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Nose-to-Brain Drug Delivery of Donepezil Loaded Lipid-Based Nanoemulsion for Alzheimer

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ABSTRACT

Background: Nose-to-brain drug delivery offers a promising alternative to bypass the blood-brain barrier and directly target the central nervous system. Donepezil, a commonly used drug for Alzheimer's disease, suffers from low oral bioavailability and delayed therapeutic action. Therefore, an optimized nanocarrier system is essential to improve brain targeting and enhance treatment efficacy.

Objective: This study was designed to develop and optimize a Donepezil-loaded lipid-based nanoemulsion to enhance nose-to-brain delivery and improve therapeutic outcomes in Alzheimer's disease.

Methods: A Box-Behnken Design (BBD) was utilized to optimize three independent variables: drug-to-lipid ratio (1:2 to 1:6), surfactant concentration (1–2% w/v), and stirring speed (1500–2500 rpm). The critical quality attributes evaluated were particle size (R1), drug entrapment efficiency (R2), and drug loading (R3). Glyceryl Monostearate (GMS) and Tween 80 were selected based on solubility and hydrophilic-lipophilic balance (HLB). Seventeen formulations were developed and analyzed using response surface methodology.

Results: Optimized Formulation Extra Batch 18 exhibited a particle size of 160.12 nm, drug entrapment efficiency of 80.75%, and drug loading of 19.98%, with a desirability score of 0.977. All observed results were found to be within ±5% variation from predicted values. ANOVA results confirmed statistical significance ($p < 0.05$) with a non-significant lack of fit, indicating model adequacy and predictive reliability. Graphical analysis through 3D surface plots and predicted vs. actual plots supported the optimization outcomes.

Conclusion: The optimized lipid-based nanoemulsion of Donepezil showed potential for improved nose-to-brain delivery, enhancing brain bioavailability and minimizing systemic side effects. This formulation presents a promising therapeutic approach for Alzheimer's disease management.

Keywords: *Donepezil, Box-Behnken Design, Nose-to-brain delivery, Lipid-based nanoparticles, Glyceryl monostearate, Tween 80*

1. INTRODUCTION

Neurodegenerative disorders such as Alzheimer's disease pose a significant global health challenge due to their progressive nature and limited therapeutic efficacy of conventional treatment approaches [1]. Donepezil, a widely prescribed acetylcholinesterase inhibitor, suffers from poor brain bioavailability owing to the restrictive blood-brain barrier (BBB) and systemic side effects associated with oral administration [2]. Nose-to-brain delivery has emerged as a promising non-invasive route to bypass the BBB, offering direct drug transport to the brain via the olfactory and trigeminal pathways [3]. However, effective delivery systems are required to enhance drug absorption and retention at the nasal mucosa. Lipid-based nanoparticles, due to their biocompatibility and ability to encapsulate lipophilic drugs, have shown potential in enhancing brain targeting [4]. Schematic Representation of Nose-to-Brain Drug Delivery are shown in Figure 1, Schematic Representation of Nose-to-Brain Drug Delivery PathwayDespite existing research, there remains a gap in the systematic optimization of such nanoparticulate systems tailored for intranasal delivery of Donepezil [5]. This study aims to develop and optimize Donepezil-loaded lipid-based nanoparticles using Box-Behnken Design (BBD), focusing on critical formulation variables such as drug-to-lipid ratio, surfactant concentration, and stirring time to achieve optimal particle size, drug entrapment efficiency, and drug loading for enhanced nose-to-brain drug delivery [6].

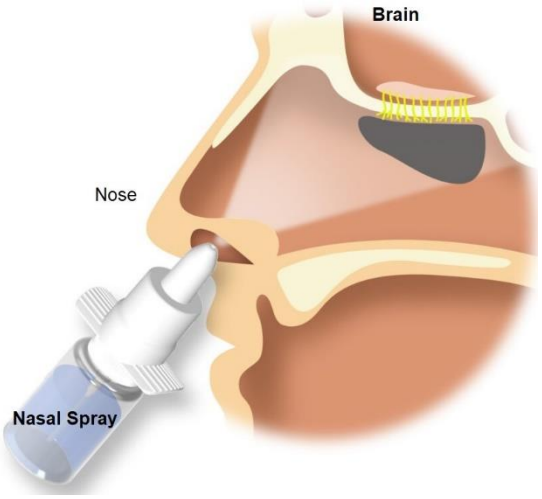

Figure 1. Schematic Representation of Nose-to-Brain Drug Delivery

2. 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 [7].

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 and stability for the solid lipid nanoparticle system. This combination showed uniform

dispersion and enhanced particle size reduction [8].

Experimental Design

A three-factor, three-level Box-Behnken Design (BBD) was employed to optimize the formulation parameters. The independent variables selected were: A: Drug to lipid ratio (1:2 to 1:6), B: Surfactant concentration (1–2% w/v), C: Stirring time (1500–2500 rpm) and the dependent variables (responses) were: R1: Particle size (nm)-To be minimized, R2: Drug entrapment efficiency (%)-To be maximized and R3: Drug loading (%), To be maximized, From Table 1 show Seventeen experimental runs were conducted, including five center points to estimate pure error and reproducibility and Table 2 gives Coded and Actual Values of Independent Variables [9, 10].

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

DPL-loaded SLNs were prepared using a modified solvent emulsification–diffusion technique. Accurately weighed lipid (Glyceryl monostearate) was dissolved in a mixture of ethanol and chloroform (1:1, 5 mL) to form the internal oil phase. Donepezil, at a drug-to-lipid ratio ranging from 1:2 to 1:6 (as per batch formulation), was dispersed in the above solution. The mixture was heated above the melting point of the lipid (approximately 65°C) [11]. The organic phase was then added dropwise into 20 mL of hot aqueous surfactant solution (Tween 80 and Poloxamer 188 in 1:1 ratio, 1–2% w/v) maintained at the same temperature, and homogenized to form a primary o/w emulsion. The homogenization process was continued for ***2 to 4 hours***, depending on the formulation batch (as shown in Table 2). The formed emulsion was subsequently added to 80 mL of ice-cold water (2–3°C) containing surfactant, facilitating the extraction of organic solvents and solidification of nanoparticles. The dispersion was stirred continuously for complete solidification [12]. The resultant SLNs were collected by centrifugation at 18,000 rpm for 20 minutes, washed with deionized water, and redispersed in the aqueous surfactant mixture. Finally, the dispersion was sonicated (Bandelin sonoplus, Germany) for 5 minutes (1 cycle, 100% amplitude) to obtain uniform-sized SLNs [13].

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

Independent variables	**Level**		
	-1	**0**	**+1**
A: Drug to lipid ratio	1:2	1:4	1:6
B: Surfactant **(% w/v)**	1	1.5	2
C: Stirring time (hr)	2	3	4
Dependent variables	**Goal**		
R1: Particle size	Minimum		
R2: Drug entrapment	Maximum		
R3: Drug loading	Maximum		

Table 2. Coded and Actual Values of Independent Variables

Batch	**Coded Values**			**Actual Values**		
	A	**B**	**C**	**Drug : Lipid Ratio**	**Surfactant (% w/v)**	**Stirring Time (hr)**
1.	-1	1	0	1:2	2	3
2.	-1	-1	0	1:2	1	3
3.	0	0	0	1:4	1.5	3
4.	1	1	0	1:6	2	3
5.	1	-1	0	1:6	1	3
6.	0	-1	1	1:4	1	4
7.	0	-1	-1	1:4	1	2

8.	1	0	-1	1:6	1.5	2
9.	1	0	1	1:6	1.5	4
10.	0	1	1	1:4	2	4
11.	0	0	0	1:4	1.5	3
12.	-1	0	1	1:2	1.5	4
13.	0	0	0	1:4	1.5	3
14.	-1	0	-1	1:2	1.5	2
15.	0	0	0	1:4	1.5	3
16.	0	0	0	1:4	1.5	3
17.	0	1	-1	1:4	2	2

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 [14].

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:

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

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

Design and statistical evaluation were carried out using Box-Behnken Design (BBD) with three independent variables: drug-to-lipid ratio, surfactant concentration, and stirring time. The response variables (particle size, drug entrapment efficiency, and drug loading) were analyzed using **Analysis of Variance (ANOVA).** The model's adequacy was assessed through R^2 values, lack of fit, and p-values. A **desirability function approach** was applied to optimize the formulation by simultaneously minimizing particle size and maximizing drug entrapment and drug loading [17].

Optimized Formulation Batch

An additional optimized formulation batch (Batch 18) was developed using the desirability function approach based on the statistical outputs of the Box-Behnken Design, the formulation was optimized by considering the goal of achieving **minimum particle size, maximum drug entrapment efficiency,** and **maximum drug loading.** The desirability function approach was employed to determine the most suitable combination of independent variables that could yield the best response outcomes. To validate the model, the experimental values obtained for the optimized batch were compared with the predicted values [17].

3. 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.

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

4. 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 nanoemulsion 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 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 3. Observed Responses for 1-17 Runs of DPL-SLNs According to Box-Behnken Design

Run	A: Drug to lipid ratio	B: Surfactant (% w/v)	C: Stirring time (hr)	R1: Particle Size (nm)	R2: Drug Entrapment (%)	R3: Drug Loading (%)
1	-1	1	0	176.95	78.65	14.95
2	-1	-1	0	184.34	76.95	17.65
3	0	0	0	166.75	80.75	18.88
4	1	1	0	159.25	82.45	20.55
5	1	-1	0	180.45	78.15	18.32
6	0	-1	1	170.85	80.15	18.66
7	0	-1	-1	181.9	76.25	18.85
8	1	0	-1	169.95	80.95	19.41
9	1	0	1	161.95	81.55	18.91

10	0	1	1	157.35	82.85	18.32
11	0	0	0	166.25	81.55	18.58
12	-1	0	1	173.25	80.25	16.45
13	0	0	0	167.55	81.1	18.77
14	-1	0	-1	179.55	77.55	15.32
15	0	0	0	167.95	81.65	18.08
16	0	0	0	168.25	81.25	18.35
17	0	1	-1	162.45	82.65	17.85

5. 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. 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.

Table 4. ANOVA of Quadratic Model for All Responses

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)**

6. 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 between predicted and actual values was observed for all three responses, confirming the reliability and validity of the

developed statistical model. 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 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: Drug to lipid ratio: 0.99 (coded value equivalent to +1), Surfactant concentration: 1% w/v, and Stirring time: 0.42 (coded value equivalent to 3.2 hours). This formulation was predicted to yield a particle size of 157.35 nm, drug entrapment efficiency of 82.61%, and drug loading of 20.37%, with an overall desirability value of 0.977, indicating an excellent fit for the desired outcomes. To validate the model, the experimental values obtained for the optimized batch were compared with the predicted values. All observed results were found to be within ±5% variation from predicted values, confirming the accuracy, reliability, and robustness of the statistical model.

Table: 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%

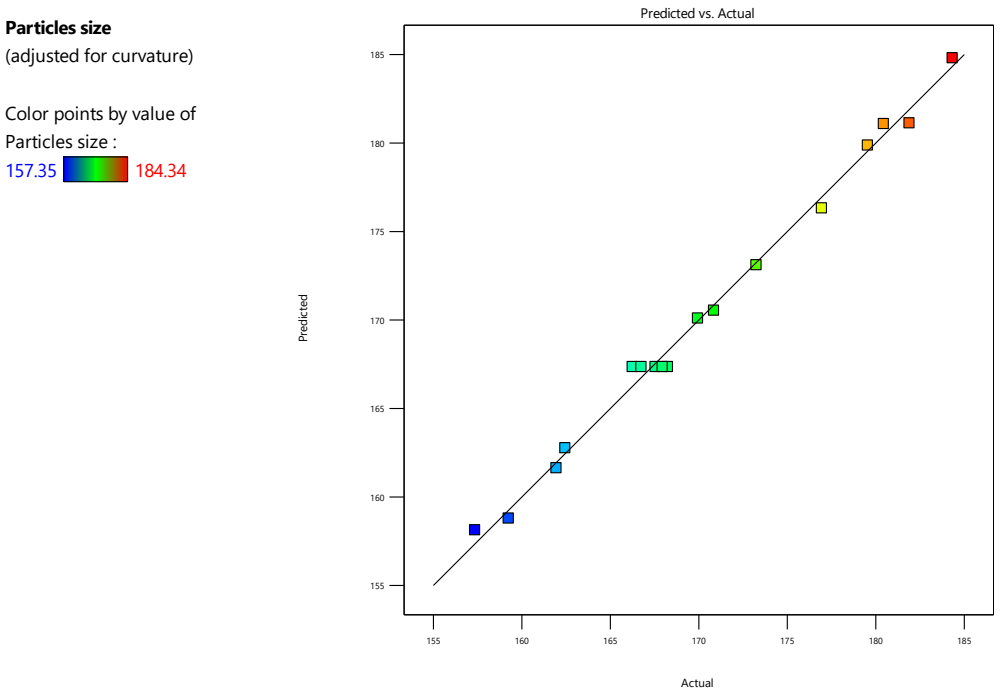

Figure 2. Predicted vs Actual Plots showing the effect of variables on Particle Size (nm)

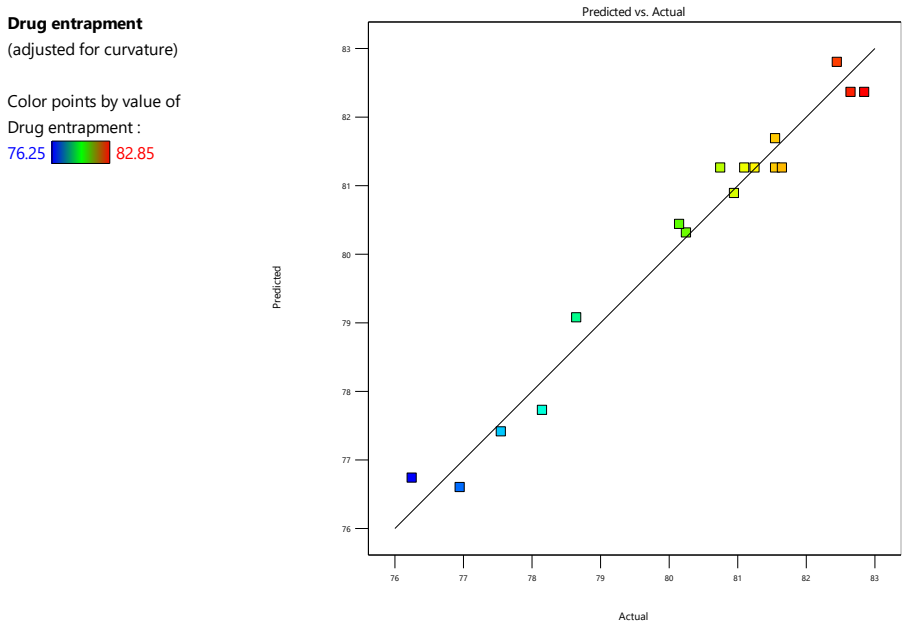

Figure 3. Predicted vs Actual Plots Depicting the Effect of Variables on Drug Entrapment Efficiency

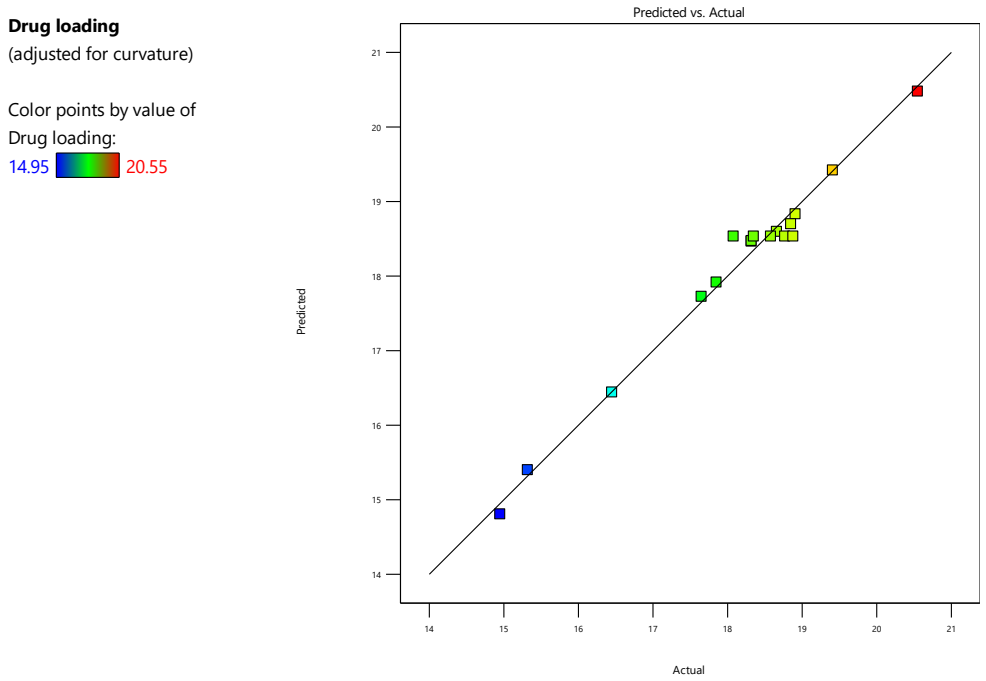

Figure 4. Predicted vs Actual Plots Showing the Effect of Variables on Drug Loading (%)

7. CONCLUSION

This present study successfully developed and optimized a Donepezil-loaded lipid-based nanoemulsion 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. The statistical analysis confirmed the significant influence of formulation variables on the responses, validating the robustness of the model. The findings suggest that the formulated nanoemulsion holds promise as a potential alternative for improving Donepezil delivery in Alzheimer's disease treatment. Further, in future *in vivo* studies are warranted to confirm its therapeutic efficacy and brain-targeting potential.

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Conflict of Interest

The authors declare that there is no conflict of interest associated with this research work.

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