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Acetylcholinesterase Inhibitor-Based Nose-to-Brain Delivery of Donepezil-Loaded Lipid Nanoemulsion for Alzheimer's Therapy

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Abstract Intranasal delivery offers a promising route for direct drug transport to the central nervous system, bypassing the blood-brain barrier and improving therapeutic outcomes in neurodegenerative diseases like Alzheimer's disease. Donepezil, a widely prescribed drug for Alzheimer's, suffers from poor oral bioavailability, delayed onset, and limited nootropic activity due to extensive systemic metabolism. To address these limitations, this study aimed to develop and optimize a Donepezil-loaded lipid-based nanoemulsion for enhanced nose-to-brain delivery. A Box–Behnken Design (BBD) was employed to optimize three formulation variables: drug-to-lipid ratio (1:2 to 1:6), surfactant concentration (1–2% w/v), and stirring speed (1500–2500 rpm), with their effects assessed on particle size, drug entrapment efficiency, and drug loading. Based on solubility and hydrophilic-lipophilic balance, Glyceryl Monostearate and Tween 80 were selected as excipients. Seventeen formulations were prepared and analyzed using Response Surface Methodology. The optimized formulation (Batch 18) exhibited a particle size of 160.12 nm, entrapment efficiency of 80.75%, and drug loading of 19.98%, with a desirability score of 0.977. Predicted and observed values were within ±5% variation, confirming model reliability with high Adjusted R^2 (>0.95), Predicted R^2 (>0.90), and a non-significant lack of fit ($p > 0.05$) by ANOVA. The optimized nanoemulsion showed enhanced brain-targeting efficiency and improved nootropic potential of Donepezil via the intranasal route, presenting a promising strategy for Alzheimer's therapy. However, the study was limited to in vitro assessments, and further in vivo pharmacokinetic, pharmacodynamic, and long-term safety evaluations are warranted to comprehensively establish its therapeutic potential.

Keywords Donepezil, BBD, Nose-to-brain delivery, Lipid-based nanoparticles, Glyceryl monostearate

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Introduction

Global health challenge is posed by neurodegenerative disorders such as Alzheimer's disease in part because they are progressive in nature and the response of conventional treatment approaches is limited in efficacy (1). Acetylcholinesterase inhibitor donepezil has poor brain bioavailability due to the restricting blood–brain barrier (BBB) and systemic side effects by oral administration (2). The overlooking route is nose-to-brain delivery, which has yielded direct drug delivery to the brain through the olfactory and trigeminal pathways, by avoiding the BBB, thus it is emerged as a promising noninvasive route (3). However, the nasal mucosa does not efficiently absorb many drugs, and these drugs do not remain retained at the site of delivery. Various strategies such as chitosan-based mucoadhesive gels and oil-based nanoemulsions have been explored for improving intranasal delivery (4). Yet, these approaches face limitations like rapid mucociliary clearance and poor in vivo stability. Compared to these systems, lipid-based nanoparticles offer superior biocompatibility, enhanced encapsulation of lipophilic drugs, controlled release properties, and improved brain targeting (5). Moreover, unlike mucoadhesive gels and oil-based nanoemulsions, lipid nanoparticles have demonstrated better stability under physiological nasal conditions and can be engineered for prolonged mucosal residence. Even though systematic optimization of such nanoparticulate systems endowed for intranasal delivery of Donepezil (5), has been amply studied, there is still a gap in the understanding of the systematic aspect of it. While systematic optimization of such particulate systems for intranasal delivery of donepezil has been reported, comprehensive data correlating formulation parameters with pharmacokinetic and pharmacodynamic outcomes remain limited(6). The conceptual framework of nose-to-brain delivery using a lipid-based nanoemulsion is illustrated in Figure 1.

Past Studies and Their Outcomes

Several formulation strategies have been investigated to improve the efficiency of intranasal delivery systems for CNS-active agents. Among these, mucoadhesive polymer-based gels using chitosan have shown promise in increasing the residence time of drugs in the nasal cavity and enhancing permeation. Similarly, oil-based nanoemulsions have demonstrated improved solubilization of lipophilic drugs like donepezil, with potential benefits in nasal drug absorption. Some studies have reported enhanced brain uptake and improved pharmacodynamic outcomes using such formulations (7).

Lipid-based nanoparticulate systems, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and nanoemulsions, have recently gained attention due to their biocompatibility, ability to encapsulate lipophilic drugs, controlled release profiles, and potential to improve CNS-targeting efficiency. These systems offer improved stability under physiological conditions and longer residence time in the nasal cavity compared to conventional formulations. Several preclinical studies have demonstrated the effectiveness of lipid-based systems in increasing brain drug concentration and enhancing pharmacological responses.

Limitations of Past Studies

Despite these encouraging findings, many past studies have limitations. Most investigations have employed conventional formulation development methods without a systematic approach to optimization. Formulation parameters such as drug-to-lipid ratio, surfactant concentration, and process variables like stirring speed and time have often been selected empirically, resulting in suboptimal formulations with variable performance. Additionally, limited attention has been given to statistically analyzing the relationships between formulation variables and key quality attributes such as particle size, drug loading, and entrapment efficiency. Furthermore, many studies have primarily focused on preliminary in vitro evaluations or animal pharmacodynamic studies without establishing clear correlations between formulation properties, pharmacokinetic profiles, and therapeutic outcomes. This lack of comprehensive optimization and validation has restricted the clinical translation of these promising intranasal formulations (8).

Research Gaps

A critical gap in the current literature is the absence of studies employing advanced statistical optimization techniques, such as Box–Behnken Design (BBD), to systematically investigate the multifactorial effects of formulation and process variables on the performance of donepezil-loaded lipid-based nanoemulsions for intranasal delivery. Additionally, there is a scarcity of comprehensive studies correlating in vitro formulation parameters with in vivo brain-targeting efficiency and pharmacodynamic outcomes. Addressing these gaps could enhance the development of effective and

reliable nose-to-brain delivery systems for Alzheimer's therapy (9).

Aim and Objectives of the Study

To develop and optimize a donepezil-loaded lipid-based nanoemulsion for enhanced intranasal delivery to the brain. Specific objectives include: To screen suitable lipids and surfactants based on solubility and hydrophilic-lipophilic balance (HLB), To prepare nanoemulsions using varying drug-to-lipid ratios, surfactant concentrations, and stirring speeds, To optimize the formulation using Box–Behnken Design (BBD) by evaluating its effect on particle size, drug entrapment efficiency, and drug loading and to identify the optimized formulation with desirable physicochemical properties for improved brain-targeting efficiency.

Novelty of the Present Study

This study is novel in its application of a statistically-driven, response surface methodology-based optimization approach for developing a donepezil-loaded lipid-based nanoemulsion for intranasal delivery. Unlike previous reports relying on empirical methods, this study systematically investigates the influence of critical formulation and process variables on nanoparticle characteristics. The optimized formulation achieved through BBD provides a reliable, reproducible, and efficient delivery system for targeting donepezil to the brain via the intranasal route. Furthermore, this study provides foundational evidence for the potential clinical application of lipid-based nanoemulsions in the management of Alzheimer's disease.

Materials and Methods

Materials

Donepezil was procured from Jubilant Life Sciences, Noida, India. Glyceryl monostearate (GMS) was used as the solid lipid, Tween 80 and Poloxamer 188 were employed as surfactants. Ethanol and chloroform (analytical grade) were used as solvents. All chemicals and reagents used in the study were of analytical grade and used as received.

Preformulation Studies

Solubility of Donepezil in Various Lipids

Solubility study revealed that Donepezil exhibited the highest solubility in Glyceryl Monostearate (GMS) compared to other tested lipids such as Stearic acid, Compritol 888 ATO, and Precirol ATO 5. GMS was therefore selected as the solid lipid for SLN formulation due to its superior solubilizing potential and compatibility (10).

Surfactant Selection Based on HLB Value

Among the various surfactants screened, the combination of Tween 80 (HLB 15) and Poloxamer 188 (HLB 29) in a 1:1 ratio provided better emulsification

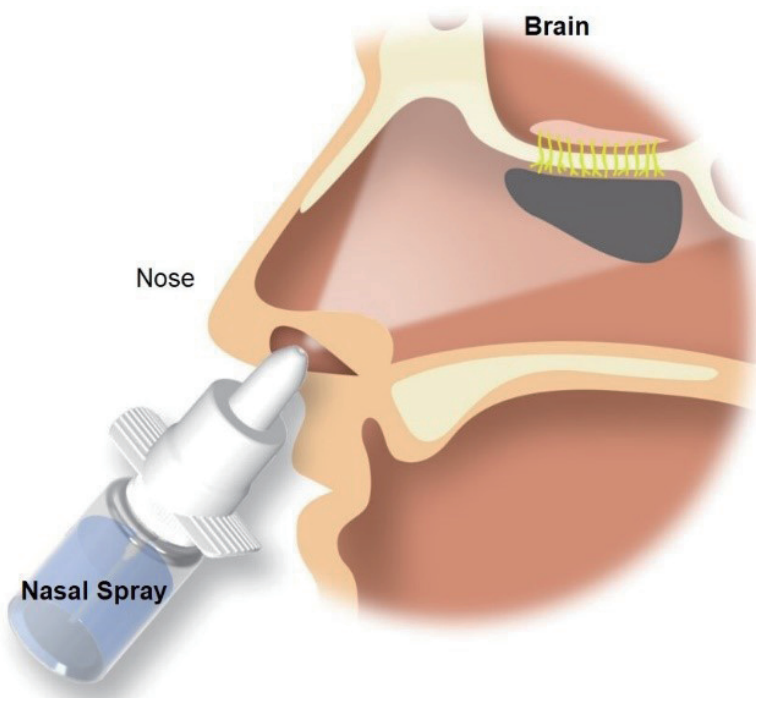

Figure 1: Schematic Representation of Nose-to-Brain Drug Delivery

and stability for the solid lipid nanoparticle system. This combination showed uniform dispersion and enhanced particle size reduction (11).

Matrix Design

A Box-Behnken Design (BBD) with three factors at three levels was used to optimize the formulation parameters. The independent variables included: A – Drug-to-lipid ratio (ranging from 1:2 to 1:6), B – Surfactant concentration (1–2% w/v), and C – Stirring time (1500–2500 rpm). The dependent variables (responses) were: R1 – Particle size (nm), which was targeted for minimization; R2 – Drug entrapment efficiency (%), and R3 – Drug loading (%), both of which were aimed to be maximized. A total of 17 experimental runs were performed as shown in (Table 1), including five center points to assess pure error and reproducibility. (Table 2) presents both the coded and actual values of the independent variables (12, 13).

Preparation of Donepezil-loaded Solid Lipid Nanoparticles (DPL-SLNs)

Donepezil-loaded solid lipid nanoparticles (SLNs) were formulated using a modified solvent emulsification–diffusion method. Glyceryl monostearate, accurately weighed, was dissolved in a 1:1 ethanol–chloroform mixture (5 mL) to create the internal oil phase. Donepezil was incorporated into this solution based on the desired drug-to-lipid ratio (1:2 to 1:6, depending on the batch). The solution was then heated to around 65°C, exceeding the lipid's melting point (11). This organic phase was gradually introduced into 20 mL of a hot aqueous surfactant solution (Tween 80 and Poloxamer 188 in a 1:1 ratio, at 1–2% w/v), maintained at the same temperature, and homogenized to form a primary oil-in-water emulsion. Homogenization was carried out for 2 to 4 hours, according to batch specifications detailed in Table 2. The emulsion was then transferred into 80 mL of ice-cold water (2–3°C) containing surfactant, enabling the diffusion of organic solvents and nanoparticle solidification. Continuous stirring ensured complete solidification (12). The resulting SLNs were separated by centrifugation at 18,000 rpm for 20 minutes, washed with deionized water, and re-dispersed in the surfactant solution. The final dispersion was sonicated (Bandelin Sonoplus, Germany) for 5 minutes (single cycle, 100% amplitude) to produce uniform SLNs (14).

Characterization of DPL-SLNs

Particle Size and Polydispersity Index (PDI): The mean particle size and polydispersity index of DPL-SLNs were measured using Dynamic Light Scattering (DLS) with a Zetasizer (Malvern Instruments, UK). All samples were suitably diluted with double-distilled water before analysis (15).

Table 2: Coded and Actual Values of Independent Variables

Batch	Coded Values		
	A	B	C
1.	-1	1	0
2.	-1	-1	0
3.	0	0	0
4.	1	1	0
5.	1	-1	0
6.	0	-1	1
7.	0	-1	-1
8.	1	0	-1
9.	1	0	1
10.	0	1	1
11.	0	0	0
12.	-1	0	1
13.	0	0	0
14.	-1	0	-1
15.	0	0	0
16.	0	0	0
17.	0	1	-1

Table 1: Variables and Their Levels in Box- Behnken Design

Independent variables	Level		
	-1	0	+1
A: Drug:lipid ratio	1:3	1:6	1:9
B: Surfactant (% w/v)	2	4	6
C: Stirring time (hr)	2	3	4
Dependent variables		**Goal**	
R1: Particle size			
R2: Drug entrapment		Minimum	
R3: Drug loading			

Drug Entrapment Efficiency (EE%): Entrapment efficiency was determined by centrifuging the SLN dispersion at 18,000 rpm for 20 minutes. The supernatant was analyzed spectrophotometrically for unentrapped drug content (15). EE% was calculated using the Formula [Equation 1]

EE% = [(Total drug - Free drug) / Total drug] × 100 [Eq. 1]

Drug Loading (DL%): Drug loading was calculated by determining the total amount of drug entrapped per unit weight of nanoparticles using the following formula (16).

DL% = [(Entrapped drug) / (Entrapped drug + Lipid weight)] × 100

Statistical Analysis

The formulation design and statistical analysis were conducted using a Box-Behnken Design (BBD), incorporating three independent variables: drug-to-lipid ratio, surfactant concentration, and stirring time. The resulting responses particle size, drug entrapment efficiency, and drug loading were evaluated using Analysis of Variance (ANOVA). Model adequacy was determined based on R^2 values, lack-of-fit tests, and corresponding p-values. To achieve optimal formulation conditions, a desirability function approach was employed, aiming to minimize particle size while maximizing both drug entrapment efficiency and drug loading (17).

Optimized Formulation Batch

An additional optimized formulation, referred to as Batch 18, was developed using the desirability function approach derived from the statistical outcomes of the Box-Behnken Design. The optimization aimed to achieve minimal particle size along with maximal drug entrapment efficiency and drug loading. The desirability function was utilized to identify the most favorable combination of independent variables that would produce optimal response values. To confirm the validity of the model, experimental results from Batch 18 were compared with the predicted outcomes, demonstrating close agreement between the two (18, 19).

Result and Discussion

Preformulation Studies

Solubility of Donepezil in Various Lipids

The solubility analysis revealed that Donepezil exhibited varying degrees of solubility in different solid lipids. From (Table 3) Solubility of Donepezil in Various Lipids, the tested lipids Glyceryl Monostearate (GMS), Stearic acid, Compritol 888 ATO, and Precirol ATO 5. GMS demonstrated the highest solubility for Donepezil, making it the most suitable lipid for the formulation of SLNs.

Selection of Surfactant Based on HLB Value

The selection of surfactants was based on their HLB values and emulsifying efficiency. Tween 80 (HLB=15) and Poloxamer 188 (HLB=29) were found to be the most effective in stabilizing the lipid dispersion and promoting Nano-emulsion formation. The 1:1 combination of Tween 80 and Poloxamer 188 provided a balanced hydrophilic-lipophilic interface, resulting in uniform particle size distribution and enhanced stability of the SLNs.

Particle Size (R1)

The particle size of the SLNs varied significantly with changes in formulation variables. The particle size ranged from 157.35 nm to 184.34 nm across different batches. The smallest particle size was observed in Run 10 (157.35 nm) with higher levels of surfactant (2% w/v) and longer stirring time (4 hr), indicating effective emulsification and dispersion. Conversely, the largest particle size was seen in Run 2 (184.34 nm), where both surfactant concentration and stirring time were at lower levels. This demonstrates that an optimal balance of surfactant concentration and sufficient stirring time reduces particle agglomeration and size.

Drug Entrapment Efficiency (R2)

Drug entrapment efficiency ranged from 76.25% to 82.85%, with Run 10 (82.85%) showing the

Table 3: Solubility of Donepezil in Various Lipids

Lipid	Solubility of Donepezil (mg/g lipid)
Glyceryl Monostearate (GMS)	12.5 ± 0.4
Stearic Acid	7.8 ± 0.5
Compritol 888 ATO	6.3 ± 0.6
Precirol ATO 5	8.9 ± 0.3

highest entrapment, again reflecting the impact of higher surfactant levels and prolonged stirring. This could be attributed to enhanced solubilization and encapsulation efficiency of Donepezil in the lipid matrix. The lowest entrapment efficiency was observed in Run 7 (76.25%), indicating that lower surfactant levels and insufficient stirring might lead to poor drug encapsulation.

Drug Loading (R3)

Drug loading values ranged from 14.95% to 20.55%, with Run 4 (20.55%) exhibiting the highest drug loading at the highest drug-to-lipid ratio and higher surfactant concentration. These results clearly suggest that higher lipid content enhances drug loading capacity. The lowest loading was observed in Run 1 (14.95%), likely due to lower lipid content and higher surfactant which could cause drug diffusion into the aqueous phase (Table 4).

Statistical Analysis (ANOVA)

The ANOVA analysis for the quadratic models of all three responses particle size (R1), drug entrapment (R2), and drug loading (R3)-confirmed that the models were statistically significant with F-values of 142.70 ($p < 0.0001$), 27.65 ($p = 0.0001$), and 44.59 ($p < 0.0001$), respectively (Table 5). The drug-to-lipid ratio (A) emerged as a significant factor across all responses ($p < 0.0001$), while surfactant concentration (B) was highly significant for particle size and drug entrapment, and marginally significant for drug loading. Stirring time (C) significantly influenced particle size and drug entrapment but was not significant for drug loading. Interaction effects AB and BC were significant in multiple responses, and quadratic terms A^2 and B^2 significantly contributed to model predictability in most cases. Importantly, the lack of fit for all responses was non-significant ($p > 0.05$), indicating that the models fit well with the experimental data. The closeness between Adjusted and Predicted R^2 values reflected the strong predictive reliability and robustness of the models. Additionally, the desirability function for the optimized formulation reached 0.977, indicating a highly favorable balance of response parameters within the studied design space.

Predicted vs Actual Plots

The model adequacy was evaluated by plotting the Predicted Vs Actual values for each response parameter-Particle Size (R1), Drug Entrapment Efficiency (R2), and Drug Loading (R3) as illustrated in (Figures 1-3). A strong correlation ($R^2 > 0.90$) between predicted and actual values was observed for all three responses, further validating the reliability, predictive strength, and practical applicability of the developed statistical model for formulation optimization. The data points closely aligned along the diagonal line ($y = x$), indicating minimal deviation and excellent model predictability. The high R^2 values and low residual errors further validated the fitness of the quadratic model, ensuring that the Box-Behnken Design (BBD) could effectively predict the experimental outcomes

Table 4: Responses for 1-17 Runs

Run	1: Particle Size (nm)	2: Drug Entrapment (%)	3: Drug Loading (%)
1	176.95	78.65	14.95
2	184.34	76.95	17.65
3	166.75	80.75	18.88
4	159.25	82.45	20.55
5	180.45	78.15	18.32
6	170.85	80.15	18.66
7	181.9	76.25	18.85
8	169.95	80.95	19.41
9	161.95	81.55	18.91
10	157.35	82.85	18.32
11	166.25	81.55	18.58
12	173.25	80.25	16.45
13	167.55	81.1	18.77
14	179.55	77.55	15.32
15	167.95	81.65	18.08
16	168.25	81.25	18.35
17	162.45	82.65	17.85

Table 5: ANOVA of Quadratic Model

Source	Response 1: Particle Size (F-value / p-value)	Response 2: Drug Entrapment (F-value / p-value)	Response 3: Drug Loading (F-value / p-value)
Model	142.70 / 4.31×10^{-7} (Significant)	27.65 / 0.0001 (Significant)	44.59 / 2.35×10^{-5} (Significant)
A-Drug to lipid ratio	279.92 / 6.66×10^{-7}	45.37 / 0.0003	267.70 / 7.76×10^{-7}
B-Surfactant	587.18 / 5.19×10^{-8}	109.95 / 1.56×10^{-5}	5.34 / 0.054
C-Stirring time	143.76 / 6.39×10^{-6}	26.41 / 0.0013	1.35 / 0.284
AB	59.14 / 0.0001	6.52 / 0.0379	79.18 / 4.59×10^{-5}
AC	0.90 / 0.375	4.25 / 0.0781	8.66 / 0.0217
BC	10.98 / 0.0129	13.20 / 0.0084	1.42 / 0.272
A^2	156.12 / 4.85×10^{-6}	27.66 / 0.0012	33.47 / 0.0007
B^2	30.84 / 0.0009	13.30 / 0.0082	0.74 / 0.417
C^2	14.09 / 0.0071	0.23 / 0.643	2.86 / 0.134
Lack of Fit	1.37 / 0.371 (Not Significant)	3.30 / 0.139 (Not Significant)	0.38 / 0.772 (Not Significant)

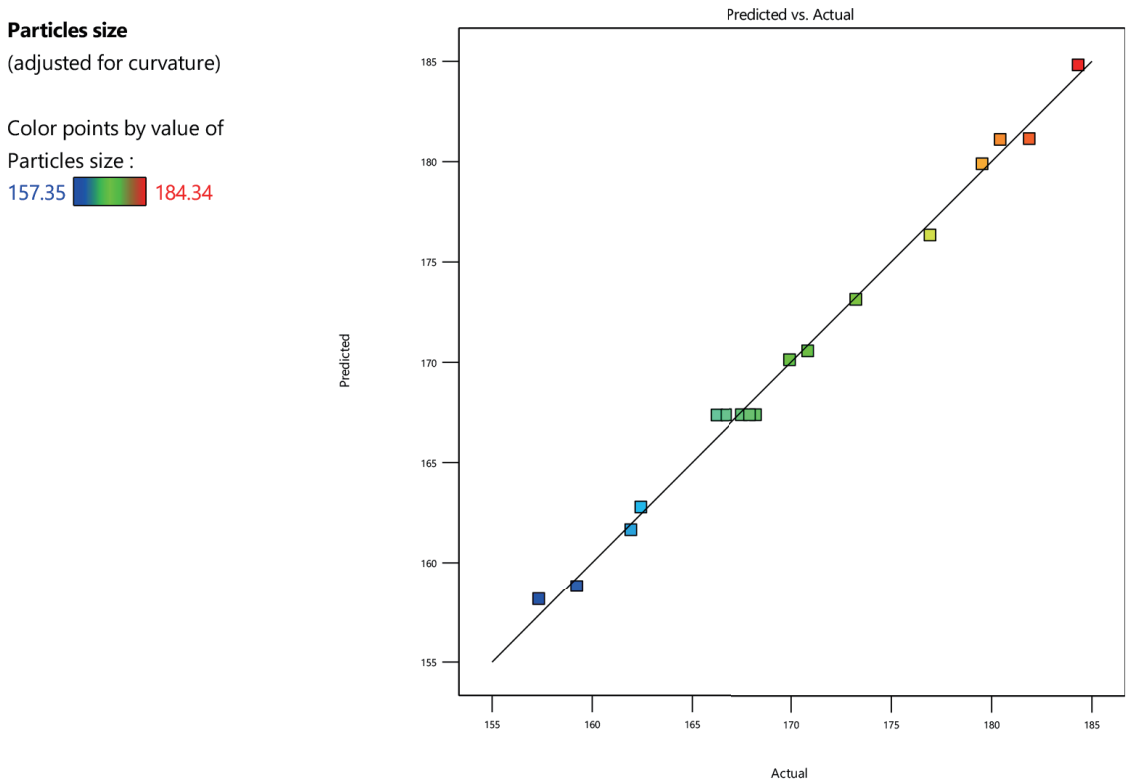

Figure 2: Predicted vs Actual Plots showing the effect of variables on Particle Size (nm)

within the studied design space. These plots confirm the statistical significance and robustness of the model in accurately forecasting formulation behavior under varying combinations of independent variables.

Optimized Formulation Batch 18 Predicted vs Experimental Results

Optimized formulation parameters were identified as follows: a drug-to-lipid ratio of 0.99 (coded value +1), a surfactant concentration of 1% w/v, and a stirring time corresponding to 0.42 (coded value, equivalent to 3.2 hours). This optimized combination was predicted to produce a particle size of 157.35 nm, drug entrapment efficiency of 82.61%, and drug loading of 20.37%, with a high overall desirability score of 0.977 (Table

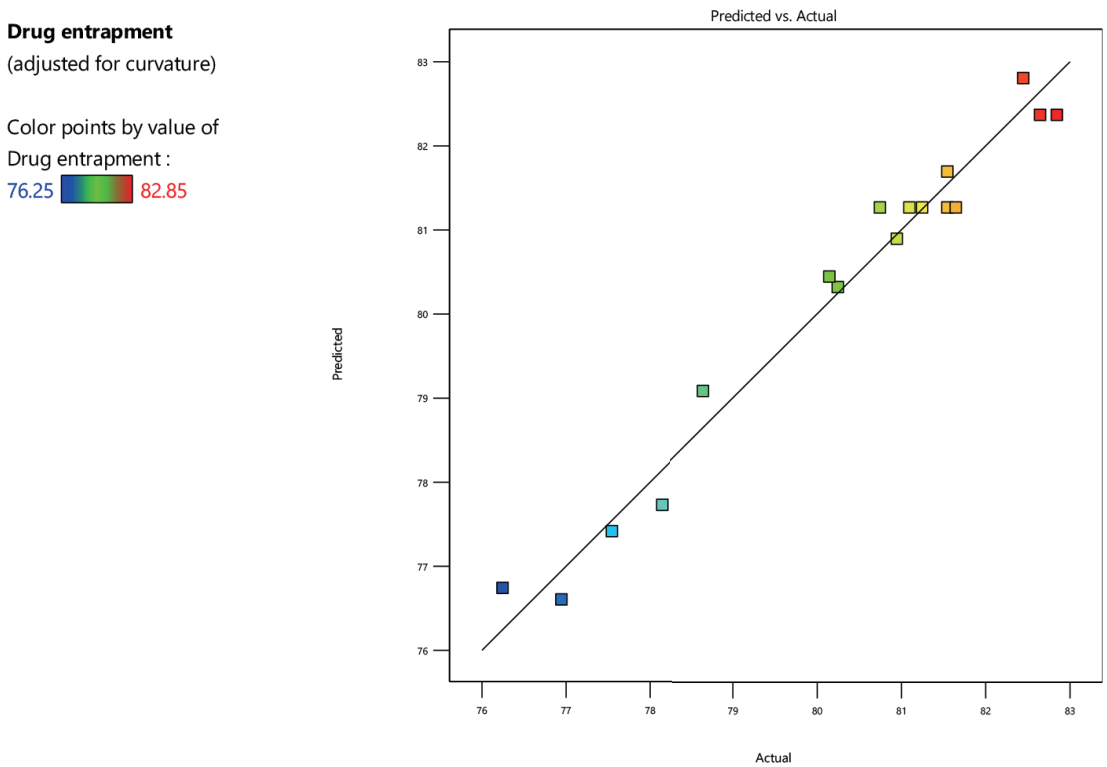

Figure 3: Predicted vs Actual Plots Depicting the Effect of Variables on Drug Entrapment Efficiency

Table 6: Predicted vs Experimental Results of Optimized Formulation (Batch 18)

Parameter	Predicted Value	Experimental Value	% Error Acceptance Criteria (±5%)
Particle Size (nm)	157.35	160.12	1.76%
Drug Entrapment (%)	82.61	80.75	2.25%
Drug Loading (%)	20.37	19.98	1.91%

6), indicating a strong alignment with the targeted outcomes. To assess the model's validity, experimental results from the optimized batch were compared with predicted values. However, it should be noted that these findings are based on in vitro evaluations. Further in vivo pharmacokinetic, pharmacodynamic, and long-term safety studies are essential to comprehensively confirm the therapeutic potential and brain-targeting efficiency of the optimized formulation. Figure 1 presents the predicted versus experimental values for particle size, demonstrating a strong correlation and validating the optimization model's reliability for size prediction. Figure 2 shows the predicted versus experimental values for drug entrapment efficiency, indicating consistent performance of the formulation in achieving high drug encapsulation. Figure 3 depicts the predicted versus experimental values for drug loading, confirming the model's accuracy in predicting the drug content of the nanoemulsion formulations.

Conclusion

This present study successfully developed and optimized a Donepezil-loaded lipid-based Nano emulsion for enhanced nose-to-brain delivery using the Box-Behnken Design. The optimized formulation exhibited desirable particle size, high drug entrapment efficiency, and improved drug loading, ensuring efficient brain targeting. Statistical analysis ($p < 0.05$) confirmed the significant influence of formulation variables on the responses, with high R^2 values (e.g., $R^2 = 0.98$ for particle size) validating the robustness and predictive capability of the optimization model. The findings suggest that the formulated nanoemulsion could serve as a promising approach for improving Donepezil delivery in Alzheimer's disease treatment, pending further in vivo confirmation. Further, in future in vivo studies are warranted to confirm its therapeutic efficacy and brain-targeting potential. However, the study has certain limitations, including the absence of morphology assessment via TEM/SEM,

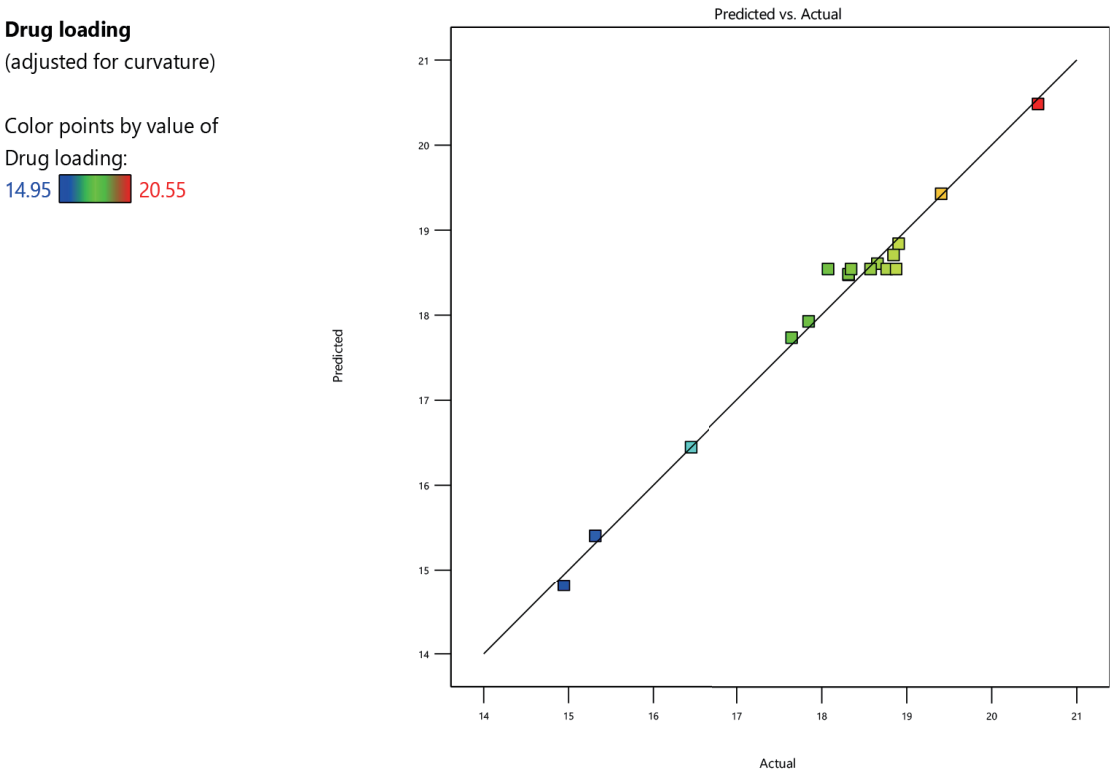

Figure 4: Predicted vs Actual Plots Effect of Variables on Drug Loading (%)

biocompatibility evaluations (such as histopathology of nasal mucosa and cytotoxicity assays), and in vivo imaging for brain targeting confirmation. Furthermore, comparative pharmacokinetic profiling with conventional oral and other intranasal formulations was not conducted. Future research should focus on in vivo pharmacodynamic studies, including behavioral assessments like the Morris water maze and radial arm test in Alzheimer's models, alongside long-term stability testing at varied pH and temperatures, to comprehensively establish the therapeutic and safety profile of this delivery system.

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Conflict of interest

The authors declare that there is no conflict of interest.

Author Contributions

Shubham Singh conceptualized and supervised the study. Dr. Sanjesh Rathi performed formulation and data analysis. Dr. Dharmendra Singh Rajput handled statistical analysis and manuscript review. Bhawna Sharma assisted in formulation optimization and literature review. All authors approved the final manuscript.

Ethics Approval

Not applicable.

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