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Original Article

Development and Optimization of Memantine-PEGylated PLGA Liposomal Formulation for Nose-to-Brain Delivery in Alzheimer's Disease: A Quality-by-Design (QbD) Approach

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ABSTRACT

Aim: This study aimed to develop and evaluate Memantine-PEGylated-PLGA Liposomal Formulation for Nose-to-Brain Delivery in Alzheimers Disease: A Quality-by-Design (QbD) Approach. **Background:** Alzheimer's disease is a progressive neurodegenerative disorder characterized by neuronal degeneration and the accumulation of β-amyloid plaques and hyperphosphorylated tau proteins. Conventional drug delivery systems face significant challenges in achieving effective brain targeting due to the presence of the Blood-Brain Barrier (BBB). Therefore, the development of alternative delivery strategies such as nose- to-brain targeting has gained considerable attention for enhancing therapeutic efficacy. **Materials and Methods:** Liposomal formulations, PEGylated PLGA-based memantine liposomes (PEG-MEM-PLGA-LIPO), were developed using the thin-film hydration method. A Quality by Design (QbD) approach with Box- Behnken design was employed for systematic optimization of formulation variables. The prepared multilamellar vesicles were characterized for particle size, entrapment efficiency, morphology, compatibility, and in vitro drug release. Analytical techniques such as Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR) were utilized. **Results:** The optimized liposomal formulations exhibited nanoscale particle sizes, with PEG-MEM- PLGA-LIPO 262.5 nm. High entrapment efficiencies were achieved 82%. SEM analysis confirmed spherical morphology with smooth surfaces. DSC and FTIR studies indicated compatibility between drug and excipients and successful incorporation within the lipid matrix. In vitro drug release studies demonstrated sustained release of memantine over 72 hr, indicating controlled drug delivery behavior. **Conclusion:** The developed liposomal formulations demonstrated significant potential as non-invasive drug delivery systems for nose-to-brain targeting. The integration of PEG and PLGA enhanced stability and performance, while the QbD approach ensured optimized formulation characteristics. These findings suggest that the proposed liposomal systems could effectively overcome BBB limitations and improve therapeutic outcomes in Alzheimer's disease management.

Keywords: Alzheimer's disease, Beta-amyloid plaque, Quality by Design approach, Entrapment Efficiency, PEGylated liposomes.

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INTRODUCTION

Alzheimer's Disease (AD) is a type of dementia that gets worse over time. The 2023 report on Alzheimer's Disease Facts and Figures shares some eye-opening numbers about the state of this condition and what we can expect moving forward. Right now, more than 55 million people around the world are living with dementia, and this number keeps increasing every day. By 2030, that figure could climb to 78 million, which highlights how urgently we need better treatments and support.[1] According to Alzheimer's Disease International, about 75% of people with dementia globally have not been diagnosed.

To treat Alzheimer's, doctors often use acetylcholinesterase inhibitors like Donepezil, Rivastigmine, and Galantamine, all approved by the USFDA. These medications help to address the chemical changes in the brain caused by Alzheimer's. Because people with AD have lower levels of acetylcholine, these drugs are designed to boost that level.[2] However, their effectiveness has limitations, so researchers are looking into other treatment options. One new drug, MEM, has been approved for neurodegenerative disorders, including AD. Memantine works differently as it targets NMDA receptors and offers some protection for the brain. The FDA approved it in 2003.[3]

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In addition to MEM, there are monoclonal antibodies that have shown promise in treating Alzheimer's. The FDA has already approved two of these, and more are in the works. Traditional drugs like acetylcholinesterase inhibitors can sometimes cause unpleasant side effects, such as nausea and confusion, which can seriously affect how patients feel day-to-day.[4,5] When looking at how these drugs work in the body, rivastigmine is underutilized for its low bioavailability. On the other hand, Donepezil tends to bind to proteins too effectively, which could lead to interactions and side effects. Galantamine has a short half-life, which has led scientists to seek out newer and better ways to treat AD. Compared to these older treatments, MEM is noted for its high bioavailability and generally mild side effects, making it a candidate for further study. Additionally, liposomes provide various benefits for targeted and longer-lasting drug delivery, which is essential in treating AD refer Figure 1 for structure of MEM.[6-11]

As we learn more about AD diseases, we are finding new ways to treat them, such as controlled drug delivery, drug targeting etc. However, this also brings the challenge of creating effective systems to deliver these drugs. One of the most important advancements in AD drug delivery over the past few decades has been the development of liposomes for the treatment of AD.[7-11]

Traditional liposomes are essentially simple bubbles made of a layer of lipids that surround a watery center. This unique design allows them to hold both water-soluble and fat-soluble medications.[12-16] Additionally, liposomes are friendly to the body, break down naturally, and are safe to use. They can be made in different sizes. This special structure works well for encapsulating various types of drugs, whether they are very fat-loving, water-loving, or somewhere in between. This makes it a great option for delivering AD medications directly into the brain.[17]

However, regular liposomes have some downsides, like being unstable, clumping together, and being easily taken up by immune cells. To address these issues and to achieve longer-lasting and targeted delivery of medicines, a new generation of liposomes has been developed that is use of sustained and stealth liposomes for drug targeting into the brain region.[18,19]

One of the common methods used for treatment is PLGA PEGylated liposomes, which help address various diseases. The FDA has approved PLGA for biomedical applications because it breaks down easily in the body, releases drugs in a controlled manner, can be modified for targeted delivery, and works well with biological systems.[20,21] Given the limitations of existing treatments for Alzheimer's disease, there's a growing need for more research on using liposomes in this area. Traditional forms of medication often fall short because they are not very effective and can cause many side effects.[22] By delivering drugs directly to the brain at lower doses, we can reduce these side effects and make a meaningful improvement in treatment. The use of liposomes to target specific areas in the brain is a big step forward in managing Alzheimer's.[23] In this study, the PLGA PEGylated liposomes were made with Soya lecithin and cholesterol, which offer several benefits for drug delivery. These benefits include being compatible with the body, being sourced from natural materials, improving how well drugs dissolve, and enhancing how they pass through membranes. Choosing the right balance of lipids is critical when making these liposome systems.[24-28]

To enhance the delivery of memantine for the treatment of Alzheimer's disease, the nasal route has been chosen due to its ability to bypass the blood-brain barrier and other systemic obstacles, allowing for direct access to the brain. This non-invasive method is potentially more appealing and can improve patient adherence. However, several challenges remain, particularly regarding medication stability within the nasal cavity, mucociliary clearance, and the proper administration technique.

Potential Compliance Challenges in Nose-to-Brain Drug Delivery

Elderly patients, especially those with cognitive decline, may have difficulty using nasal delivery systems correctly. Ensuring ease of use is critical. One approach to mitigate this issue is the use of nasal sprays, which are generally easier for patients to handle and administer independently.

Stability of the Drug in the Nasal Environment and Mucociliary Clearance

The nasal cavity has protective mechanisms, such as mucociliary clearance, that can remove drugs before they are absorbed. To counteract this, formulations must be carefully designed to enhance drug retention and absorption. Strategies include the use of PEGylation and mucoadhesive polymers, which can increase the residence time of the drug within the nasal cavity and enhance its stability in this environment.

Formulation Stability

To ensure effective absorption and prolonged retention in the nasal cavity, reducing the particle size of drug-loaded liposomes is beneficial. Smaller particles offer improved stability and facilitate more efficient drug delivery through the nasal mucosa.[29]

The Quality by Design (QbD) approach in pharmaceuticals starts with clear goals and focuses on understanding the product and process, as well as controlling them based on solid scientific principles and effective risk management. This careful management of how the formulation is made leads to a stable and effective product.[30,31] The formulation was fine-tuned using the Box Behnken design and later confirmed through a prediction method. The resulting formulation was tested for how well it releases the drug, showing that it can maintain drug release for up to 72 hr using PLGA PEGylated liposomes. This is in contrast to

plain memantine hydrochloride and its marketed version, which release the drug immediately.

MATERIALS AND METHODS

Materials

We obtained PLGA-PEG Resomer® RGP d 5055 and Memantine (MEM) from Sigma Aldrich. For all our experiments, we used water filtered through the Millipore MilliQ system. Other reagents were also sourced from Sigma Aldrich and met analytical grade standards. Soya lecithin and cholesterol were kindly provided by VAV Life Sciences VAV Lipids. Ethanol and chloroform were also bought from Sigma Aldrich, ensuring they were of analytical grade.

QbD approach

Starting with the target product profile and key quality aspects

The first part of a Quality by Design (QbD) study involves figuring out the Target Product Profile (TPP) and the important Quality Aspects (CQAs) of the formulation. We gathered CQAs from existing literature on the formulation and preliminary formulation tests. As a result, we identified formulation particle size and entrapment efficiency as the main CQAs that influence the product's quality.

Risk Evaluation

We conducted a risk evaluation to find out which material and process factors really impact the quality of our formulation. To do this, we created a fishbone diagram, also called a cause-effect diagram, to help us spot the key material attributes and process parameters. From our analysis using this diagram and some initial studies, we identified three main factors that play a big role in shaping the formulation; the ratio of drug to lipid, which is a key material attribute, and the times for sonication and hydration, which are important process parameters.

Experimental Setup

From our risk evaluation, we chose three variables for our optimization study: the molar ratio of drug to lipid (X1), sonication time (X2; in minutes), and hydration time (X3; in minutes). We tested each of these factors at two different levels, and we also included four center points. To explore how these variables affect the creation of liposomes, we used a Box Behnken design. For the analysis, we employed Design Expert 7.0.2 software, evaluating two response variables: particle size (in nanometers) (Y1) and entrapment efficiency (percentage) (Y2).

MEM-PEG-PLGA loaded liposome development

To create Multilamellar Vesicles (MLVs), we used a method called thin-film hydration, mixing the drug with a specific amount of phospholipid. The phospholipid mixture included soya lecithin and cholesterol in a ratio of 7:3. We dissolved Memantine HCl in equal parts of absolute ethanol and chloroform in a round-bottom flask. By evaporating the solvents with a rotary vacuum evaporator at 60°C for 20 min, we formed a thin film of the drug combined with lipid. After letting the dry film sit in a vacuum oven at 40°C overnight to eliminate any leftover solvent, we hydrated it with 5 mL of Milli-Q water. This was done by shaking it well and then gently rotating it at 50°C for a certain time at 150 rpm in a water bath to form the MLVs. We used bath sonication to reduce the size of the MLVs. To separate any unentrapped drug, we centrifuged the liposomal mixture at 10,000 rpm and re- dispersed the resulting particles in Milli-Q water. We measured the particle size and zeta potential using a Malvern particle size analyzer and calculated the entrapment efficiency for the formulation.

Numerical optimization of the design

We analyzed the experimental results and adjusted the process to minimize risks using numerical optimization and point prediction techniques. The parameters included a 1:3 ratio of drug to lipid, hydration times ranging from 30 to 90 min, and sonication times between 5 and 15 min. The software recommended running the process 30 times, from which we selected one run for point prediction, carrying it out three times to confirm the results. We aimed for a particle size between 100 and 400 nm and an entrapment efficiency of 60 to 80%. Based on the software's suggestions from the 30 runs, we found an ideal ratio of drug to lipid at 1:9.20, hydration time at 54.13 min, and sonication time at 5.71 min. This setup predicted a particle size of 385.82 nm and an entrapment efficiency of 69.10%. We executed the run in triplicate and then compared the results with our predictions, calculating the liposomal particle size and percentage entrapment efficiency after making the liposomes.

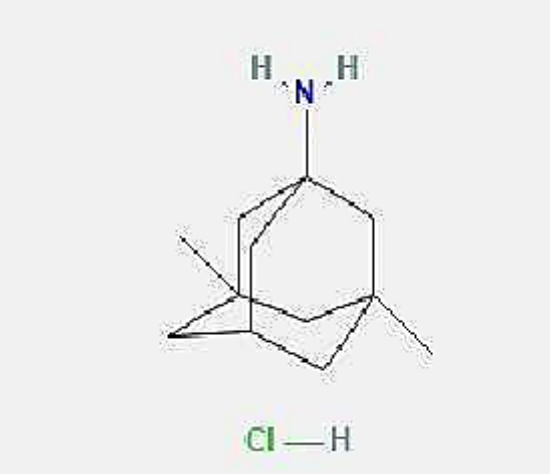


Figure 1: Molecular structure of the Memantine hydrochloride.

Optimizing the freeze-drying process with the Sf/Si ratio

We used a Labconco freeze dryer (FreeZone 4.5, USA) to lyophilize our liposomal formulation, adding 1%, 5%, and 10% (w/v) lactose as cryoprotectants. The process began by freezing the samples at -40ºC for 24 hr. Next, we conducted primary drying at 0ºC for 5 hr, followed by 10ºC for 2.5 hr, and then 15ºC for another 2 hr. Finally, secondary drying took place at 25ºC for 2.5 hr. Throughout this process, we kept the chamber pressure at 20 Pa and the cold trap at 50ºC. Once the liposomal powder was freeze-dried, we resuspended it in 2 mL of Milli-Q water and measured the particle size to calculate the Sf/Si ratio, where Sf represents the final particle size after freeze-drying and Si indicates the initial particle size before the process. Additionally, we evaluated the freeze-dried liposomes for aspects like powder appearance, particle size, entrapment efficiency, and overall look Refer Table 1.

Evaluation of the MEM-PEG-PLGA loaded liposome formulation

We measured liposomal size and Polydispersity Index (PDI) three times at 25ºC using the Dynamic Light Scattering (DLS) method with a Zetasizer Nano ZS (Malvern Instruments Ltd., Worcestershire, UK). To prepare the samples, we diluted them with Milli-Q water at least 50 times and then assessed their size and PDI in a 1 mL disposable polystyrene cuvette. We recorded the values as Z-average, which reflects the average diameter of the sample, while PDI shows the breadth of the size distribution. We also measured the zeta potential at 25 ºC, using the same Zetasizer Nano ZS device, applying a 50 V electric field through a polycarbonate folded capillary cell. This measurement is based on the average of 30 readings, reflecting the electrophoretic mobility in the electric field.

Determining Drug Loading and Encapsulation Efficiency

To measure how much drug was loaded and the efficiency of encapsulation, we diluted 10 µL of the prepared liposomes with Milli-Q water to make a total of 1 mL in a microcentrifuge tube. After spinning it at 13,000 rpm for 15 min, we collected the supernatant to find out the concentration of free drug (MEMfree). To calculate the total drug concentration (MEMtotal), we mixed another 10 µL of the liposomes with methanol to reach a volume of 1 mL and vortexed it. We measured both MEM free and MEM total using a UV Spectrophotometer set at 245 nm, performing each test three times. The results were averaged and presented as mean±standard deviation (n=3). We calculated the encapsulation efficiency using this formula:

$$\% \text{ Entrapment Efficiency} = (\text{MEM total} - \text{MEM free})/\text{MEM total} \times 100.$$

Differential Scanning Calorimetry

For the Differential Scanning Calorimetry (DSC) analysis, we carefully weighed 5 mg of powdered samples and placed them in aluminum pans. After sealing the pans, we used a Perkin-Elmer Pyris 6 DSC, driven by Pyris software and a thermal analyzer, to heat the samples in a nitrogen atmosphere from 35 to 300ºC at a rate of 10ºC per minute. An empty aluminum pan served as the reference for recording the thermograms.

Fourier Transform Infrared Spectroscopy

We analyzed the FTIR spectrum of both the pure drug and the memantine liposomal powder using a Shimadzu model 8033 FTIR spectrophotometer. The samples were ground into a fine powder, mixed with anhydrous potassium bromide, pressed into thin pellets, and then analyzed via FTIR.

Scanning Electron Microscopy

To observe the structure of the memantine liposomal formulation, we employed Scanning Electron Microscopy (SEM) with a CM 200 device from Philips. Imaging was carried out at a voltage of 200 kV and a magnification of 0.23 nm. We suspended the freeze-dried formulation in Milli-Q water, placed a drop on Formvar®-coated copper grids, and added a drop of 2% (w/v) uranyl acetate. After letting it sit for 3 min, we drained the excess liquid, let the grid air dry, and then captured the images using SEM.

Table 1: Liophilisation studies of PLGA PEGylated Memantine liposome.

	Memantine PEGylated PLGA loaded liposomes
Sf Final particle size of the formulation after reconstitution	275.6
Si initial particle size of the formulation without freeze-drying	262.5
Sf/Si ratio	1.049
Powder flow ability	Good powder flow
Particle size aggregation	Inhibiting particle aggregation
Effect on particle size	Resisting change in particle size

In vitro Release Study

For the *in vitro* release study of MEM-PEG-PLGA liposomes, we compared it against free MEM and the marketed form of MEM in a PBS solution, using a bulk equilibrium direct dialysis bag method over 72 hr (n=6). We placed 2 mL of each formulation into a dialysis bag made from a cellulose membrane with a size of 12-14 kDa. Each bag was then submerged in 150 mL of isotonic phosphate-buffered saline at pH 7.8 and maintained at 37°C. At set intervals, we withdrew 1 mL of sample from the stirring release medium and replaced it with an equal amount of fresh buffer at the same temperature refer Table 2.

RESULTS

Quality by Design approach Understanding the TPPs

When we looked into the QTPP, we considered various factors to shape our approach. Our goal was to create a liposomal version of memantine HCl for treating alzheimer's, using the QbD method. The specific QTPPs we settled on can be found in Table 3.

Identifying CQAs

Based on the TPPs outlined in Table 3, we identified liposomal particle size and percentage of drug entrapment as key Quality Attributes (CQAs). Our study aimed to optimize the formulation of liposomal memantine while focusing on these CQAs. Table 4 provides a list of TPPs along with the considerations for CQAs.

Assessing Risks

In this research, we recognized that the particle size and encapsulation efficiency are vital qualities of the final product. Understanding the risks that might affect these qualities is essential. To do this, we created two Ishikawa diagrams (also known as cause and effect diagrams) to map out potential factors influencing particle size and entrapment efficiency, shown in Figures 2a and 2b.

Table 2: Cumulative Drug release Profile of PLGA PEGylated Memantine Liposome in Phosphate Buffer pH 7.4 in Comparison with Plain Drug.

Time	Marketed formulation (Tab)	Memantine PLGA-PEG Liposomes
0 min	0.000	0.000
30 min	46.000±1.527	5.333333±1.45
1 hr	68.33334±2.027	11.000±2.30
2 hr	91.66666±2.4037	22.33333±2.60
180 hr		31.33333±2.02
4 hr		42.66667±2.60
12 hr		54.33333±4.05
24 hr		66.66666±3.48
36 hr		73.66666±3.84
48 hr		82.000±3.78
72 hr		94.33334±2.18

Table 3: TPP elements for the liposomal Memantine hydrochloride formulation.

Sl. No.	TPP element	Target	Justification
1.	Dosage form	Dry powder Formulation for reconstitution	Formulation needs to be given by nasal drop.
2.	Route of administration	Nasal route	To deliver the formulation at the site of action brain.
Drug product quality attributes			
1.	Physical properties	White/opalescent dispersion	-
2.	Particle size	180 to 300 nm	-
3.	Entrapment efficiency and content Uniformity	70 to 95%	-
4.	Stability	As per the ICH guidelines	This ensures the stability of the active in the formulation.

Analyzing Risks-Particle Size and Entrapment Efficiency

From the Ishikawa diagrams, we ranked the identified Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) according to their level of impact on

the CQAs. In Table 5, we can see that the drug-to-lipid ratio and sonication time are anticipated to significantly impact particle size, while the drug-to-lipid ratio and hydration time are expected to have the greatest effect on entrapment efficiency.

Box Behnken Design

We employed the Box Behnken design and analyzed the results for particle size and entrapment efficiency using software that assessed various influencing factors. The experimental framework, which included 17 different formulations, is displayed in Table 6. The results showed that particle size ranged from 258.6 to 336.9 nm, while entrapment efficiency varied between 33.99% and 89.53%, with data points spread evenly throughout this range. For particle size, the software evaluated four mathematical models: linear, 2FI, cubic, and quadratic. The linear and quadratic models were recommended for their predictive accuracy, while the cubic model was deemed less reliable. Following ANOVA, the quadratic model proved to be significant, while the lack of fit ($p<0.05$) was not significant. The final equation for predicting particle size is:

particle size=+6272.80765-1546.67296*Drug:Lipid+46.697*Hydration time-187.25214*Sonication time-0.36071*Drug:Lipid *Hydration time+16.48571 *Drug:Lipid *Sonication time-0.83633 *Hydration time *Sonication time+85.82347 *Drug:Lipid^2-0.30368 *Hydration time^2+5.56250 *Sonication time^2 (see Figures 3 and 4 3D curve for comparison of drug lipid ratio, sonication time and hydration time). For entrapment efficiency, the software recommended the linear model for the best prediction, while the cubic model was again seen as less reliable. The ANOVA results indicated that the linear model was significant, and the lack of fit ($p<0.05$) was also not significant. The corresponding equation for entrapment efficiency is:

Entrapment Efficiency=+58.74411+2.71821*Drug:Lipid+0.044917*Hydration time-2.99175*

Sonication time.

Optimization of the design using point prediction method

We checked how well the design worked through numerical optimization and then used the point prediction method. The run was done three times at the chosen levels. We got a particle size of 276.86±33 nm, and the entrapment efficiency came to

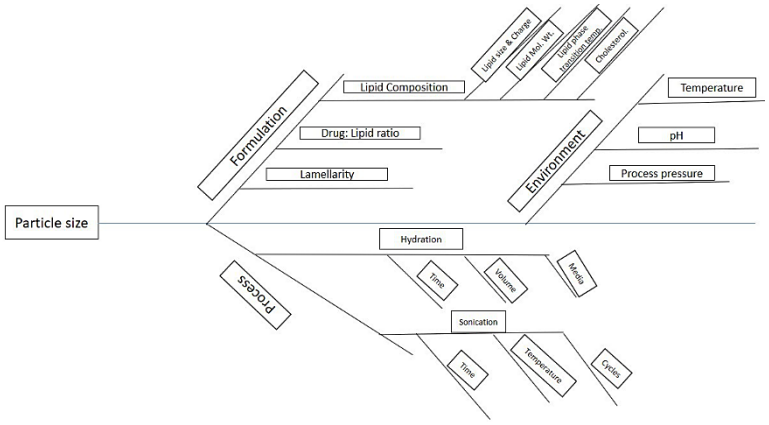
86.14±4.32%. This showed that our design was on point, as the numbers we got were very close to what we expected and well within the 95% confidence interval. For our optimized liposomal formulation, the zeta potential measured at 4.76 mV (Figure 5 Particle size of PLGA PEGylated Memantine liposome).

Table 4: Selection of CQAs for liposomal Memantine hydrochloride formulation.

Sl. No.	TPP element	Is this a CQA	TPP element
1.	Physical property No	No	The dispersion will be finally converted into the powder dosage form by suitable technique.
2.	Particle size	Yes	The particle size is necessary for the desired delivery at the site of action.
3.	Entrapment efficiency	Yes	This will ensure maximum drug loading into the system necessary for the action.
4.	Content uniformity	No	The drug will be uniformly distributed within the formulation if the particle size and entrapment efficiency are controlled.
5.	Assay	No	The assay of optimized formulation will be within the limit as content uniformity is ensured.

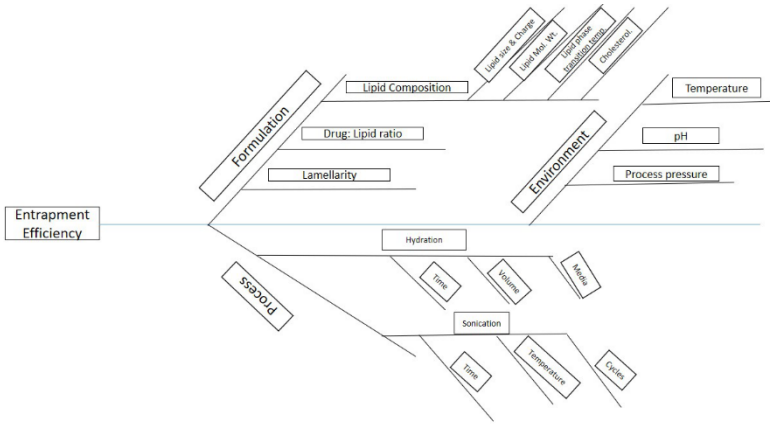
Table 5: Risk assessment of the CQAs for liposomal Memantine Hydrochloride Formulation.

Sl. No.	Responses	CMA	CPP	
		Drug to Lipid Ratio	Hydration time	Sonication time
1	Particle Size	High	Low	High
2	Entrapment efficiency	High	High	low
3	Assay	Low	Low	Low



Dia. Ishikawa fish bone diagram showing the factors affecting (a) particle size and (b) entrapment efficiency

Figure 2A: Ishikawa fish bone diagram (cause-effect diagram) for PLGA PEGylated Memantine liposomal (Particle Size)



Dia. Ishikawa fish bone diagram showing the factors affecting (a) particle size and (b) entrapment efficiency

Figure 2 B: Ishikawa fish bone diagram (cause-effect diagram) for PLGA PEGylated Memantine liposomal (Entrapment Efficiency).

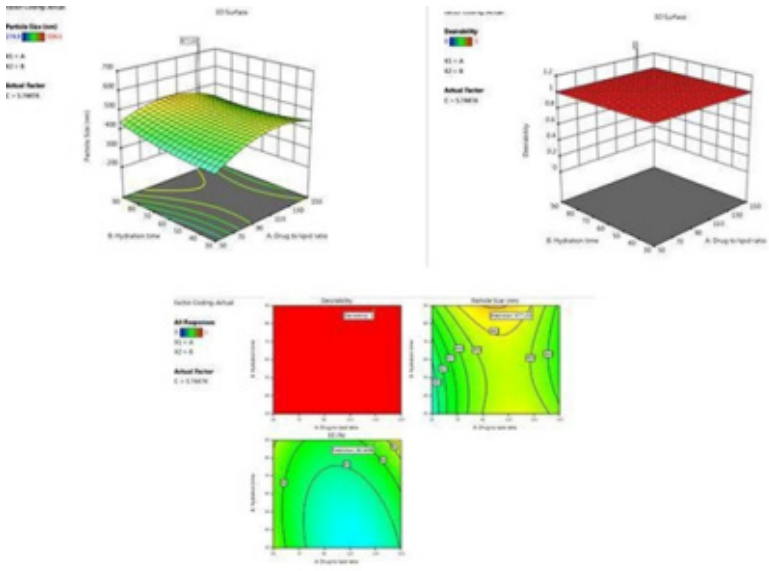


Figure 3: Comparison of factors with drug lipid ratio, sonication time and hydration time.

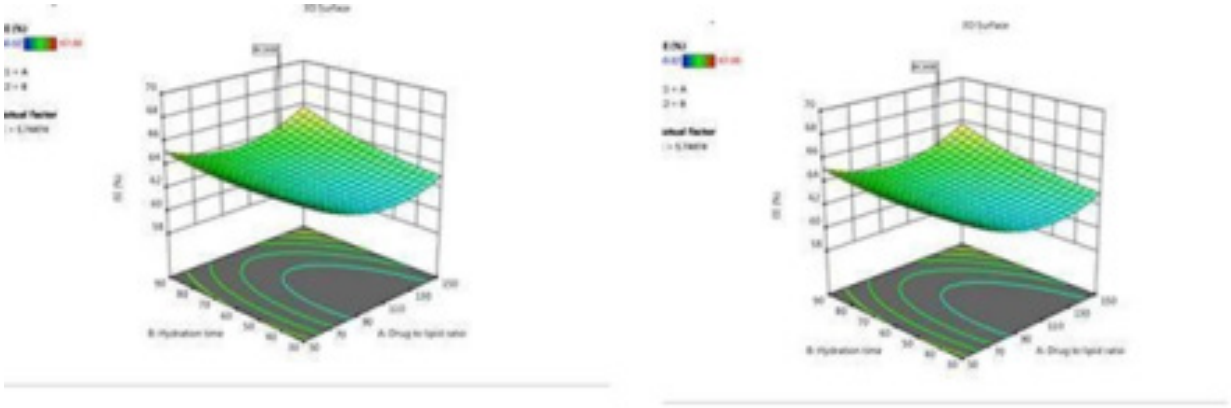


Figure 4: Comparison of factors with drug lipid ratio, sonication time and hydration time.

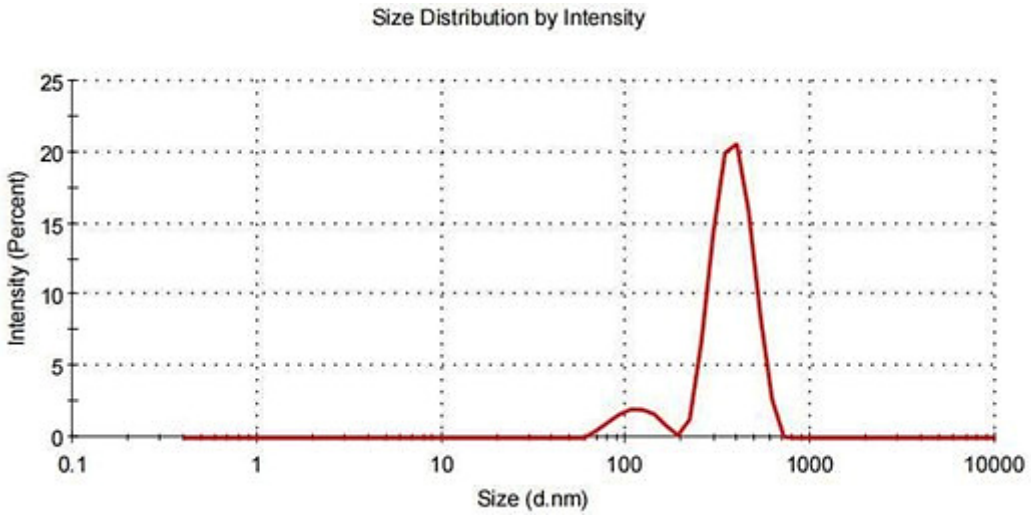


Figure 5: Particle size of PLGA PEGylated Memantine liposome.

Freeze-drying process and the Sf/Si ratio

This ratio helps us see how particle size changes before and after freeze-drying. Among the cryoprotectants we tested, 5% lactose stood out with an Sf/Si ratio of 1.27. It did a great job at preventing particle clumping and keeping the size and PI stable after freeze-drying. In contrast, the formulation with only 1% lactose didn't give us a dry, free-flowing powder post-freeze-drying. So, we skipped calculating the Sf/Si ratio for 10% lactose Refer Table 1.

Particle size, zeta potential, and entrapment efficiency of memantine liposomal formulation

The optimized batches we created using the modified thin film hydration technique showed a particle size of 279.3 nm and a PDI value of 0.2, with an entrapment efficiency of 66.29%. The zeta potential for our developed liposomal formulation was again measured at 4.76 mV.

DSC, FTIR, and SEM of memantine liposomal formulation

When we examined the DSC thermogram, it gave us clues about the crystal habit and any polymorphic changes the drug underwent during formulation. Pure memantine HCl showed a single sharp endothermic peak at 295°C, which matched previous reports. For the freeze-dried liposomal memantine formulation, we noticed a low- intensity endothermic peak of memantine in the melting range of the drug. This suggests that the drug is trapped at a molecular level within the lipid matrix and that there is less drug present compared to the cryoprotectant (see Figure 6 for DSC thermogram of drug and liposomal formulation).

FTIR

The IR spectra revealed distinct peaks that are typical of pure memantine, such as the alkyne CH stretch at 3271 cm^{-1}, a weak C=C stretch at 2120 cm^{-1}, strong C=C and C=N stretches in the aromatic structure at 1581.63 and 1620.21 cm^{-1}, and a C-O-C stretch at 1118.71 cm^{-1}. The FTIR spectra for freeze-dried memantine liposomal powder mostly maintained these key peaks of pure memantine (Figure 7; FTIR spectra for drug, excipient and drug loaded liposomal formulation). This suggests that the drug didn't interact with any excipients or degrade. The persistence of these characteristic bands shows that the processing did not affect the drug trapped in the system.

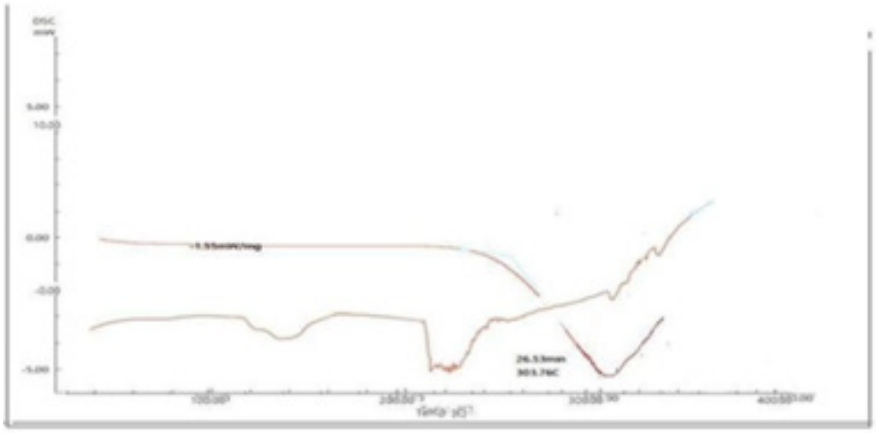


Figure 6: DSC thermogram of drug and liposomal formulation.

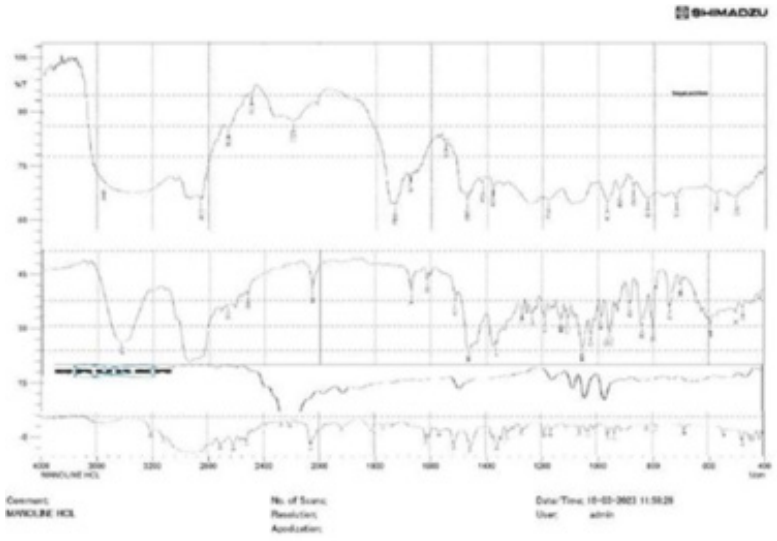


Figure 7: FTIR spectra of drug, excipients and final drug loaded liposomal formulation.

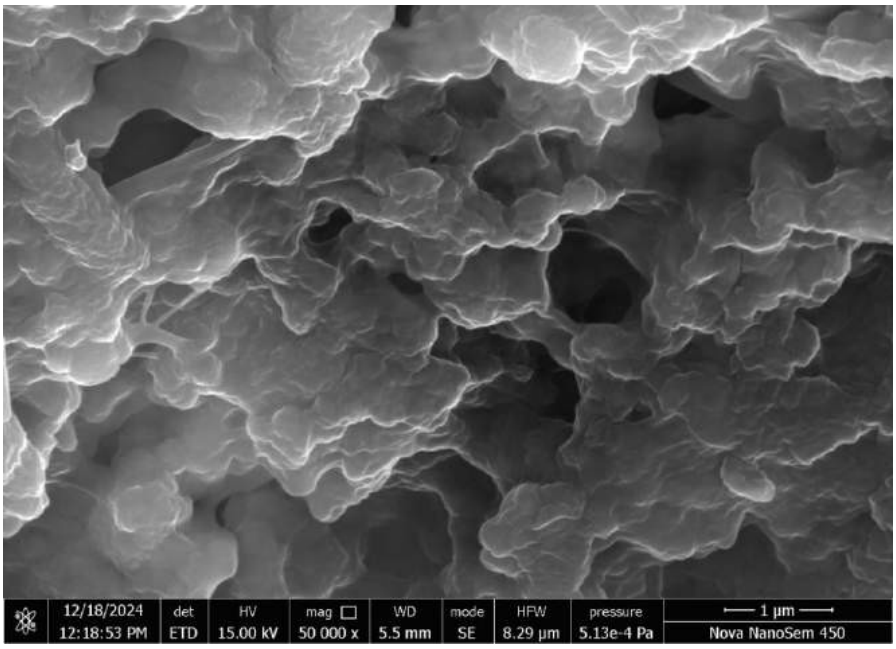


Figure 8: SEM analysis of PLGA PEGylated Memantine liposome for surface morphology.

Table 6: Box Behnken design for Memantine hydrochloride liposomal formulation.

Batch code	Factor 1 Drug to lipid ratio	Factor 2 Hydration Time	Factor 3 Sonication Time	Response 1 Particle size	Response 2 % EE
F1	6.5	0	15	575.6	70.23
F2	6.5	60	10	475.7	67.87
F3	6.5	60	10	513.8	69.55
F4	10	90	10	525.7	70.12
F5	3	60	5	372.6	72.45
F6	6.5	60	10	385.5	74.65
F7	10	30	10	614.1	69.87
F8	10	60	5	424.5	71.12
F9	6.5	30	5	525.0	68.32
F10	6.5	60	10	385.8	69.36
F11	6.5	30	15	484.6	68.38
F12	3	60	15	315.3	72.36
F13	3	30	10	274.9	86.10
F14	10	60	15	756.1	57.33
F15	6.5	90	5	526.3	55.63
F16	6.5	60	10	582.2	52.24
F17	3	90	10	475.3	61.38

SEM

Figure 8 (SEM image of liposomal formulation) shows the negative-staining SEM image of the liposomal memantine formulation, confirming that the liposomes are round with a smooth surface. The size of the liposomes aligns closely with the measurements from the DLS method.

In vitro release study

Figure 9 (Cumulative drug release profile of liposome) presents the release profile of the optimized liposomal memantine formulation in phosphate buffer at a pH of 7.8. The *in vitro* study indicated a biphasic release pattern from the formulation, beginning with a quick release in the first 8 hr followed by a slower release that continued for up to 72 hr (Refer Table 2 for drug release).

DISCUSSION

The reason for using the QbD approach is to create a formulation that meets specific quality control standards, leading to a product of the desired quality. According to ICH Q8 (R2) (2009), the Target Product Profile (TPP) is a forward-looking summary of the key quality traits of a drug product we aim to achieve, focusing on safety and effectiveness. For our formulation, we selected various TPP elements, including the route of administration and attributes like particle size, PDI, entrapment efficiency, content uniformity, assay, residual solvents, microbial limits, and packaging systems. These TPPs were set with specific goals and chosen for their relevance to the QbD development process.[31] Our goal was to develop a dry, free-flowing powder that could be reconstituted prior to use for nasal delivery. By using the nasal route, we aim to deliver the drug directly to the brain. For the nasal drug delivery, the final formulation plans to be a dry powder for reconstitution, targeting a particle size of 100 to 300 nm and an entrapment efficiency of 70 to 85%. The microbial limits will conform to compendial standards to ensure the product is free from microbes and safe for delivery. The container closure system is vital for protecting the dosage form from environmental exposure and during handling by patients, and it will be chosen based on what suits the product best. As per the ICH Q8 (R2) definition, a Critical Quality Attribute (CQA) is a physical, chemical, biological, or microbiological characteristic that needs to be maintained within a suitable limit, range, or distribution to ensure the desired quality of the product (ICH 2009).[33]

To effectively deliver a formulation to the brain, the ideal particle size is between 100 and 300 nm. As a result, the size of the liposomal particles was considered a key quality attribute for nasal delivery. Memantine HCl, due to its amphiphilic properties, poses challenges when trying to encapsulate it in a vesicular carrier. Therefore, ensuring that memantine is well-entrapped is essential for creating a formulation that can provide a sufficient dose at the target site. This led to the encapsulation efficiency percentage being treated as another important quality attribute relevant to the formulation's therapeutic effectiveness.[29,33,34]

Once we identified these key attributes, we proceeded with a risk assessment using the Ishikawa fishbone diagram. According to the ICH guideline Q9, risk combines both the likelihood of harm happening and how serious that harm could be. Evaluating risks helps us spot potential hazards and analyze how they might affect the final product. This also allows for improvements in the quality processes involved.[35]

From existing literature, we gathered and categorized factors influencing liposomal particle size and encapsulation efficiency into three groups: formulation, process, and environment. Notably, no environmental factors were chosen since they can be easily managed. Among the formulation factors, the ratio of drug to lipid emerged as vital for determining the size of the liposomal vesicles. Phospholipids, being the core components of the liposomal membranes, directly affect particle size. These phospholipids, along with cholesterol, are essential for trapping the drug within the structure. We optimized the ratio of soya lecithin to cholesterol to 7:3, ensuring a stable liposomal formulation. An excess of cholesterol might lead to leaky liposomes, risking system instability.[34,35]

Entrapment efficiency also hinges on the drug-to-lipid ratio, which needs to be higher for effectively trapping an amphiphilic molecule like memantine. Thus, this ratio was classified as a critical material attribute influencing both particle size and entrapment efficiency. As for process factors, both hydration and sonication times significantly affect liposomal particle size; longer times generally yield smaller particles. Sonication breaks down multilamellar vesicles, creating smaller unilamellar vesicles, which can reduce particle size but may also cause drug leakage, compromising entrapment efficiency. Conversely, longer hydration times allow better contact for the vesicles to capture the drug, enhancing entrapment efficiency. After assessing the risks connected to these attributes, the next step was to implement control strategies aimed at developing a liposomal formulation that is of high quality and stable.[30-35]

After assessing the risks, we looked at three important factors to improve particle size and how well we trap the drug: the drug-to-lipid ratio, hydration time, and sonication time. We used a method called Box-Behnken design to evaluate these factors.[36,37]

A stable liposomal formulation can be achieved by optimizing and maintaining an appropriate soya lecithin to cholesterol ratio in the lipid phase. Excessive cholesterol content can destabilize the system by making the liposomes more permeable, leading to leakage. Additionally, the drug-to-lipid ratio plays a crucial role in determining entrapment efficiency. For amphiphilic drugs like memantine, a higher drug-to-lipid ratio is often required to achieve effective encapsulation. Therefore, this ratio is considered a critical material attribute influencing both entrapment efficiency and particle size.

Among the various process parameters, hydration and sonication times have a direct impact on liposomal particle size. Increasing both these times generally leads to smaller particle sizes. During sonication, Multilamellar Vesicles (MLVs) are disrupted and converted into Smaller Unilamellar Vesicles (SUVs), which contributes to a reduction in particle size. However, excessive sonication may also lead to drug leakage from the vesicles, thereby decreasing the entrapment efficiency.[36] In contrast, extending the hydration time allows for better interaction between the

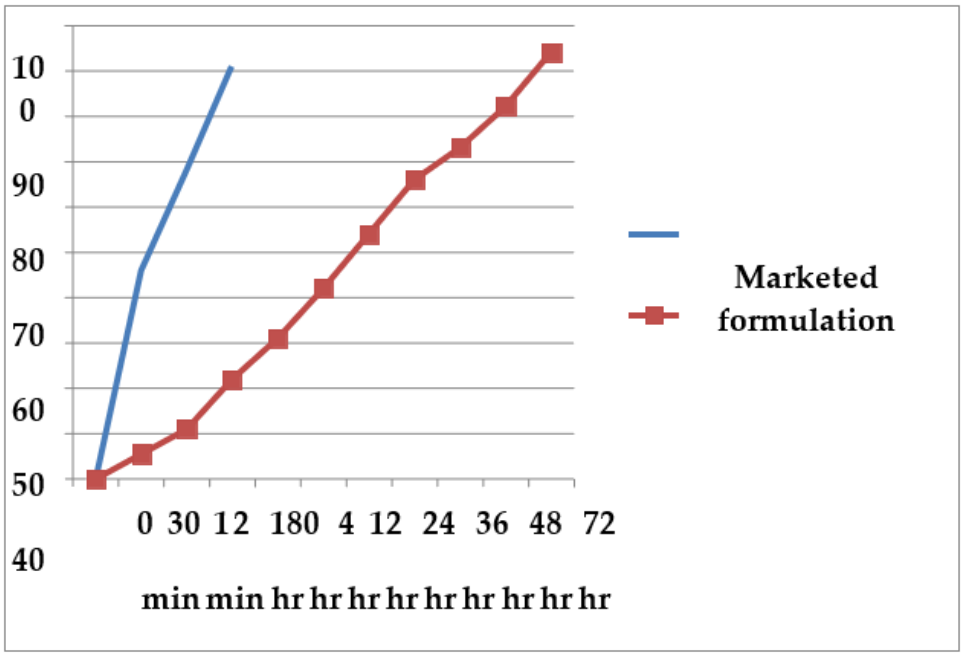


Figure 9: Cumulative drug release profile of PLGA PEGylated Memantine liposome in phosphate buffer pH 7.8 in comparison with plain drugs.

Table 7: Stability studies of PLGA PEGylated Memantine liposome.

	Memantine PEGylated PLGA loaded liposomes
4°C	Visually unchanged
	No change in Particle size and zeta potential
	Liposomes are stable
25°C	Visually unchanged
	Slight increase in Particle size and zeta potential
	Liposomes are stable
38°C	Transparent and unstable
	Change in particle size and zeta potential
	Liposomes are unstable

lipid bilayers and the drug, improving the likelihood of drug entrapment and resulting in higher entrapment efficiency.

Particle size is significantly influenced by both the drug-to-lipid ratio and sonication time. The results showed that while particle size decreases with increasing sonication time, it increases as the drug-to-lipid ratio rises. Additionally, hydration time and drug-to-lipid ratio have the most notable effects on entrapment efficiency. Longer hydration times tend to result in larger particles due to the formation of clumps and aggregates, while the drug-to-lipid ratio has a more complex impact. An increased drug-to-lipid ratio can reduce entrapment efficiency, cause leakage from the liposomes, and potentially destabilize the system.

The results showed that both linear and quadratic models worked best for predicting particle size, while the cubic model didn't fit well. We checked if the leftover values from our model had a normal distribution, which is shown in the normal probability plot (Figure 2). The Box Cox plot (Figure 3) suggested that we didn't need any transformations to our data.

From our equations, it was clear that the drug-to-lipid ratio significantly influenced particle size, having a negative effect. The 3D contour plot (Figure 3) illustrated that increasing the drug-to-lipid ratio actually reduced the particle size. This can be explained by how hydrogen bonding occurs between nearby phospholipid molecules. At neutral pH, the repulsion between soya lecithin molecules is stronger than the hydrogen bonds, which leads to smaller vesicles. Instead of forming Multi-Lamellar Vesicles (MLVs), we saw the creation of smaller layered structures.[33,34]

For entrapment efficiency, the linear model performed well, and we analyzed it using ANOVA. When the values for BProb>F were less than 0.0500, it showed that our factors were significant. Here, both the drug-to-lipid ratio and sonication time played key roles in affecting how well we trap the drug. The normal residuals plot (Figure 4) confirmed that our model was fitting well, as the data points grouped closely around the expected line. This proximity indicated our model was strong and reliable. Both the drug-to-lipid ratio and sonication time were essential for entrapment efficiency, but they impacted it differently. Increasing the drug-to-lipid ratio improved efficiency because more lipids help encapsulate the amphiphilic drug. The contour plots supported this, showing that as the drug-to-lipid ratio went up, so did the entrapment efficiency. However, longer sonication times negatively affected entrapment efficiency, as they can disturb liposomal structures and release the drug. This was also evident in our contour plots that looked at sonication time's effects[31-34]

We validated our model through a method called numerical optimization using point prediction. Running our levels three times showed that both particle size and entrapment efficiency were close to what we expected.

PLGA-PEG liposomes modify the pharmacokinetics of memantine by enhancing its transport to the brain, prolonging drug release, and reducing the frequency of administration compared to free memantine. The Polyethylene Glycol (PEG) coating on PLGA nanoparticles contributes to a more sustained and potentially safer drug delivery by extending circulation time in the bloodstream, minimizing uptake by the Mononuclear Phagocyte System (MPS), and increasing the overall stability of the formulation.

Memantine's amphiphilic nature significantly influences its formulation and encapsulation efficiency, particularly in the development of drug delivery systems such as liposomes. Its ability to interact with both hydrophilic and hydrophobic environments facilitates its incorporation into these systems. This dual solubility allows memantine to dissolve in a wider range of solvents, enhancing its compatibility with liposomal formulations.[36,37]

The amphiphilic properties of memantine help prevent its precipitation or degradation within the delivery system, thereby improving its overall stability. These characteristics also contribute to higher encapsulation efficiency, making it feasible to successfully incorporate memantine into liposomal carriers.

Moreover, memantine's amphiphilicity plays a key role in modulating its release from the carrier. It can interact with both hydrophilic and hydrophobic components of the formulation, depending on the nature of the carrier materials and specific formulation conditions. For example, it may bind to hydrophobic regions of lipids or polymers or be adsorbed onto the surface of the liposome.

Memantine can also be encapsulated within the aqueous core of liposomes, providing protection from degradation and enabling a controlled release profile. Overall, its amphiphilic character makes it well-suited for liposomal drug delivery, enhancing solubility, encapsulation efficiency, and targeted release. This ultimately improves therapeutic efficacy while minimizing potential side effects.

This result confirmed that our design was validated, and our control strategy effectively reduced risks. We then reproduced the formulation, achieving a particle size of 300.86±33 nm with a PDI of 0.2 and an entrapment efficiency of 87.14±4.32%. As illustrated in Figure 8, the size of the liposomal particles matched what we saw in the SEM images. The TEM images revealed that the liposomes were round and had smooth surfaces. Characterization of the formulation using techniques like DSC and FTIR confirmed that memantine remained stable through the liposomal process. In the DSC analysis (Figure 6), we noted that a small endothermic peak was preserved in the formulation's thermogram. The FTIR results in Figure 7 showed that most of the unique bands from pure memantine HCl were still present.[30-34] stability study conforms liposomes are stable for longer duration (Refer Table 7).

CONCLUSION

Alzheimer's is a disease that harms nerve cells in the brain. To fight this, treatment needs to focus on new targets that can help stop further damage. Memantine, which works as an NMDA receptor blocker, is suggested to protect nerves and prevent degeneration. To ensure that the drug is released steadily in the brain, a special liposomal formulation of memantine HCl was created using a planned approach called QbD. This method aims to make a product that is both safe and of good quality.

To find out how different factors like the ratio of drug to lipid, hydration, and sonication time affect the size of the particles and how well the drug is trapped, we used a design called Box Behnken. We then verified this design with a numerical method known as point prediction. The results showed an average particle size of 287±33 nm and an entrapment efficiency of 87.14±4.32%. Further studies using FTIR and DSC confirmed that the form of memantine did not change during the formulation process. SEM images showed that the liposomes were round and that their size was consistent with results from another measurement technique called DLS. In conclusion, this research successfully created a liposomal version of memantine using the QbD strategy, showing promise in fighting Alzheimer's. The PLGA PEGylated Memantine liposome released the drug steadily for 72 hr, suggesting that a consistent release in the brain may achievable, which is confirmed through *in vitro* drug release studies. Challenges during optimization was to select a range of drug to lipid ratio, sonication time and hydration time was the best challenge but it was resolved with the help of preformulation studies and prior batches which was evaluated for particle size and entrapment efficiency and from that desired range of drug to lipid ratio, sonication time and hydration time was selected for optimization.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AD: Alzheimer's Disease; **CNS:** Central Nervous System; **BBB:** Blood Brain Barrier; **IN:** Intra Nasal; **LP:** Liposomes; **PEG:** Polyethylene Glycol; **PLGA:** Poly (lactic-co-glycolic acid); **QBD:** Quality By Design; **CQA:** Critical Quality Attributes; **CPP:** Critical Process Parameter; **CMA:** Critical Material Attributes; **EE:** Entrapment Efficiency.

AUTHORS CONTRIBUTIONS

Mr. Abhish Jadhav[1]: writing, analysis of data, interpretation of data. Dr. Mrudula Bele: Verification and scrutiny of data.

SUMMARY

A novel liposomal formulation for nose-to-brain delivery of memantine, an FDA-approved NMDA receptor antagonist used in the treatment of Alzheimer's disease (AD), was successfully developed and optimized. The primary goal was to address the drawbacks of conventional oral delivery and enhance direct brain targeting. To achieve this, PEGylated PLGA-based liposomes were designed for intranasal administration, enabling drug transport through the olfactory and trigeminal nerves, thus bypassing the blood-brain barrier (BBB). A Quality-by-Design (QbD) approach was applied, utilizing Design of Experiments (DoE) to systematically optimize both formulation and process variables. Key factors such as drug-to-lipid ratio, sonication time, and hydration time were evaluated to obtain liposomes with optimal particle size and encapsulation efficiency. The optimized formulation exhibited a particle size below 300 nm, ideal for nose-to-brain targeting, along with a stable zeta potential, high drug entrapment efficiency (up to 86%), and controlled release extending up to 72 hr. Characterization using Scanning Electron Microscopy (SEM), Fourier Transform Infrared Spectroscopy (FTIR), and Differential Scanning Calorimetry (DSC) confirmed the stability, compatibility, and structural integrity of the formulation. Results from *in vitro* release studies supported its potential for effective brain delivery. In conclusion, this memantine-loaded PEGylated PLGA liposomal system demonstrates strong potential as a non-invasive and efficient delivery platform for Alzheimer's therapy, with the QbD approach ensuring a systematic and reproducible formulation process.

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