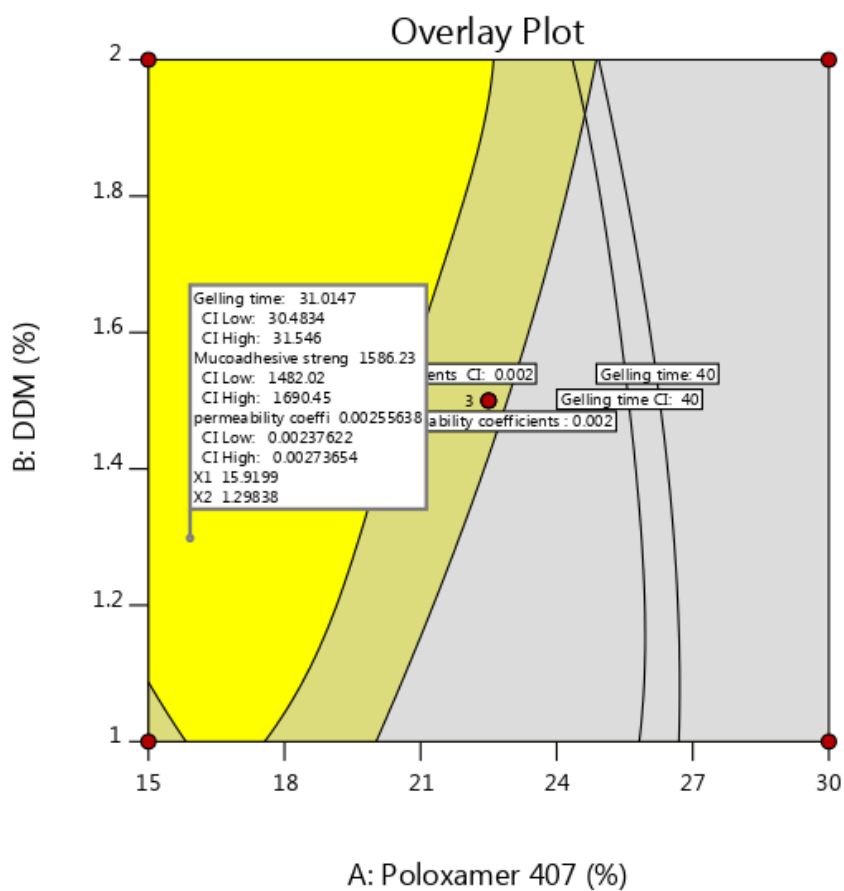


Figure 5

Overlay plot of region highlighting the optimized space and values

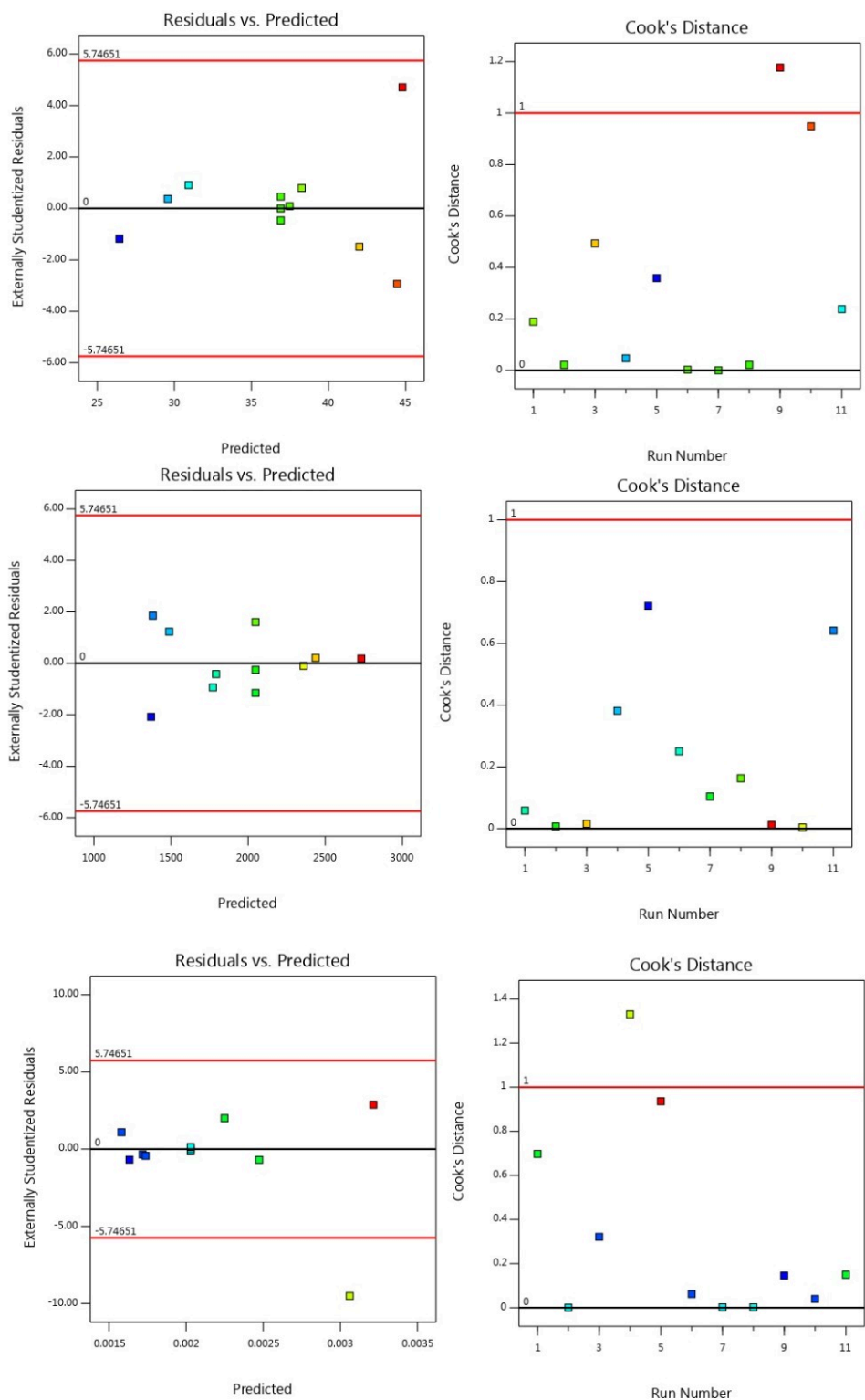


Figure 6

Diagnostic plots for model validation of the optimized RM nasal in situ gel formulation.

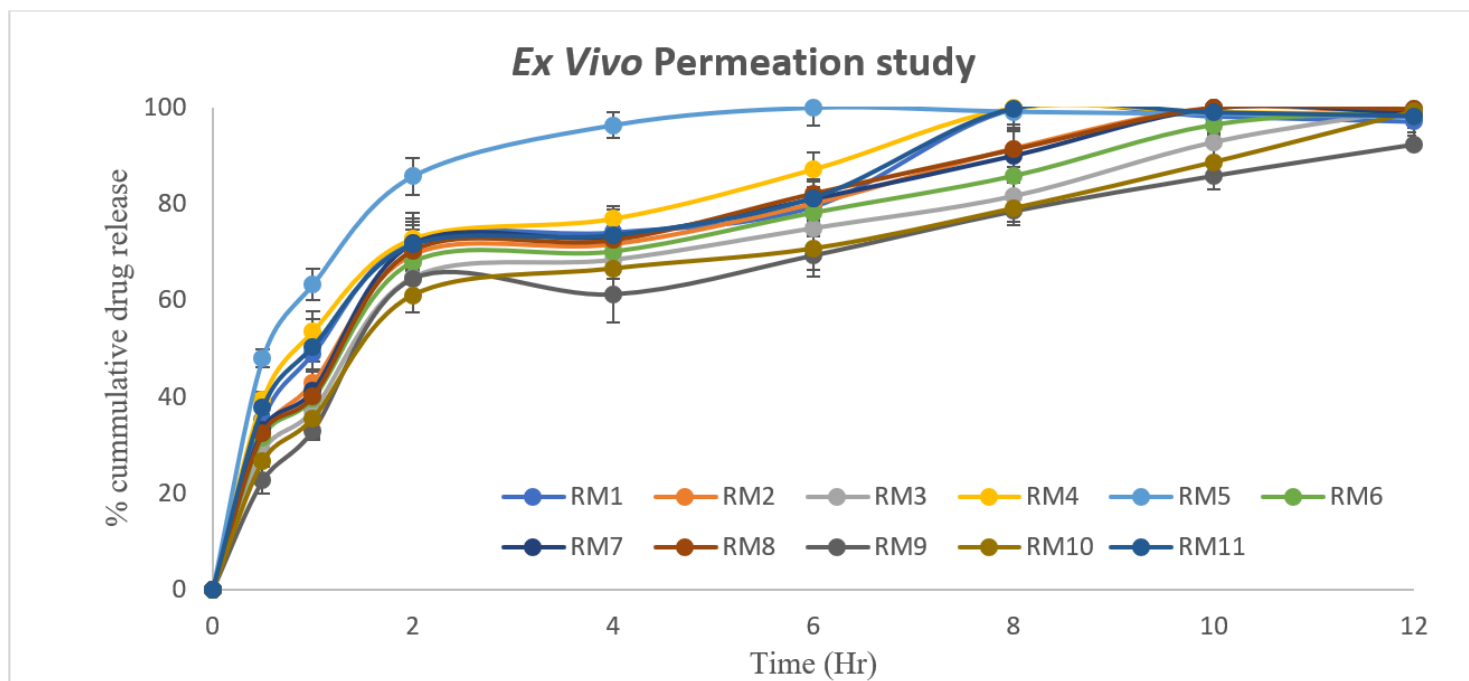


Figure 7

Time vs Cumulative drug release of all the trial runs (mean $\pm$ SD, n=3)

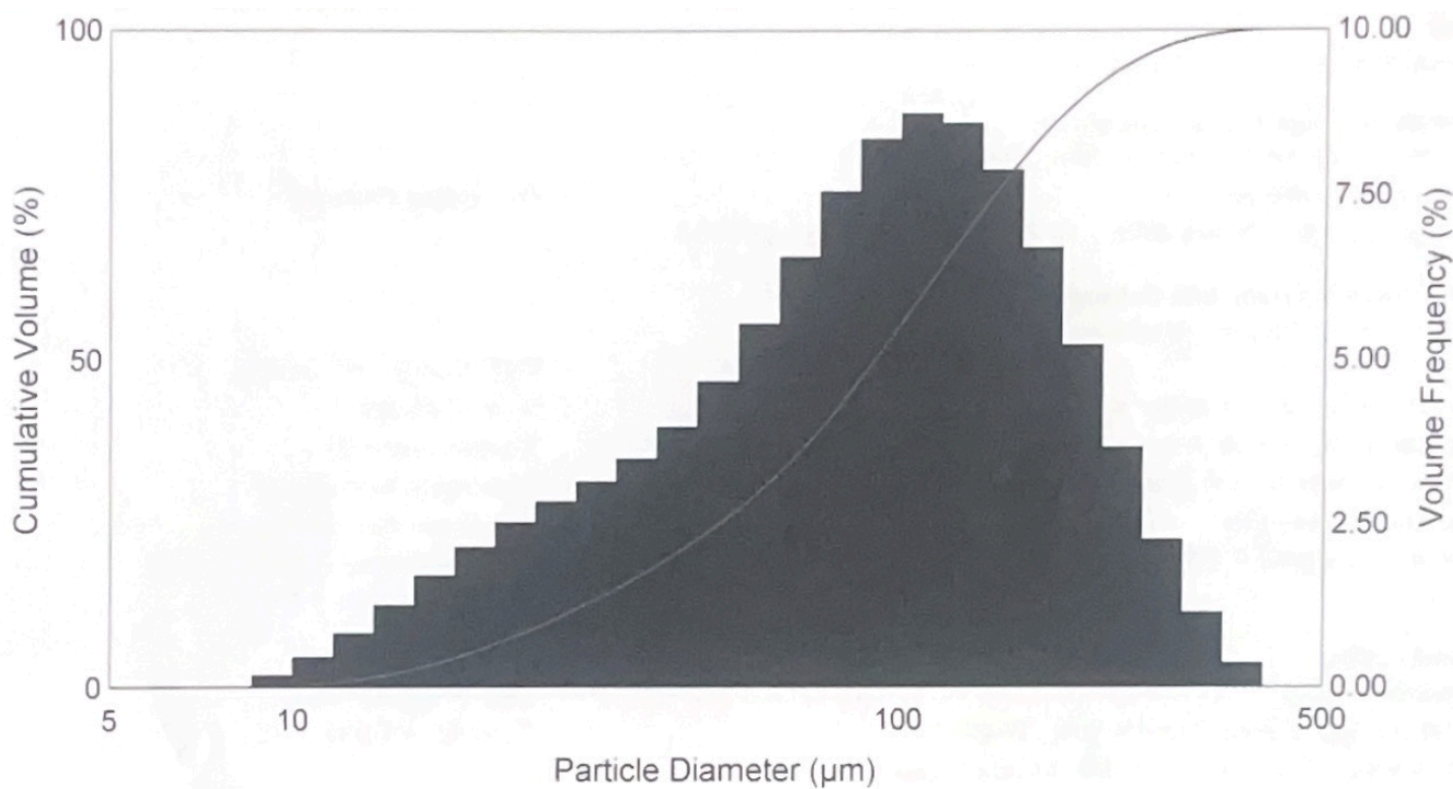


Figure 8

Particle size distribution of Optimized nasal formulation

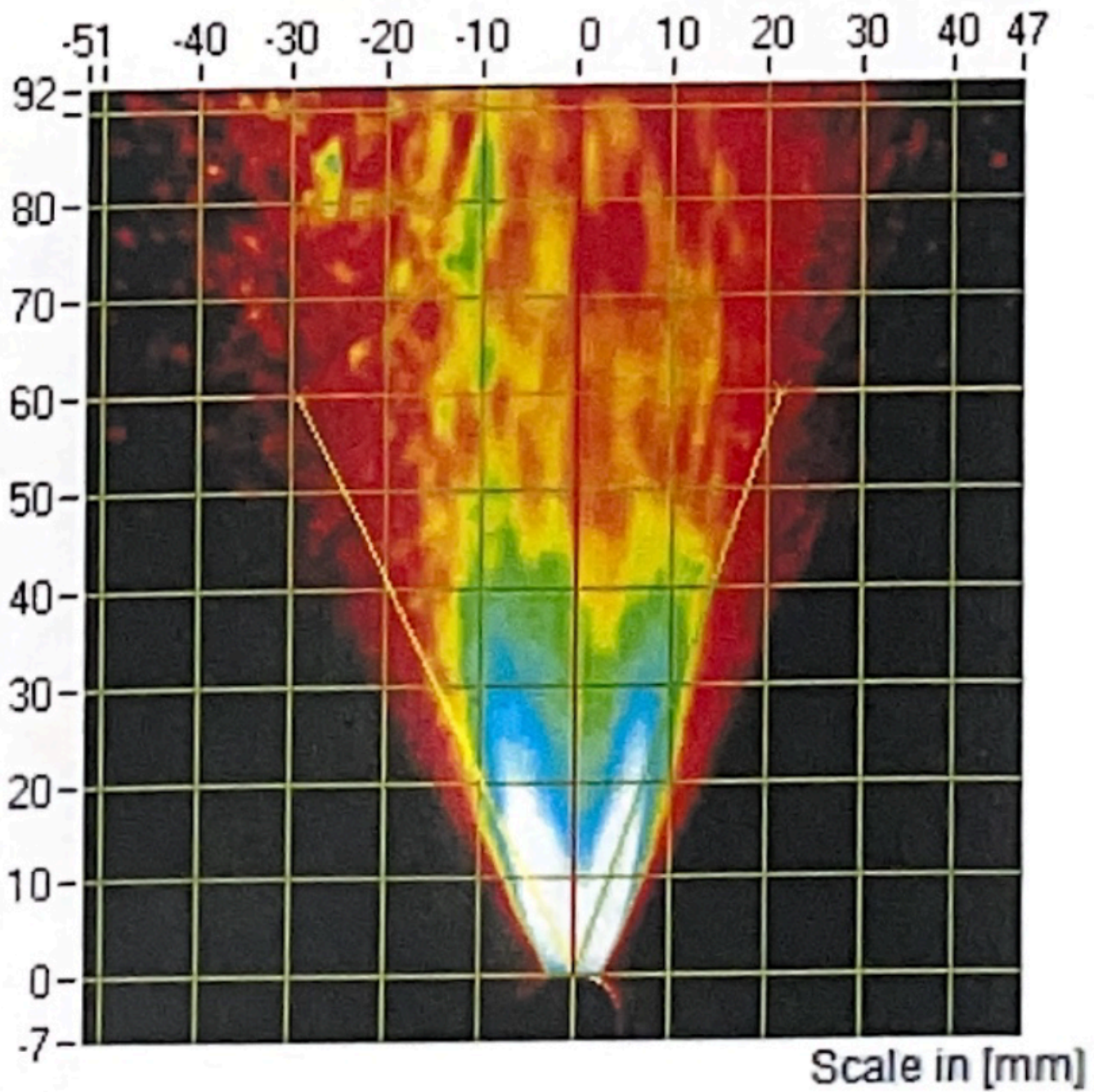


Figure 9

Plume geometry assessment of the optimized nasal spray formulation demonstrating spray pattern and dispersion characteristics