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DEVELOPMENT AND OPTIMIZATION OF MEMANTINE-LOADED NANOSTRUCTURED LIPID CARRIERS USING A QUALITY BY DESIGN APPROACH

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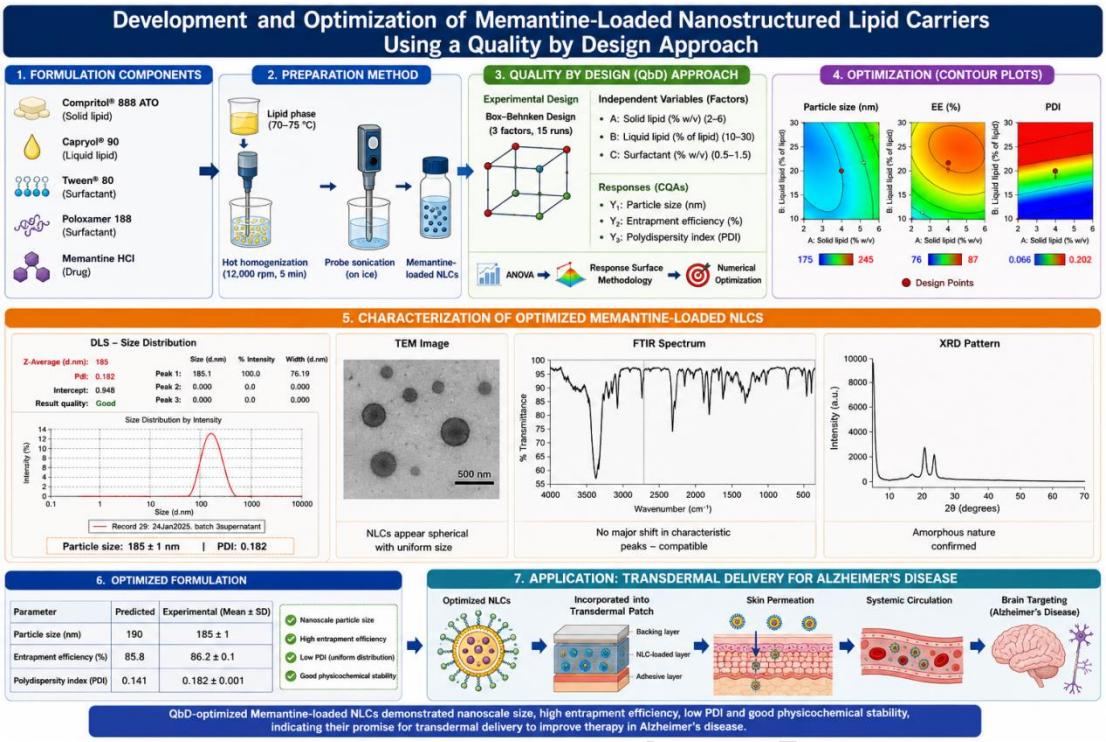
ABSTRACT

Background: Nanostructured lipid carriers (NLCs) offer a promising strategy to enhance the delivery of memantine by improving drug encapsulation and providing controlled release. This study aimed to develop and optimize memantine-loaded NLCs using a Quality by Design (QbD) approach to achieve a robust formulation with desirable physicochemical characteristics. Methods: Memantine-loaded NLCs were prepared by hot homogenization followed by probe sonication. A Box–Behnken Design was employed to evaluate the influence of critical material attributes, including solid lipid concentration, liquid lipid concentration, and surfactant concentration, on particle size, entrapment efficiency, and polydispersity index. The optimized formulation was characterized for particle size, zeta potential, morphology, crystallinity, drug encapsulation, and in vitro drug release. Results: Statistical optimization identified significant formulation variables affecting the critical quality attributes. The optimized NLCs exhibited nanoscale particle size, high entrapment efficiency, narrow size distribution, and sustained drug release with satisfactory physicochemical stability. Conclusion: The QbD-based optimization successfully produced a robust memantine-loaded NLC formulation suitable for further incorporation into a transdermal drug delivery system for Alzheimer's disease management.

KEYWORDS: Memantine; Nanostructured lipid carriers; Quality by Design (QbD); Box–Behnken Design; Hot homogenization; Probe sonication; Entrapment efficiency; Particle size; Controlled drug release; Alzheimer's disease.

Graphical Abstract



1. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia worldwide, responsible for roughly 60-70% of all dementia cases. The condition presents as a gradual decline in memory, cognition, language, and executive function that ultimately compromises independence and quality of life. As life expectancy rises, the global prevalence of AD continues to grow, generating major clinical, social, and economic burdens. Despite intensive research, the drugs currently approved for AD mainly relieve symptoms and do not stop disease progression.

Memantine hydrochloride, a low-to-moderate affinity uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, is one of the few licensed treatments for moderate-to-severe AD. Excessive NMDA receptor stimulation drives glutamate-mediated excitotoxicity, which damages neurons and accelerates cognitive decline. Because memantine blocks pathologically excessive receptor activity while sparing normal synaptic transmission, it can enhance cognition, daily functioning, and overall clinical outcomes. Oral therapy, however, is limited by inconsistent gastrointestinal absorption, systemic adverse effects, fluctuating plasma concentrations, and poor adherence, particularly in elderly patients with swallowing difficulties. These drawbacks highlight the need for alternative delivery systems that improve both efficacy and patient compliance.

Nanostructured lipid carriers (NLCs) have gained attention as a lipid-based nanocarrier platform for poorly permeable and lipophilic drugs. As second-generation lipid nanoparticles, NLCs combine solid and liquid lipids stabilized by suitable surfactants. The inclusion of liquid lipids creates imperfections in the solid matrix that increase drug accommodation, raise entrapment efficiency, reduce drug expulsion during storage, and provide sustained release. NLCs also offer good biocompatibility, low toxicity, high drug-loading capacity, and physicochemical stability, and their nanoscale size yields a large surface area that improves membrane interaction and drug permeation.

For transdermal use, NLCs further improve drug partitioning into the stratum corneum, increase skin hydration through their occlusive properties, and enable sustained drug release. These features make NLCs attractive for long-acting transdermal systems that reduce dosing frequency and improve adherence in chronic neurological disorders such as AD. A stable NLC formulation with controlled particle size, narrow size distribution, and high entrapment efficiency is therefore essential for optimal therapeutic performance.

The successful development of lipid-based nanocarriers requires systematic optimization, because lipid composition, surfactant concentration, and processing conditions can strongly influence the critical quality attributes (CQAs) of the final product. Conventional trial-and-error methods are slow, resource-intensive, and unable to capture interactions among formulation variables. Consequently, the pharmaceutical industry has increasingly adopted the Quality by Design (QbD) paradigm, which builds robust formulations through scientific understanding and risk-based optimization.

QbD is a systematic, science-driven methodology promoted by the International Council for Harmonisation (ICH Q8(R2), Q9, and Q10) that emphasizes predefined product quality, process understanding, and risk management throughout development . Development begins by defining the Quality Target Product Profile (QTPP), followed by identification of CQAs, Critical Material Attributes (CMAs), and Critical Process Parameters (CPPs). Design of Experiments (DoE) is then applied to evaluate the effects and interactions of variables, enabling statistical optimization with fewer experimental runs. Among experimental designs, the Box-Behnken Design (BBD) is widely used because it efficiently models quadratic response surfaces with relatively few combinations.

In the present study, memantine-loaded NLCs were prepared by hot homogenization followed by probe sonication. A Box-Behnken Design within a QbD framework was used to optimize the solid lipid, liquid lipid, and surfactant concentrations, and their influence on particle size, entrapment efficiency, and polydispersity index was systematically examined. The optimized formulation was characterized by dynamic light scattering, transmission electron microscopy, Fourier-transform infrared spectroscopy, and X-ray diffraction. This QbD-based strategy aims to establish a robust memantine-loaded NLC formulation with desirable quality attributes, providing a promising platform for a transdermal delivery system for the management of AD.

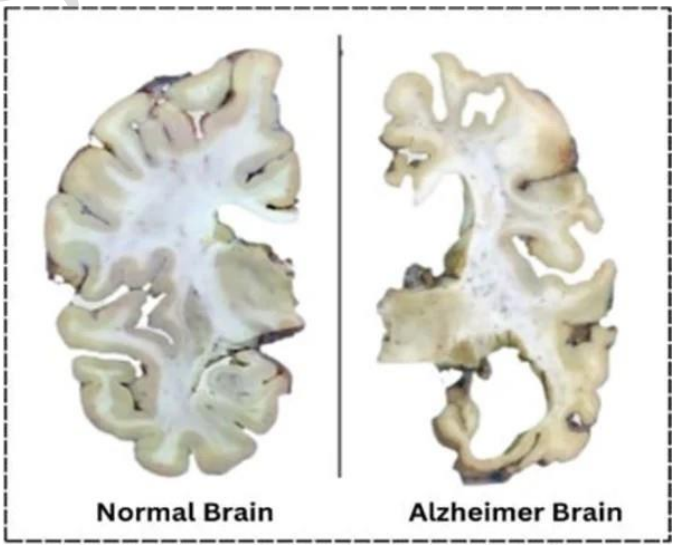


Fig. 1: Normal-Brain-vs-Alzheimer-Brain(21).

2.1 MATERIALS

Memantine hydrochloride, an anti-Alzheimer's agent that exerts its action by non-competitive antagonism of the N-methyl-D-aspartate (NMDA) receptor, was provided as a gift sample by Cadila Healthcare Ltd., Ahmedabad, India. The solid lipid Compritol® 888 ATO was obtained from BLD Pharm, whereas Capryol® 90, Poloxamer 188, Tween® 80, and mannitol were purchased from Sigma-Aldrich. All other reagents and solvents employed were of analytical grade and used without further purification.

2.2 Excipient Selection for Nanostructured Lipid Carriers (NLC)

The choice of excipients governs the stability, drug-loading capacity, and release behaviour of NLCs, and each component was selected on the basis of its established role in lipid-based nanocarrier design.[22,23]

Compritol® 888 ATO (glyceryl behenate). This solid lipid possesses a high melting point that confers good physical stability to the dispersion. When blended with a liquid lipid it forms an imperfect lipid matrix characteristic of true NLCs, and it is widely applied in NLCs intended for transdermal administration.[22,24] Typical concentration: 2–6% w/v of the total NLC dispersion.

Liquid lipid: Capryol™ 90 (propylene glycol monocaprylate). Incorporation of the liquid lipid introduces lattice imperfections that raise drug-loading capacity, improves permeation across the skin, and shows excellent miscibility with Compritol.[24] Typical concentration: 10–30% of the total lipid phase, with 25–30% more likely to generate additional structural pockets.

Surfactant: Poloxamer 188 (Pluronic® F68). Chosen for its non-ionic character and low toxicity, it provides steric stabilization and is a common stabilizer in lipid nanoparticle systems.[23,25] Typical concentration: 0.5–2% w/v.

Co-surfactant: Tween® 80 (polysorbate 80). This co-surfactant lowers interfacial tension, narrows the particle size distribution, and further enhances skin permeation.[23,25] Typical concentration: 0.1–0.5% w/v.

Aqueous phase: purified water. Selected because it is safe, regulatory accepted, and suitable for hot homogenization processing.[22,23]

2.3 Drug–Excipient Compatibility Studies

Before developing the nanoformulation, the physicochemical characteristics of memantine hydrochloride and its compatibility with the selected excipients were assessed, since drug–excipient interactions can compromise the stability, safety, and performance of the final product. Fourier Transform Infrared (FTIR) spectroscopy was used to detect possible interactions between the drug and the formulation components.[26]

FTIR spectra were recorded for the pure drug and for its physical mixtures with each individual excipient. Samples were prepared by the potassium bromide (KBr) pellet technique, and spectra were collected over the 4000–400 cm^{-1} range using an FTIR spectrophotometer. The pure drug exhibited characteristic absorption bands corresponding to the functional groups of its molecular structure. The spectra of the mixtures were then compared with those of the pure materials; notable peak shifts, disappearance of characteristic bands, or marked changes in peak intensity would indicate potential physicochemical interactions, whereas retention of the principal absorption bands without substantial alteration was taken as evidence of compatibility.[26]

2.4 Preparation of Memantine HCl-Loaded Nanostructured Lipid Carriers

Memantine-loaded NLCs were prepared by hot homogenization followed by probe sonication, a widely used high-energy method in which a molten lipid phase is emulsified into a heated aqueous surfactant solution and the droplet size is subsequently reduced to the nanometre range.[22,23,25]

Procedure: The solid lipid (Compritol® 888 ATO) and liquid lipid (Capryol® 90) were heated together until a clear molten lipid phase was obtained. The temperature was maintained approximately 5–10 °C above the melting point of the solid lipid (around 75–80 °C) to ensure complete liquefaction and uniform mixing. Memantine hydrochloride was then incorporated into the molten lipid phase. Because the drug is a hydrophilic salt, its partitioning into the lipid phase was promoted by converting it to the free base form in situ: a small amount of a basic buffering agent (sodium hydroxide or triethanolamine) was added to the aqueous phase or at the lipid–aqueous interface, minimizing migration of the drug into the aqueous phase.[24]

Separately, an aqueous phase containing Poloxamer 188 and Tween 80 was prepared and heated to the same temperature as the lipid phase to avoid premature solidification during emulsification.[25]

Formation of primary emulsion: The hot lipid phase was added gradually to the heated aqueous phase under high-speed homogenization at approximately 12,000 rpm for about 5 minutes, producing a coarse oil-in-water emulsion with both phases maintained in the molten state.[22,25]

Particle size reduction by probe sonication: The coarse emulsion was subjected to probe sonication to achieve nanoscale droplets. Sonication was performed at about 40% amplitude for 5 minutes in pulsed mode (10 seconds on, 5 seconds off) to limit temperature rise that could destabilize the surfactants or degrade the drug.[23,25]

Controlled cooling and solidification: The hot nanoemulsion was cooled gradually to room temperature under gentle stirring. During cooling the lipid phase recrystallized, yielding stable NLCs with the drug entrapped within the solid–liquid lipid matrix.[22,23]

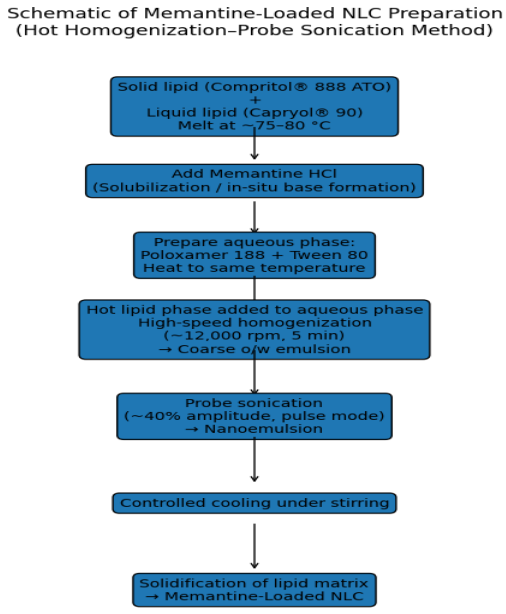


Figure 3.2 Schematic of Memantine-loaded NLC preparation by the hot homogenization–probe sonication method.

2.4 Optimization of Formulation

To achieve a robust and optimized memantine-loaded nanostructured lipid carrier (NLC) formulation, a systematic Quality by Design (QbD) approach employing Design of Experiments (DoE) was adopted. A three-factor, three-level **Box–Behnken Design (BBD)** was selected to establish the relationship between formulation variables and the critical quality attributes (CQAs) of the developed NLCs. The Box–Behnken Design is an efficient response surface methodology that enables the evaluation of both the individual and interactive effects of independent variables while minimizing the number of experimental runs.

The experimental design consisted of **17 experimental runs**, including **five center points**, generated using Design-Expert® software (Version XX, Stat-Ease Inc., USA). Three formulation variables were selected as independent factors based on preliminary formulation studies and literature reports: **solid lipid concentration (A, 2–6% w/v), liquid lipid concentration (B, 10–30% of total lipid), and surfactant concentration (C, 0.5–1.5% w/v)**. These variables were investigated for their influence on three critical quality attributes, namely **particle size (Y_1), entrapment efficiency (Y_2), and polydispersity index (Y_3)**.

All NLC formulations were prepared using the hot homogenization technique followed by probe sonication, while maintaining constant processing conditions, including homogenization speed (12,000 rpm), homogenization time (5 min), sonication conditions, and processing temperature. The selected factor levels were established based on preliminary screening experiments to ensure stable NLC formation within the desired particle size range.

Experimental data obtained from the BBD were fitted to second-order polynomial equations to evaluate the main, interaction, and quadratic effects of the formulation variables. Analysis of variance (ANOVA) were performed using Design-Expert® software to determine the significance of the developed models. Model adequacy was assessed using regression coefficients (R^2, adjusted R^2, predicted R^2), lack-of-fit analysis, adequate precision, and p-values. Three-dimensional response surface plots and two-dimensional contour plots were generated to visualize the effects of formulation variables on particle size, entrapment efficiency, and polydispersity index. Finally, numerical optimization employing the desirability function was performed to identify the optimized memantine-loaded NLC formulation exhibiting minimum particle size and PDI with maximum entrapment efficiency.

A. Quality Target Product Profile (QTPP)

The Quality Target Product Profile (QTPP) was established to define the desired characteristics of the memantine-loaded nanostructured lipid carrier intended for subsequent incorporation into a transdermal patch. The target product was designed to provide sustained drug delivery with adequate stability and patient convenience.

Table1: QTPP

QTPP Element	Target	Justification
Dosage form	Memantine-loaded NLC	Nanocarrier suitable for incorporation into a transdermal patch
Route of administration	Transdermal	Bypasses the gastrointestinal tract and improves patient compliance
Stability	Physically stable formulation	Maintains formulation quality during storage
Drug release	Sustained release	Supports prolonged therapeutic drug delivery after patch fabrication

B. Critical Quality Attributes (CQAs)

Based on the QTPP, three critical quality attributes (CQAs) were selected to evaluate formulation quality and optimize the NLC system:

- **Particle size (Y_1):** Target < 200 nm to obtain nanosized carriers suitable for transdermal application.
- **Entrapment efficiency (Y_2):** Target > 85% to achieve efficient drug incorporation within the lipid matrix.
- **Polydispersity index (Y_3):** Target < 0.25 to ensure a homogeneous particle size distribution and good physical stability.

C. Risk Assessment

A preliminary risk assessment was performed using an **Ishikawa (fishbone) diagram** to identify formulation and process variables that could influence the selected CQAs. Based on this assessment, **solid lipid concentration, liquid lipid concentration, and surfactant concentration** were recognized as the critical material attributes and were subsequently optimized using a Box–Behnken experimental design.

D. Design Space and Control Strategy

The design space was established using a **Box–Behnken Design (BBD)** to define the combination of formulation variables that consistently produced NLCs with the desired quality attributes. A control strategy was implemented by maintaining the optimized formulation variables and fixed processing conditions to ensure batch-to-batch reproducibility.

E. Excipient Selection within the QbD Framework

The formulation components were selected according to their functional role and anticipated influence on the critical quality attributes (CQAs) of the NLCs. Their contribution to formulation performance is summarized in **Table 1**.

Table 2: Functional role of formulation excipients.

Excipient	Function	Major CQAs Affected
Compritol® 888 ATO	Solid lipid	Particle size, EE, drug release
Capryol® 90	Liquid lipid	EE, drug loading
Poloxamer 188	Surfactant	Particle size, PDI, stability
Tween® 80	Co-surfactant	PDI, emulsification
Purified water	Dispersion medium	Physical stability

Experimental Design for Optimization

Selection of Independent Variables

Based on preliminary experiments and literature reports, three formulation variables were selected for optimization: **solid lipid concentration (A, 2–6% w/v), liquid lipid concentration (B, 10–30% of total lipid), and surfactant concentration (C, 0.5–1.5% w/v)**. The selected ranges were found suitable for producing stable NLC dispersions with desirable physicochemical properties.

Critical Process Parameters

Homogenization speed and processing temperature were identified as key process parameters during NLC preparation. These conditions were maintained constant throughout the experimental design (**12,000 rpm homogenization, followed by probe sonication**) to minimize process variability.

Selection of Response Variables

Three responses were selected as optimization criteria:

- **Particle size (Y_1):** Minimize (< 200 nm)
- **Entrapment efficiency (Y_2):** Maximize (> 85%)
- **Polydispersity index (Y_3):** Minimize (< 0.25)

These responses were chosen because they directly influence the quality, stability, and drug-loading performance of the developed NLC formulation.

C. Experimental Design

A three-factor, three-level **Box–Behnken Design (BBD)** was employed to optimize the memantine-loaded NLC formulation using **Design-Expert® software**. The design comprised **17 experimental runs**, including five center points. The selected formulation variables were **solid lipid concentration (A, 2–6% w/v), liquid lipid concentration (B, 10–30% of total lipid), and surfactant concentration (C, 0.5–1.5% w/v)**. The responses evaluated were **particle size (Y_1), entrapment efficiency (Y_2), and polydispersity index (Y_3)**. The experimental matrix is presented in **Table 4**.

D. Formulation Considerations

The factor ranges were established from preliminary experiments and published studies to ensure stable NLC formation. Processing conditions, including homogenization speed and temperature, were kept constant throughout the optimization to eliminate process-related variability.

Statistical Analysis

The experimental data were analyzed using **Design-Expert® software**. A quadratic polynomial model was fitted to each response, and **analysis of variance (ANOVA)** was performed to determine model significance. Model adequacy was assessed using **F-value, p-value, lack-of-fit, R^2, adjusted R^2, and predicted R^2**. Response surface and contour plots were generated to visualize the influence of formulation variables. The optimized formulation was validated by preparing the predicted optimum batch and comparing the experimental responses with the predicted values.

2.5. Characterization of Formulation

The optimized NLC formulation was characterized to evaluate its physicochemical properties and confirm compliance with the predefined critical quality attributes (CQAs).

2.5.1 Physical Stability

The optimized formulation was stored under refrigerated (5 ± 3°C) and room temperature (25 ± 2°C/60% RH) conditions for 30 days. Particle size, PDI, and entrapment efficiency were evaluated at predetermined intervals to assess formulation stability.

2.5.2 Particle Size and Polydispersity Index

Particle size and PDI were determined by **dynamic light scattering (DLS)** after appropriate dilution with purified water. Measurements were performed at **25 ± 1°C** in triplicate, and results were expressed as **mean ± SD**.

2.5.3 Entrapment Efficiency

Entrapment efficiency was determined by the **ultrafiltration–centrifugation method** using centrifugal filter units. Free memantine in the filtrate and total drug content after disruption of the lipid matrix were quantified by **HPLC**, and EE (%) was calculated using the standard equation.

$$EE\ (\%) = (\text{Total drug} - \text{Free drug}/\text{Total drug}) \times 100$$

2.5.4 Morphological Analysis

The morphology of the optimized NLCs was examined by **transmission electron microscopy (TEM)**. A diluted sample was deposited on a carbon-coated copper grid, negatively stained with **1% phosphotungstic acid**, and observed to evaluate particle shape and morphology.

2.5.5 Solid-State Characterization

X-ray Diffraction (XRD) were performed to investigate the tcrystallinity of the optimized NLCs. This analyses was used to assess changes in the lipid matrix and the physical state of memantine following encapsulation.

3. RESULTS AND DISCUSSION

3.1 Drug–Excipient Compatibility Studies (FTIR)

Fourier Transform Infrared (FTIR) spectroscopy was performed to assess the compatibility of **memantine hydrochloride** with the selected formulation excipients. FTIR spectra of the pure drugs and their respective physical mixtures were compared to identify any potential drug–excipient interactions.

The spectra of pure memantine exhibited the characteristic absorption bands corresponding to their functional groups, confirming their chemical identity. Similar characteristic peaks were observed in the physical mixture containing **Compritol® 888 ATO** (memantine). No significant peak shifts, disappearance of characteristic bands, or appearance of new peaks were detected.

Minor differences in peak intensity and band broadening were attributed to the overlapping absorption bands of the excipients and the physical mixing process rather than any chemical interaction. These findings indicate good compatibility between the drugs and the selected excipients, suggesting that the formulation components are suitable for the development of the dual-layer transdermal patch.

The FTIR spectra of the pure drugs and their corresponding physical mixtures are presented in **Figure 2**and **Figure 3**, respectively.

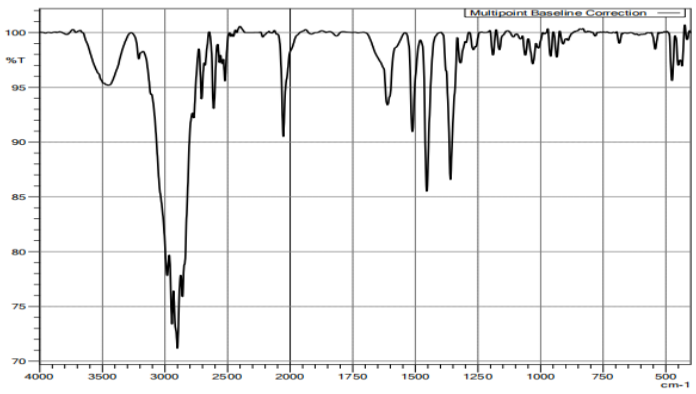


Figure 2: Pure Components MEMANTINE.

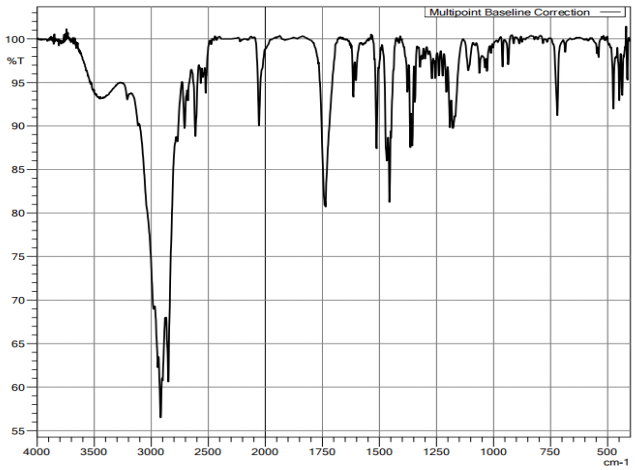


Figure 3: Physical Mixtures MEMANTINE AND COMPRITOL.

3.2 Optimization of Memantine-Loaded NLCs Using Box–Behnken Design

3.2.1 Experimental Design

A three-factor, three-level Box–Behnken Design (BBD) was employed to optimize the formulation of memantine-loaded NLCs. Solid lipid concentration (A), liquid lipid concentration (B), and surfactant concentration (C) were selected as independent variables, while particle size (Y_1), entrapment efficiency (Y_2), and polydispersity index (Y_3) were evaluated as response variables. The experimental design and observed responses are summarized in **Tables 3 and 4.**

Table 3: Factors.

Factor	Variable	Levels (−1, 0, +1)	
A	Solid lipid (% w/v)	2 – 4 – 6	Below 2%: Poor EE; Above 6%: High viscosity issues.
B	Liquid lipid (% of lipid)	10 – 20 – 30	High oil content increases drug solubility but may reduce stability.
C	Surfactant (% w/v)	0.5 – 1.0 – 1.5	Sufficient for steric stabilization without causing toxicity.

Table 4: BBD Design Matrix with Experimental Responses.

Run	A:Solid-lipid (% w/v)	B:Liquid lipid(%lipid)	C:Surfactant(% w/v)	Particle size(nm)	EE(%)	PDI
1	2	10	1.0	197 ± 3.2	78 ± 1.1	0.111 ± 0.01
2	6	10	1.0	205 ± 4.5	80 ± 1.3	0.135± 0.02
3	2	30	1.0	185 ± 2.8	84± 1.2	0.193± 0.01
4	6	30	1.0	220± 3.9	85 ± 1.4	0.173± 0.01
5	2	20	0.5	226 ± 3.5	79 ± 1.0	0.19± 0.02
6	6	20	0.5	245 ± 5.1	81 ± 1.2	0.202 ± 0.02
7	2	20	1.5	175 ± 2.5	80 ± 1.1	0.093± 0.01
8	6	20	1.5	195 ± 3.6	84± 1.3	0.066± 0.01
9	4	10	0.5	222 ± 3.8	76 ± 1.2	0.182± 0.02
10	4	30	0.5	235 ± 3.4	82 ± 1.3	0.197± 0.01
11	4	10	1.5	185 ± 2.9	79 ± 1.1	0.16± 0.01
12	4	30	1.5	190 ± 2.7	82 ± 1.5	0.122 ± 0.01
13	4	20	1.0	190± 3.0	86 ± 1.2	0.1± 0.01
14	4	20	1.0	188 ± 2.9	85 ± 1.1	0.11 ± 0.01
15	4	20	1.0	193 ± 3.1	87 ± 1.3	0.12 ± 0.01
16	4	20	1.0	188± 3.9	85± 1.1	0.15± 0.02
17	4	20	1.0	191± 3.5	86± 1.2	0.099± 0.02

3.2.2 Effect of Formulation Variables on Particle Size

Particle size was significantly affected by the formulation variables. Increasing the solid lipid concentration increased particle size (**β = +10.25, p < 0.0001**), whereas increasing surfactant concentration significantly reduced particle size (**β = –22.875, p < 0.0001**). The effect of liquid lipid concentration was comparatively small and statistically insignificant (**p = 0.0814**). Smaller particle sizes obtained at higher surfactant levels were attributed to improved emulsification and stabilization of the lipid droplets.

3.2.3 Effect of Formulation Variables on Entrapment Efficiency

Entrapment efficiency was mainly influenced by liquid lipid concentration (**β = +2.50, p < 0.0001**), followed by solid lipid (**β = +1.125, p = 0.0056**) and surfactant (**β = +0.875, p = 0.0181**). Higher lipid content enhanced drug incorporation within the lipid matrix, while increasing surfactant concentration improved formulation stability. The interaction terms were not statistically significant, indicating that the responses were predominantly governed by the individual effects of the formulation variables.

3.2.4 Effect of Formulation Variables on Polydispersity Index

Among the investigated variables, surfactant concentration had the greatest influence on PDI (**β = –0.0413, p = 0.0039**). Increasing surfactant concentration reduced PDI by improving particle stabilization and minimizing aggregation. In contrast, the effects of solid lipid and liquid lipid concentrations on PDI were not statistically significant.

3.2.5 Statistical Analysis and Model Fitting

ANOVA confirmed that the quadratic models developed for **particle size, entrapment efficiency, and PDI** were statistically significant (**p < 0.05**) with a non-significant lack of fit, demonstrating good model adequacy. The ANOVA summary is presented in **Table 5**.

Table 5: ANOVA summary.

Response	F-value	p-value
Particle size	53.51	<0.0001
Entrapment efficiency	28.20	0.0001
PDI	4.46	0.0231

3.2.6 Polynomial Models

The experimental responses were fitted to second-order polynomial equations to describe the relationship between the formulation variables and the selected responses.

Particle size (Y_1)

$Y1=190+10.25A+2.625B-22.875C+6.75AB+0.25AC-2BC+7A^2+4.75B^2+13.25C^2$ **Entrapment efficiency (Y_2)**

$Y2=85.8+1.125A+2.50B+0.875C-0.25AB+0.50AC-0.75BC-1.40A^2-2.65B^2-3.40$ **PDI (Y_3)**

$Y3=0.1414-0.0014A+0.0121B-0.0413C$

Overall, **solid lipid concentration increased particle size**, whereas **surfactant concentration reduced both particle size and PDI**. **Liquid lipid concentration showed the greatest positive effect on entrapment efficiency**, confirming its importance in enhancing drug incorporation.

3.2.7 Model Adequacy

Model performance was assessed using the coefficient of determination (R^2), adjusted R^2, and predicted R^2. The obtained values indicated satisfactory agreement between the experimental and predicted responses, confirming the suitability of the developed models. Furthermore, the difference between adjusted and predicted R^2 values was within the acceptable limit (<0.2), demonstrating good predictive capability (**Table 6**).

Table 6: Model adequacy statistics.

Response	R^2	Adjusted R^2	Predicted R^2
Particle size	0.9857	0.9673	0.8107
EE (%)	0.9732	0.9387	0.8090
PDI	0.5073	0.4936	0.3450

3.2.8 Response Surface Analysis

Response surface and contour plots illustrated the influence of formulation variables on the selected responses. Increasing surfactant concentration significantly decreased **particle size** and **PDI**, whereas increasing liquid lipid concentration enhanced **entrapment efficiency**. In contrast, higher lipid levels without sufficient surfactant resulted in larger particles and increased PDI, highlighting the importance of balancing formulation variables to achieve the desired NLC characteristics.

Figure 4shows that particle size increased with solid lipid concentration and decreased with increasing surfactant concentration. **Figure 5** demonstrates that higher liquid lipid levels improved entrapment efficiency, with the optimum region corresponding to approximately **86% EE**. **Figure 6** indicates that increasing surfactant concentration produced lower PDI values, reflecting improved particle uniformity and dispersion stability.

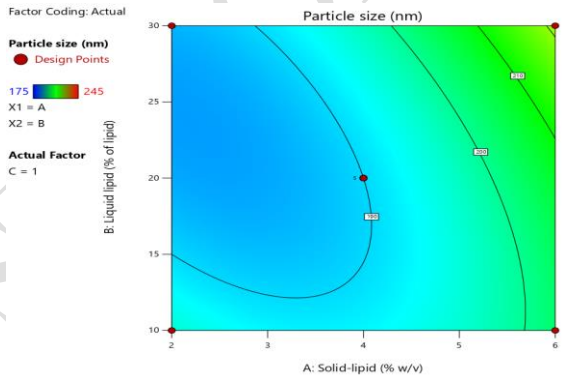


Figure 4: Contour Plot – Particle Size vs A & C.

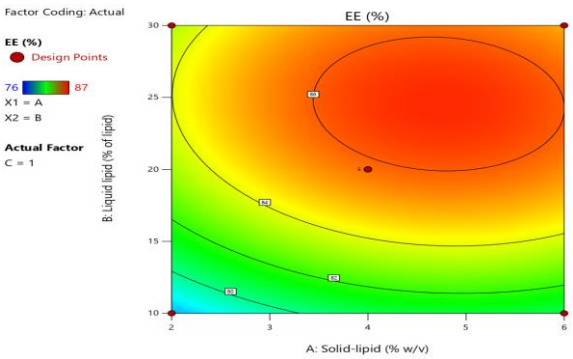


Figure 5: Contour Plot – EE vs A & B.

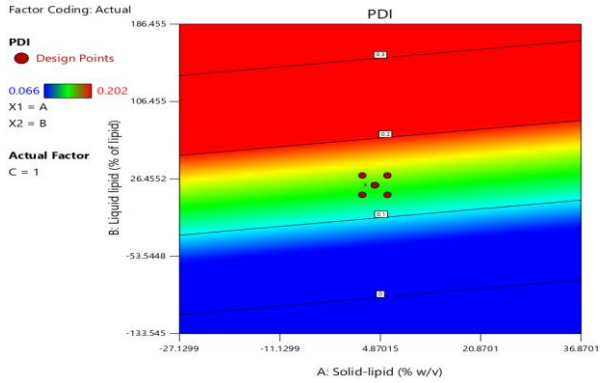


Figure 6: 3D Surface Plot – PDI vs B & C.

3.2.9 Optimization and Design Space

Numerical optimization was performed using the desirability function to obtain **minimum particle size**, **maximum entrapment efficiency**, and **minimum PDI**. The optimized formulation consisted of **4% (w/v) solid lipid, 20% liquid lipid, and 1% (w/v) surfactant**. The overlay plot identified a design space in which all predefined response criteria were simultaneously achieved, indicating a robust formulation (**Figure 7**).

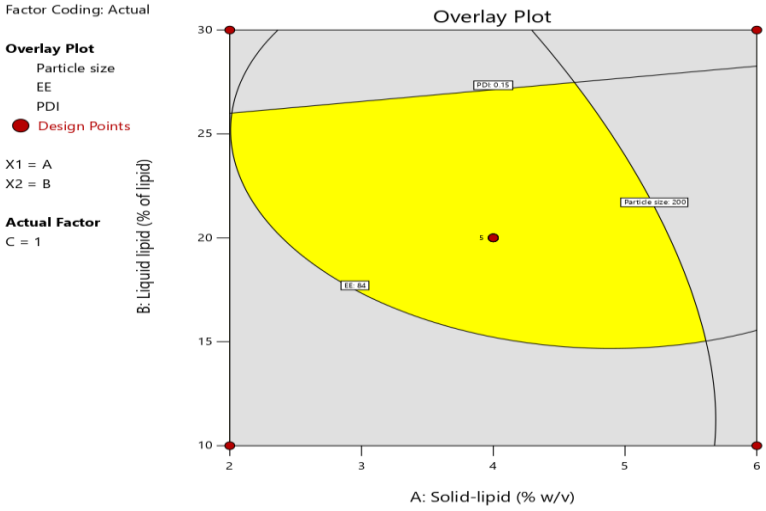


Figure 7: Overlay Contour Plot (Design Space).

3.2.10 Validation of the Optimized Formulation

The optimized formulation was prepared in triplicate to verify the predictive capability of the developed model. The experimental values showed good agreement with the predicted responses, with particle size, entrapment efficiency, and PDI all falling within the corresponding **95% prediction intervals**, confirming the validity of the optimization model (**Table 7**).

Table 7: Validation of the optimized formulation.

Parameter	Predicted	Experimental (Mean ± SD)
Particle size (nm)	190	185 ± 1
Entrapment efficiency (%)	85.8	86.2 ± 0.1
PDI	0.141	0.182 ± 0.001

3.2.11 Summary of Optimization

The QbD-based optimization successfully identified an NLC formulation with the desired quality attributes. The optimized formulation exhibited a **particle size of 185 ± 1 nm**, **entrapment efficiency of 86.2 ± 0.1%**, and **PDI of 0.182 ± 0.001**, satisfying the predefined optimization criteria. These findings demonstrate the suitability of the optimized NLCs for further formulation development.

3.3 Characterization of Memantine-Loaded Nanostructured Lipid Carriers

3.3.1 Particle Size, PDI and Zeta Potential

The optimized memantine-loaded NLCs exhibited a **mean particle size of 185 ± 1 nm**, confirming the formation of nanosized particles suitable for transdermal delivery. The **PDI (0.182 ± 0.001)** indicated a narrow size distribution, while the **zeta potential (−22.4 ± 1.8 mV)** suggested adequate electrosteric stabilization of the formulation. The particle size distribution is shown in **Figure 8**.

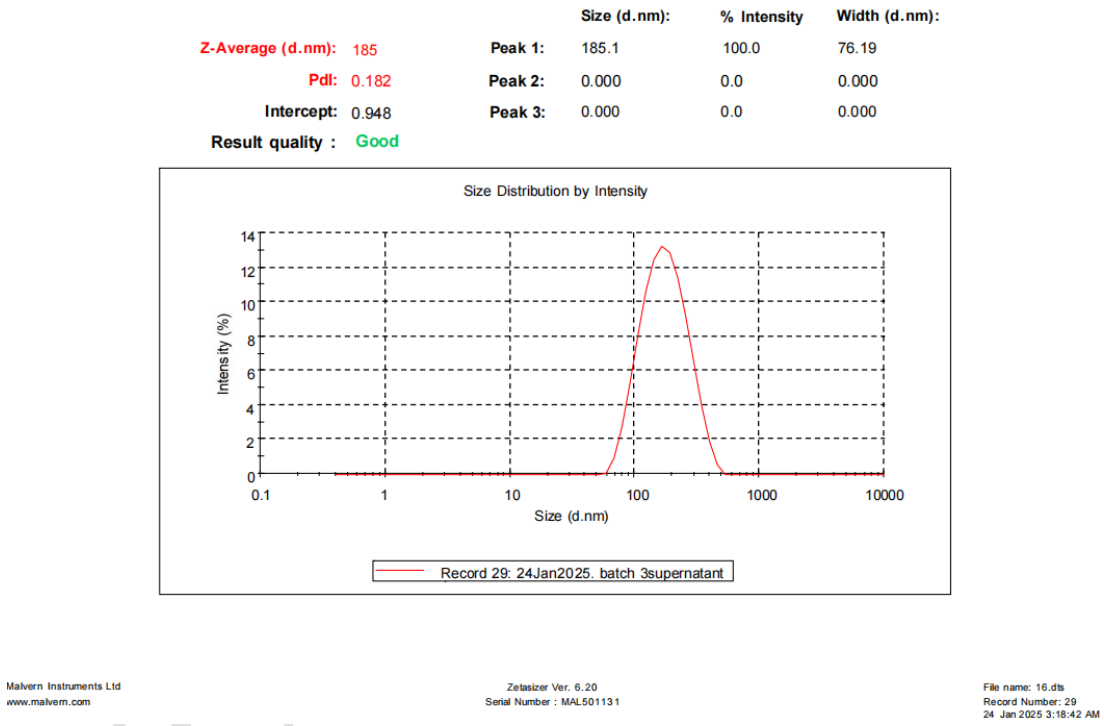


Figure 8: Particle size analysis and PDI of optimized Memantine-loaded NLC.

3.3.2 Entrapment Efficiency

The optimized formulation showed an **entrapment efficiency of 86.2 ± 0.1%**, demonstrating efficient incorporation of memantine into the lipid matrix. The high encapsulation efficiency may be attributed to the presence of liquid lipid, which enhances drug accommodation within the nanostructured carrier.

3.3.3 Morphological Analysis

TEM analysis (**Figure 9**) revealed predominantly spherical nanoparticles with smooth surfaces and uniform distribution. No noticeable aggregation was observed, and the particle size was consistent with the DLS measurements, confirming successful formation of the NLCs.

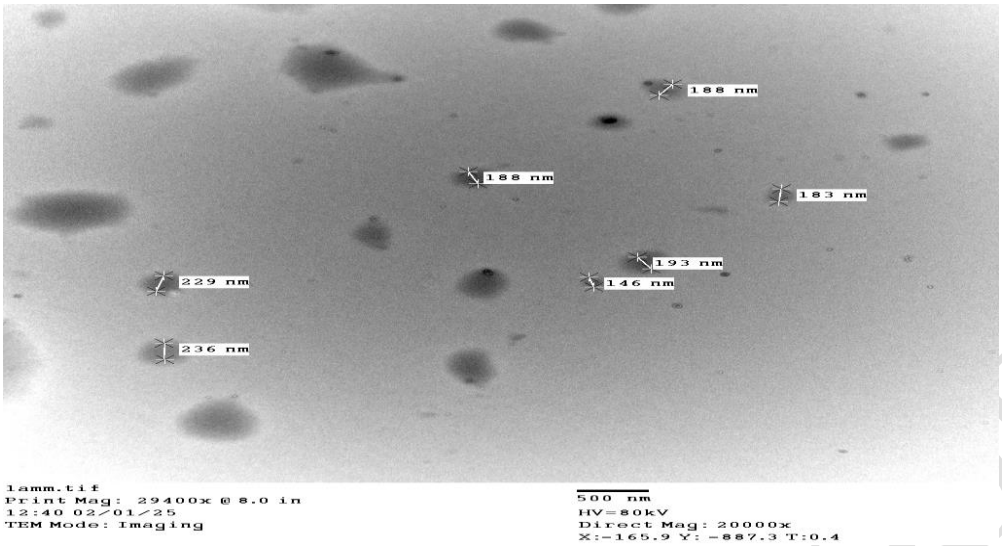


Figure 9: TEM micrograph of optimized Memantine-loaded NLC showing spherical nanoparticles with smooth surface and uniform size distribution.

3.3.4 Solid-State Characterization

FTIR

FTIR spectra of the optimized formulation retained the characteristic functional group bands of memantine and formulation components without the appearance of new peaks or significant spectral shifts, indicating the absence of chemical interactions and confirming drug–excipient compatibility.

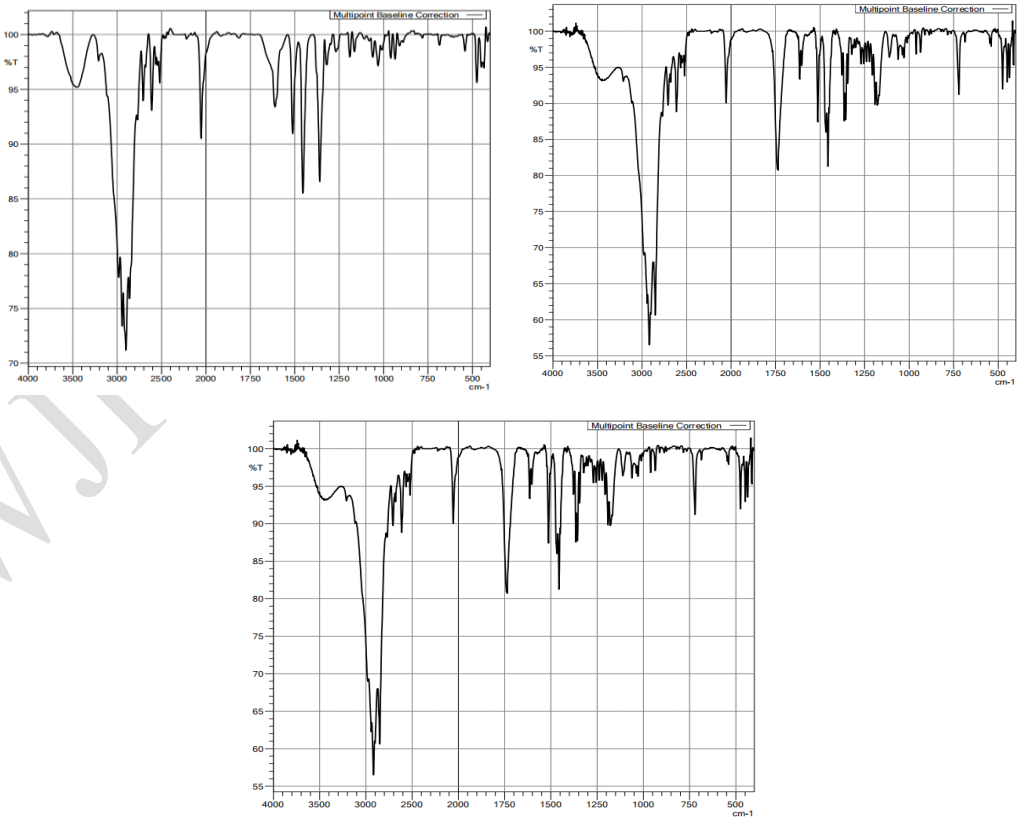


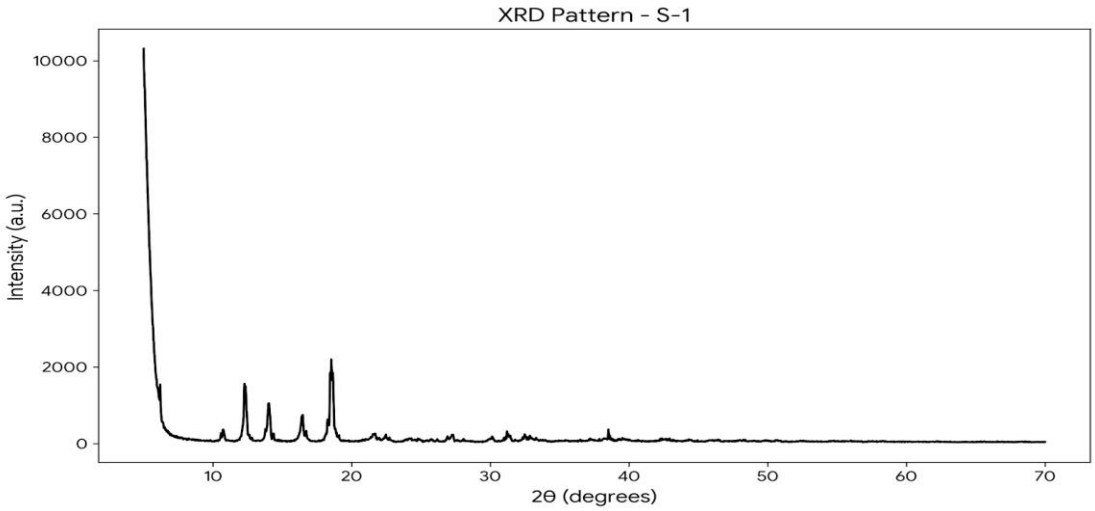
Fig. 10: FTIR analysis of Pure Memantine, Physical Mixture and Optimized Memantine-loaded NLC.

Table 8: Comparative FTIR analysis of Pure Memantine, Physical Mixture and Optimized Memantine-loaded NLC.

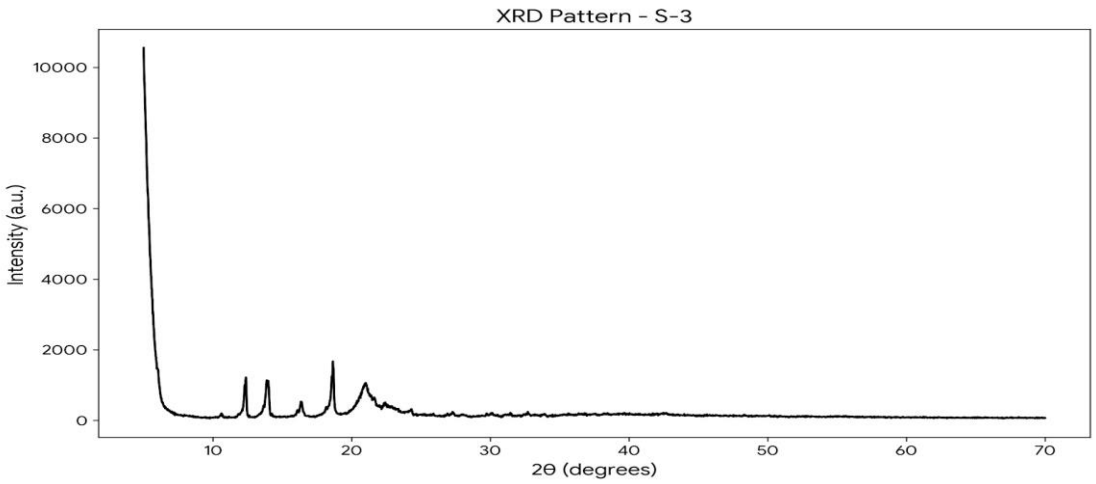
Functional Group / Vibration	Pure Memantine (cm^{-1})	Physical Mixture (cm^{-1})	Memantine-loaded NLC (cm^{-1})	Interpretation
N–H stretching (Primary amine)	~3340–3390	~3340–3390	~3350–3400 (broad)	Broadening with slight reduction in intensity due to overlap with lipid/surfactant matrix; no significant shift indicating compatibility.
Aliphatic C–H asymmetric stretching	~2918–2925	~2920	~2920	Strong absorption retained; attributed mainly to Compritol 888 ATO and Capryol 90.
Aliphatic C–H symmetric stretching	~2848–2855	~2850	~2850	Characteristic lipid peak retained, confirming integrity of the lipid matrix.
Ester carbonyl (C=O) stretching	Absent	~1735	~1735	Characteristic ester band of Compritol 888 ATO and Capryol 90 retained without significant shift.
NH_2 bending	~1600–1630	~1600–1630	~1600–1630 (reduced intensity)	Drug band retained with reduced intensity due to encapsulation and overlap.
CH_2 bending (Scissoring)	~1455–1465	~1465	~1465	Characteristic hydrocarbon vibration of the lipid matrix retained.
CH_3 bending	~1370–1380	~1375	~1375	Lipid-associated vibration retained after formulation.
Ester C–O stretching	Weak	~1240	~1240	Characteristic ester linkage of lipid excipients retained.
C–O–C stretching	~1100–1160	~1100–1160	~1100–1160	Characteristic bands of Tween 80 and Poloxamer 188 retained.
C–N stretching	~1030–1060	~1030–1060	~1030–1060	Drug band retained but partially masked due to molecular dispersion within the lipid matrix.

XRD

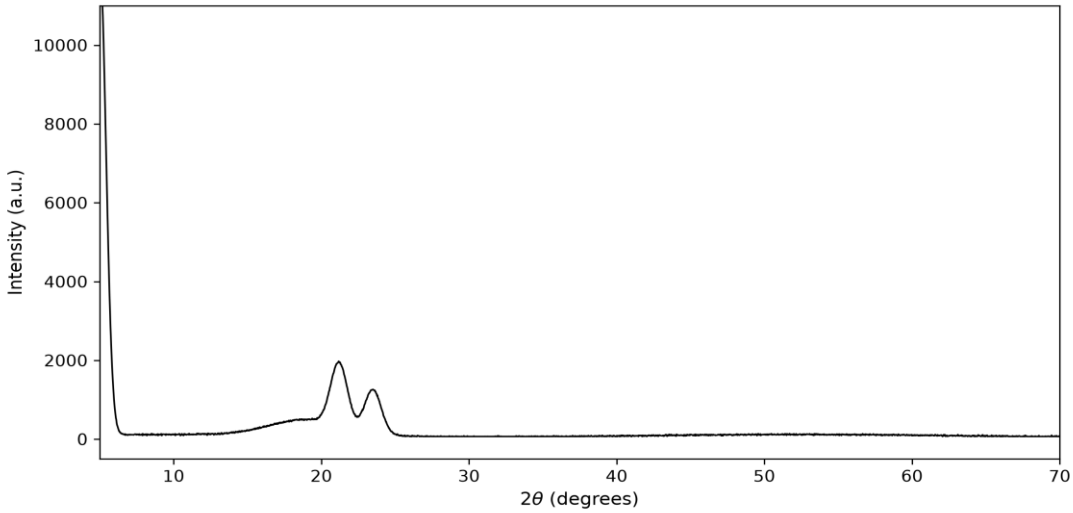
The XRD pattern of the optimized NLCs showed a marked reduction or disappearance of the characteristic crystalline peaks of memantine, indicating its conversion into an amorphous or molecularly dispersed state within the lipid matrix. This suggests successful drug encapsulation and reduced crystallinity.



(a)



(b)



(c)

Figure 11: X-ray diffraction patterns of (a) Memantine hydrochloride, (b) Compritol® 888 ATO, and (c) optimized NLC formulation indicating reduced crystallinity and amorphous dispersion of drug.

Table 9: Peak Table.

Sample	Key Peak Positions (2θ, degrees)	Peak Nature / Appearance	Crystalline Phase / Assignment
a (Pure Memantine)	**12.3°**, **14.1°**, **16.5°**, **18.6°** (Sharp doublet), 21.8°, 31.2°, 38.6°	Sharp, high-intensity, narrow Bragg diffraction peaks	Highly Crystalline Drug
b (Physical Mix)	**12.5°**, 13.1°, 16.1°, **21.2°**, **23.3°**, 23.8°	Overlay of reduced drug peaks + lipid diffraction peaks	Semi-crystalline Mixture (Drug + Lipid)
c(NLC Formulation)	**21.2°** (Broad), **23.5°** (Broad)	Broad diffuse peaks; complete disappearance of sharp drug peaks	Amorphous / Molecularly Dispersed State in Lipid Matrix

3.3.5 Physical Stability

The optimized NLC formulation remained physically stable during **30 days** of storage under both refrigerated and room-temperature conditions. No significant changes were observed in **particle size, PDI, or entrapment efficiency**, indicating good colloidal stability without evidence of aggregation or drug leakage.

CONCLUSION

Memantine-loaded nanostructured lipid carriers (NLCs) were successfully developed and optimized using a **Quality by Design (QbD)** approach coupled with a **Box–Behnken Design**, enabling a systematic understanding of the influence of formulation variables on critical quality attributes. The optimized formulation exhibited a **particle size of 185 ± 1 nm**, **entrapment efficiency of 86.2 ± 0.1%**, and a **polydispersity index of 0.182 ± 0.001**, demonstrating excellent physicochemical characteristics and satisfactory physical stability. Statistical validation confirmed the robustness and predictive capability of the optimization model, highlighting the effectiveness of the QbD framework in developing reproducible lipid-based nanocarriers. Overall, the study establishes a rational and statistically validated formulation strategy for memantine-loaded NLCs and provides a promising platform for improving drug delivery in Alzheimer's disease.

Future Perspective: The optimized memantine-loaded NLCs can serve as a promising carrier system for incorporation into sustained-release transdermal patches and other advanced lipid-based drug delivery platforms for Alzheimer's disease.

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