RESEARCH ARTICLE

Formulation, Development and Evaluation of Memantine and Memantine-Curcumin Co-loaded Liposomes for Intranasal Delivery in Alzheimer's

Abhish Jadhav*, Mrudula Bele

Department of Pharmaceutics, *NDMVP's College of Pharmacy, Nasik-422005, Maharashtra, India*

Received: 15th Jun, 2025; Revised: 28th Jul, 2025; Accepted: 17th Aug, 2025; Available Online: 25th Sep, 2025

ABSTRACT

Creation of amyloid β (Aβ) peptides involved in disease progression is the important pathway in Alzheimer's disease (AD) progression and that is a crucial target for the treatment of AD. NMDA receptor antagonists have emerged as a promising strategy to lower Aβ levels and slow AD development. However, because the blood-brain barrier (BBB) is so restrictive, their efficacy is restricted when administered systemically. In AD, inflammation, oxidative stress, and the buildup of abnormal proteins like amyloid and tau are common and recent research suggests use of curcumin may help counteract these damaging processes and protect neurons. Unfortunately, both NMDA receptor antagonists and curcumin face challenges crossing the BBB, resulting in poor brain uptake. The nose-to-brain (NtB) delivery route offers a potential solution by bypassing the BBB and allowing direct access to the brain. Liposomal drug delivery systems enhances drug reach by improving efficient transport to the brain as well as greater drug stability. This study used the rotary evaporation method to prepare memantine liposomes and coupled memantine-curcumin liposomes, which were then evaluated *In-vitro*. The findings indicate that liposomal formulations of memantine and memantine-curcumin can promote effective intracellular drug delivery, potentially cross tight junctions in the BBB, and may help reduce amyloid plaque formation and inflammation, highlighting their promise as an AD treatment via NtB delivery having good physicochemical properties and stability of drug.

Keywords: Alzheimer's disease, Memantine hydrochloride, Curcumin, Liposomes, Nose-to-brain delivery, QbD approach.

How to cite this article: Abhish Jadhav, Mrudula Bele. Formulation, Development and Evaluation of Memantine and Memantine-Curcumin Co-Loaded Liposomes for Intranasal Delivery in Alzheimer's. International Journal of Drug Delivery Technology. 2025;15(3):1205-11. doi: 10.25258/ijddt.15.3.40

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Nearly about more than half of population i.e 60–80% are having dementia, memory loss which is caused by Alzheimer's disease (AD), a degenerative illness to the neurological system. Although the exact cause of AD remains unclear, the accumulation of beta-amyloid (Aβ) plaques is widely regarded as a key hallmark of the disease[1-3]. The transmembrane protein known as the amyloid precursor protein (APP) is cleaved sequentially to produce Aβ peptides[4]. α-secretase, an enzyme belonging to the ADAM (a disintegrin and metalloproteinase) family, cleaves APP initially in the non-amyloidogenic pathway. ADAM10 has been identified as the primary α-secretase for APP processing. The soluble N-terminal segment of APP (sAPPα), which is produced by this cleavage, is known to have neurotrophic and neuroprotective properties[4]. On the other hand, the amyloidogenic pathway produces the Aβ40 and Aβ42 peptides by cleavage by β-secretase-1 (BACE1) and γ-secretase. Aggregation, oxidative stress, and neurotoxicity are characteristics of these peptides. These days, cholinesterase inhibitors like donepezil and N-methyl-D-aspartate (NMDA) receptor antagonists like memantine are the two primary pharmacological classes used to treat Alzheimer's disease. AD is characterized by cholinergic dysfunction, which impairs memory and cognitive functions; thus, ChEIs work by preventing the breakdown of acetylcholine and butyrylcholine to restore cholinergic signaling[5]. As the second ChEI approved by the FDA, donepezil was approved in 1996 and has been the subject of substantial research in the treatment of AD. As an uncompetitive NMDA receptor antagonist, memantine, which is licensed for moderate to severe AD, shields neurons from glutamate-induced excitotoxicity and cell death linked to AD pathogenesis[6]. With numerous preclinical and clinical studies demonstrating its ability to lessen neurodegeneration and alleviate AD symptoms, curcumin has gained interest recently as a possible neuroprotective agent in the treatment of AD[7].

One of the primary challenges in treating Alzheimer's disease (AD) is ensuring efficient delivery of therapeutic agents to the brain. The brain's intricate protective architecture, which consists of the skull, several membrane layers which are highly impervious which we called blood brain barrier is the cause of this challenge. Over 98% of small molecules are prevented from entering the central nervous system (CNS) by the highly selective BBB. It also has efflux transporters, which actively eliminate a lot of medicinal substances. Drug delivery must take place through particular processes such transcellular diffusion, receptor-mediated endocytosis, or carrier-mediated transport in order to effectively reach the central nervous system (CNS) because endothelial cells have tight

**Author for Correspondence: abhish5666@gmail.com*

junctions. However, these pathways are frequently insufficient for optimal drug delivery and require certain conditions[8]. To bypass these limitations, intranasal administration has been explored as a promising method for CNS drug delivery. Traditionally used to treat local nasal conditions such as allergies and congestion, intranasal delivery offers several advantages for systemic drug administration, including noninvasiveness, ease of use, a porous endothelial barrier, and avoidance of first-pass metabolism[9]. Crucially, this route provides direct access to the brain by bypassing the BBB, as the olfactory mucosa lacks BBB protection and connects directly to brain tissue. This pathway also helps reduce drug accumulation in systemic circulation and major organs, potentially lowering side effects. Advances in nanotechnology, particularly lipid-based and polymeric Nano liposomes, have enhanced targeted drug delivery.

Liposomes—composed of one or multiple phospholipid bilayers combined with lipids like cholesterol or phosphatidylcholine—are widely used to improve drug efficacy and safety, including for cancer treatments, antimicrobials, and vaccines. Liposomal formulations are especially advantageous for nose-to-brain (NtB) delivery due biocompatibility, encapsulation efficiency for both lipophilic and lipophobic drugs, controlled release properties, prolonged residence time at absorption sites, and reduced systemic toxicity[10].

Memantine (MEM) is recognized for its excellent bioavailability and relatively mild side effect profile, making it a strong candidate for continued research.

Furthermore, liposomal drug delivery systems offer significant advantages, such as targeted delivery and sustained release, which are particularly valuable in the treatment of Alzheimer's disease (AD)[11]. Curcumin, a powerful bioactive compound found in turmeric (derived from the Curcuma longa plant), has shown promising neuroprotective properties. A large-scale epidemiological study reported a lower prevalence of Alzheimer's disease in the Indian population, which was attributed to regular dietary intake of curcumin. While various *In-vitro* and in vivo studies have demonstrated curcumin's potential to combat neurodegenerative conditions, its clinical effectiveness remains limited due to poor oral bioavailability. To overcome this challenge, curcumin-loaded liposomes with surface modifications are being explored as a powerful strategy to enhancing curcumin targeting to the brain region through the digestive tract[12].

Table 1: Formulation and evaluation of batches of MEM liposomal formulation

Batch code	Drug to lipid concen.	Time of Hydration	Time of Sonication	Particle size (nm)	% EE
F1	6.5	0	15	541.6	71.23
F2	6.5	60	10	432.7	69.87
F3	6.5	60	10	510.8	70.55
F4	10	90	10	502.7	73.12
F5	3	60	5	368.6	71.45
F6	6.5	60	10	340.5	73.65
F7	10	30	10	601.1	71.87
F8	10	60	5	411.5	73.12
F9	6.5	30	5	495.0	69.32
F10	6.5	60	10	355.8	74.36
F11	6.5	30	15	463.6	72.38
F12	3	60	15	301.3	78.36
F13	3	30	10	376.9	76.10
F14	10	60	15	656.1	67.33
F15	6.5	90	5	516.3	55.63
F16	6.5	60	10	562.2	54.24
F17	3	90	10	485.3	69.38

This study focuses on preparing liposomal formulations of memantine alone and in combination with curcumin, followed by *In-vitro* characterization and evaluation of their morphology, physicochemical properties, drug release profiles, and stability, with the goal of developing an effective nose-to-brain delivery system for combined therapy.

MATERIALS AND METHODS

Materials

Memantine (MEM) and curcumin (CUR) were procured from Sigma Aldrich. Throughout the experiments, ultrapure water obtained via the Millipore MilliQ system was used. Additional chemicals and reagents, all of analytical grade, were also sourced from Sigma Aldrich. Soya lecithin and cholesterol were generously supplied by VAV Lipids, a division of VAV Life Sciences. Analytical grade ethanol and chloroform were likewise purchased from Sigma Aldrich.

Development of MEM-loaded Liposomes

Using the thin-film hydration process, the medication was mixed with phospholipids in a certain ratio to create multilamellar vesicles (MLVs). The lipid mixture consisted of soya lecithin and cholesterol at an 8:2 ratio. Memantine hydrochloride was dispersed in equal volumes of ethanol

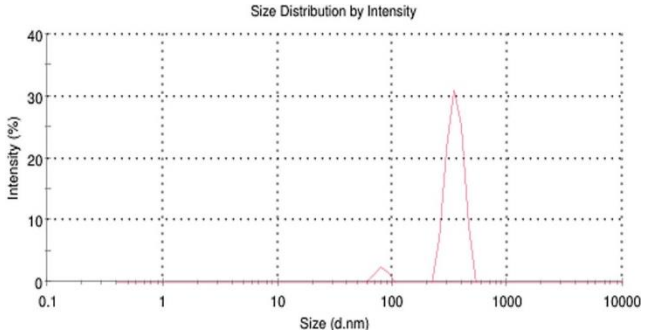

Figure 1: Particle size of MEM liposome

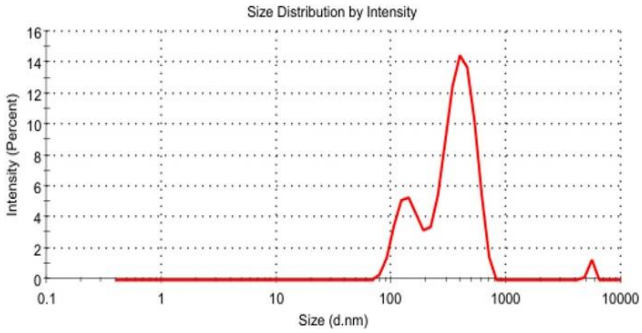

Figure 2: Particle size of MEM-CUR liposome

and organic solvent chloroform within a round-bottom flask.

The solvents were then removed by rotary evaporation at 65 °C for 15 minutes, resulting in the formation of a thin lipid-drug film. To guarantee total solvent elimination, this film was further dried for an entire night at 40 °C in a vacuum oven. To promote MLV production, the dry film was next hydrated with 5 mL of Milli-Q water, shaken vigorously, and then gently rotated in a water bath at 50 °C and 150 rpm for a predetermined amount of time. Bath sonication was used to reduce the size of the vesicles. Centrifugation at 10,000 rpm was used to extract the unencapsulated medication, and the pellet was then resuspended in water. A Malvern particle size analyzer was used for the measurement of the liposomes' zeta potential and particle size, and the formulations' entrapment efficiency. Formulation and evaluation of batches presented in Table 1.

Development of MEM CUR Liposome

MLVs were made using the thin film or thin layer hydration technique, where the drug was combined with a defined amount of phospholipids. The lipid mixture consisted of soya lecithin and cholesterol in a 8:2 ratio. Memantine hydrochloride was dissolved in equal volumes of absolute ethanol and chloroform in a round-bottom flask, with curcumin powder added simultaneously. The subsequent steps followed the same procedure as used for the preparation of memantine-loaded liposomes. Formulation and evaluation of MEM CUR liposome batches presented in Table 2.

Evaluation of the MEM Loaded Liposome Formulation and MEM CUR Loaded Liposome

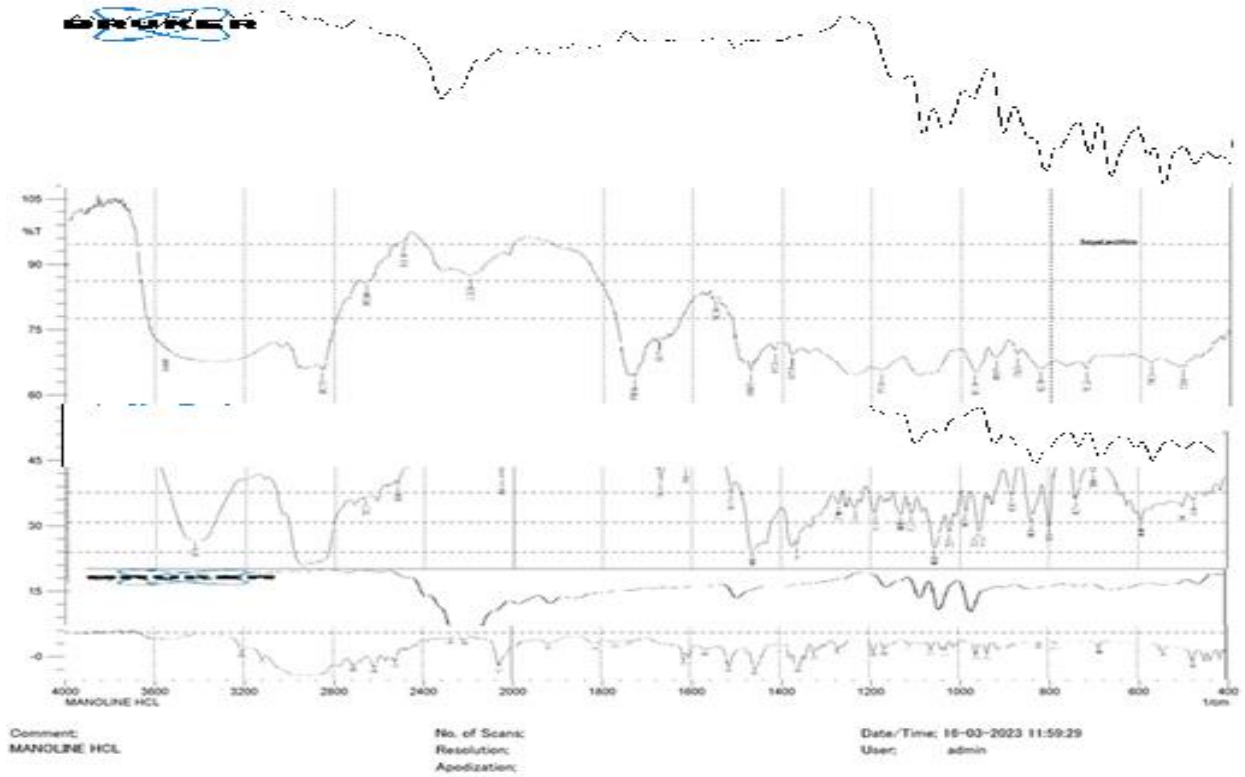

Figure 3: FTIR spectra

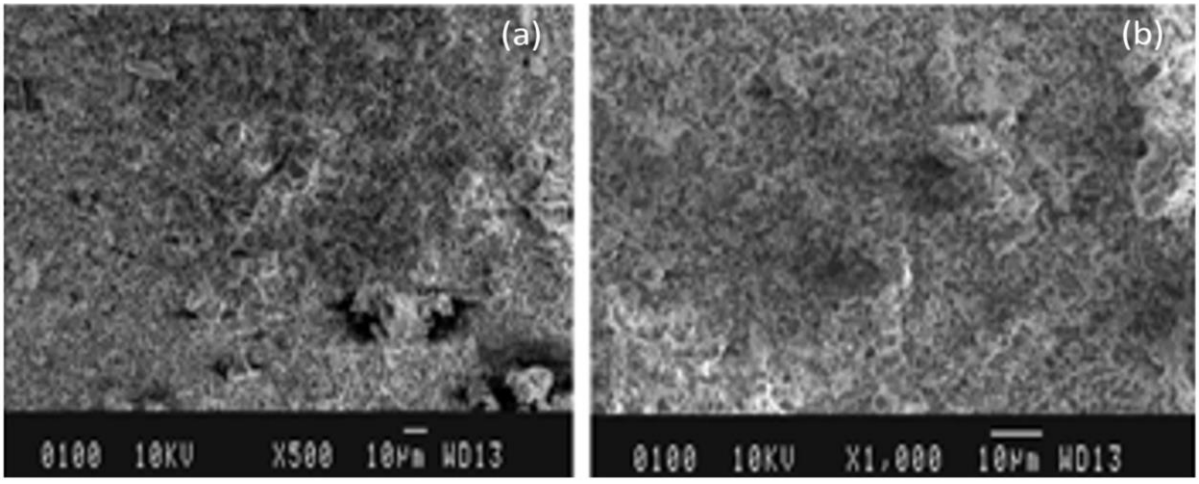

Figure 4: (a) SEM analysis of MEM liposome; (b) MEM-CUR for surface morphology

Table 2: Formulation and evaluation of batches of MEM CUR liposome

Batch code	Drug to lipid concentration	Time of Hydration	Time of Sonication	Curcumin [mg]	Particle size [nm]	% EE
F1	6.5	0	15	3	475.6	68.23
F2	6.5	60	10	3	375.7	65.87
F3	6.5	60	10	3	413.8	68.55
F4	10	90	10	3	425.7	70.12
F5	3	60	5	3	472.6	71.45
F6	6.5	60	10	3	485.5	73.65
F7	10	30	10	3	514.1	69.87
F8	10	60	5	3	524.5	71.12
F9	6.5	30	5	3	425.0	69.32
F10	6.5	60	10	3	395.8	70.36
F11	6.5	30	15	3	464.6	69.38
F12	3	60	15	3	325.3	72.36
F13	3	30	10	3	396.9	76.10
F14	10	60	15	3	656.1	67.33
F15	6.5	90	5	3	546.3	65.63
F16	6.5	60	10	3	562.2	62.24
F17	3	90	10	3	565.3	63.38

Table 3: Cumulative drug release profile of MEM Liposomes and MEM-CUR liposomes in phosphate buffer pH 7.4 in comparison with plain drug

Time	Marketed formulation (Tab)	Memantine drug solution	Memantine Liposomes	Memantine Curcumin Liposomes
0 min	0.000	0.000	0.000	0.000
30 min	46.000 ± 1.527	55.000 ± 2.886	5.666667 ± 1.20	9.333333 ± 1.45
1 hrs.	65.33334 ± 2.027	68.33334 ± 2.333	12.000 ± 2.30	16.66667 ± 2.90
2 hrs.	88.66666 ± 2.4037	94.000 ± 2.64	26.000 ±	28.33333 ± 3.75
180 hrs.			32.000 ± 2.88	34.66667 ± 3.48
4 hrs.			42.33333 ± 3.75	48.33333 ± 2.72
12 hrs.			61.66667 ± 2.90	67.33334 ± 3.75
24 hrs.			86.000 ± 2.88	91.000 ± 3.21
36 hrs.			91 ± 2.86	95 ± 3.36
48 hrs.			94 ± 2.61	97 ± 3.36
72 hrs.				

Using a Zetasizer Nano ZS (Malvern Instruments Ltd., Worcestershire, UK) and dynamic light scattering (DLS), liposomal size and polydispersity index (PDI) were measured three times at 25 °C. Samples were evaluated in a 1 ml disposable polystyrene cuvette after being diluted at least 50 times with Milli-Q water for the procedure. The PDI displayed the range of particle sizes, whereas the size displayed a Z-average, or mean particle diameter.

Additionally, using the same device, zeta potential measurements were made at 25 °C. A 50 V electric field moved through a polycarbonate folded capillary cell next to the final value arrived from the average of 30 readings, showing the electrophoretic mobility of the particles.

Determining Drug Loading and Encapsulation Efficiency MEM Loaded Liposome Formulation

A 10 microliter portion of the prepared liposomes underwent dilution with Milli-Q water to reach a final volume of one milliliter within a microcentrifuge tube. Samples experienced centrifugation at 13,000 revolutions per minute for 15 minutes. Following this, the liquid above the solid pellet was taken to determine the concentration of the drug not contained within the liposomes, referred to as MEM_free. For the total amount of drug present, MEM_total, a separate 10 microliter portion of liposomes combined with methanol reached one milliliter and was mixed thoroughly. The concentrations of MEM_free and MEM_total received quantification through a UV spectrophotometer at 245 nanometers. Each measurement occurred three times, with the average values presented as a mean plus or minus a standard deviation, with n equal to three. The calculation of encapsulation efficiency used the formula:

$$\%\ Entrapment\ Efficiency = \frac{[MEM_{total} - MEM_{free}]}{MEM_{total}} \times 100$$

Determining Drug Loading and Encapsulation Efficiency MEM-CUR Loaded Liposome Formulation

For drug loading and encapsulation efficiency evaluation, 10 microliters of the liposomal formulation underwent dilution with Milli-Q water to reach one milliliter in a microcentrifuge tube. Centrifugation of the sample followed at 13,000 revolutions per minute for 15 minutes. The supernatant collection permitted determination of the unencapsulated curcumin concentration, identified as CUR_free. Regarding the total drug content, labeled as CUR_total, another 10 microliters of liposomes combined with methanol reached one milliliter and was vortexed thoroughly. Measurement of both CUR_free and

CUR_total occurred via a UV spectrophotometer at 245 nanometers. Each assay had three repetitions. Averages of the results are presented as mean plus or minus standard deviation, with n equal to three. Encapsulation efficiency calculation used the formula:

$$\%\ Entrapment\ Efficiency = \frac{[CUR_{total} - CUR_{free}]}{CUR_{total}} \times 100$$

Fourier Transform Infrared Spectroscopy of MEM Loaded Liposome Formulation and MEM CUR Loaded Liposome

The FTIR spectra of pure memantine, curcumin, memantine-loaded liposomal powder, and memantine-curcumin-loaded liposomal powder were recorded using a Shimadzu model 8033 FTIR spectrophotometer. Each sample was finely ground, blended with anhydrous potassium bromide, compressed into thin pellets, and then subjected to FTIR analysis.

Scanning Electron Microscopy of MEM Loaded Liposome Formulation and MEM CUR Loaded Liposome

The morphological characteristics of memantine liposomes and memantine-curcumin co-loaded liposomes were assessed using scanning electron microscopy (SEM) with a Philips CM 200 system. Imaging was carried out at an accelerating voltage of 200 kV, offering a resolution of 0.23 nm. Freeze-dried formulations were first reconstituted in Milli-Q water, and a small volume of the resulting suspension was deposited onto copper grids coated with Formvar®. For contrast enhancement, a 2% (w/v) uranyl acetate solution was added and left to stain the samples for approximately 3 minutes. After carefully removing the excess solution, the grids were air-dried before SEM imaging was performed.

In-vitro Release Study of MEM Liposomes

For the *In-vitro* release study of MEM 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 hours (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 the sample from the stirring release medium and replaced it with an equal amount of fresh buffer at the same temperature refer to Table 3.

Table 4: Cumulative drug release profile of curcumin from Liposomes in comparison with plain curcumin in phosphate buffer pH 7.4

Time	Curcumin drug solution	Memantine Curcumin Liposomes
0 min	0.000	0.000
30 min	57.000 ± 2.886	6.967 ± 1.20
1 hrs.	79.234 ± 2.333	11.30 ± 2.30
2 hrs.	93.000 ± 2.64	24.23 ±1.23
180 hrs.		38.280 ± 2.88
4 hrs.		47.2333 ± 3.75
12 hrs.		64.97 ± 2.90
24 hrs.		87.000 ± 2.88
36 hrs.		91 ± 2.86
48 hrs.		93 ± 2.61

In-vitro Release Study of MEM-CUR Liposomes

In the *In-vitro* release study of memantine-curcumin (MEM-CUR) liposomes, their release profiles were compared with those of free memantine, free curcumin, and a marketed memantine formulation using the bulk equilibrium direct dialysis bag method over a period of 72 hours (n=6). Two milliliters of each formulation were enclosed in dialysis bags made from cellulose membranes with a molecular weight cutoff of 12–14 kDa. These bags were then placed in 150 ml of isotonic phosphate-buffered saline (PBS) at pH 7.8 and maintained at 37 °C. At predetermined time points, 1 ml samples were collected from the stirred release medium and replaced with an equal volume of fresh buffer pre-warmed to the same temperature (Table 4).

RESULTS

Characterization of MEM Liposomal and MEM-CUR Liposomal Formulation

The optimized batches showed a particle size of 346.3 nm and a PDI value of 0.2 for MEM liposome and 396.6 nm and a PDI value of 0.3 MEM-CUR liposome, with an entrapment efficiency of 73.29%. The zeta potential for our developed liposomal formulation was again measured at 3.96 mV. Refer Figure 1 for Particle size of MEM liposome and Figure 2. for Particle size of MEM-CUR liposome.

FTIR, and SEM of MEM Liposomal and MEM-CUR Liposomal Formulation

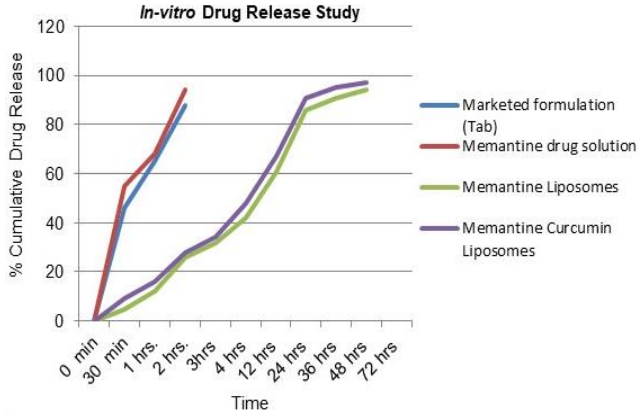

Figure 5: Cumulative drug release profile of Memantine liposome in phosphate buffer pH 7.8 in comparison with plain drugs

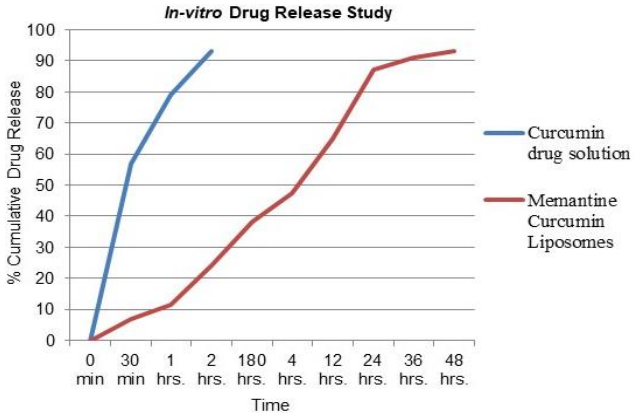

Figure 6: Cumulative drug release profile of Memantine liposome in phosphate buffer pH 7.8 in comparison with plain drugs

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 (Fig. 3). 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.

In the phospholipids of MEM- CUR liposomes, the CH_2 groups exhibit distinctive vibrational peaks, with the symmetric stretching observed at 2850 cm^{-1} and the asymmetric stretching at 2924 cm^{-1}. Meanwhile, curcumin displays its own characteristic absorption bands, including a peak at 1428 cm^{-1} corresponding to the bending vibrations of olefinic C–H bonds, and another at 1024 cm^{-1}, which is attributed to the stretching vibrations of C–O–C linkages.

SEM

The SEM images of the MEM liposomal formulation and the MEM-CUR liposomal formulation are displayed in Figures 4a and 4b, showing the round shape and smooth surface of the liposomes. The liposomes' dimensions closely match those determined by the DLS technique.

In-vitro Release Study of MEM Liposomal and MEM-CUR Liposomal Formulation

The release profiles of the MEM-CUR liposomal formulation and the optimized liposomal MEM-liposomal formulation in phosphate buffer at a pH of 7.8 are shown in Figures 5 and 6. According to the *In-vitro* investigation, the formulation had a biphasic release pattern, with a rapid release during the first eight hours and a delayed release lasting up to 72 hours. (table 3 and table 4).

DISCUSSION

The objective was to develop a dry, free-flowing powder formulation that can be reconstituted prior to nasal administration, enabling direct drug delivery to the brain. For nasal delivery, the final product is intended as a reconstitutable dry powder with a target particle size range of 100 to 300 nm and entrapment efficiency between 70 and 85%. Microbial limits will comply with pharmacopeial standards to guarantee the product's sterility and safety. Selecting an appropriate container to protect formulation from external factors and ensure safe handling by patients, with the choice tailored to the product's requirements. Critical Quality Attribute (CQA) is a physical, chemical, biological, or microbiological property that must be controlled within specific limits to assure the desired product quality (ICH 2009)[13].

For effective brain targeting, particle size should ideally fall between 100 and 300 nm. Memantine hydrochloride's amphiphilic nature presents challenges for encapsulation within vesicular carriers, making high entrapment efficiency critical to ensure adequate drug delivery at the target site. Consequently, encapsulation efficiency is considered a key quality attribute linked directly to the therapeutic performance of the formulation[14].

Based on a review of existing literature, factors affecting liposomal particle size and encapsulation efficiency were grouped into three categories: formulation, process, and environmental. Environmental factors were excluded as they are generally easy to control. Among formulation variables, the drug-to-lipid ratio was identified as a key determinant of liposome size. Phospholipids, which form the main structure of liposomal membranes, directly influence particle size and, together with cholesterol, are critical for drug entrapment. The optimal ratio of soya lecithin to cholesterol was established at 8:2 to ensure liposome stability, as excessive cholesterol can cause membrane leakage and destabilize the system. Encapsulation efficiency also depends heavily on the drug-to-lipid ratio, which must be sufficiently high to effectively encapsulate amphiphilic compounds like memantine, designating this ratio as a crucial material attribute impacting both particle size and drug loading. Regarding process factors, hydration and sonication times were found to significantly influence particle size; extended sonication typically reduces particle size by breaking down multilamellar vesicles into smaller unilamellar forms but may risk drug leakage and reduced entrapment efficiency. In contrast, longer hydration periods improve drug encapsulation by facilitating better interaction between the drug and lipid vesicles. Following a risk assessment of these factors, control strategies were implemented to develop a high-quality, stable liposomal formulation. Ultimately, focusing on the drug-to-lipid ratio, hydration time, and sonication time enabled the production of smaller, multilamellar vesicles with improved drug entrapment[15]. As shown in Fig.1 & 2, the measured size of the liposomal particles was consistent with the observations from the SEM images, which depicted the liposomes as spherical with smooth surfaces. Further characterization using techniques such as DSC and FTIR confirmed the stability of memantine throughout the liposome formulation process. Similarly, the FTIR spectra (Fig. 3) revealed that most characteristic peaks of pure memantine HCl and curcumin remained intact.

CONCLUSION

Alzheimer's disease causes damage to neurons in the brain, and effective treatment requires targeting mechanisms that can prevent further neural deterioration. Memantine, an NMDA receptor antagonist, is believed to offer neuroprotection and slow degeneration. To achieve controlled drug release within the brain, a specialized liposomal formulation of memantine HCl was developed. The formulation exhibited an average particle size of 287 ± 33 nm and an entrapment efficiency of 87.14 ± 4.32%. Characterization by FTIR and DSC analyses confirmed that memantine's chemical structure remained unchanged during the formulation process. SEM imaging revealed spherical liposomes, with size measurements aligning well with dynamic light scattering (DLS) data. Overall, this study successfully developed a memantine liposomal formulation using a Quality by Design (QbD) approach, demonstrating potential for Alzheimer's therapy. The PEGylated PLGA memantine liposomes provided a

sustained drug release over 72 hours *In-vitro*, indicating the potential for consistent brain delivery.

Future Plans

The same formulations will be used further for animal study to assess the neuroprotective effect and anti-alzheimer's effect on albino mice.

Author Contributions

Abhish Jadhav- Conception, design, drafting of paper, revising, final approval.

Mrudula Bele- Interpretation revising and final approval.

Acknowledgements

Authors are thankful to Savitribai Phule Phule Pune University, Pune Maharashtra India and Management and Principal of NDMVP's College of Pharmacy, Nashik, Maharashtra for providing necessary support and facilities.

REFERENCES

1. Neugroschl J, Wang S. Alzheimer's disease: diagnosis and treatment across the spectrum of disease severity. Mount Sinai journal of medicine, New York. 2011 Jul;78(4):596-612. https://doi.org/10.1002/msj.20279
2. Regelin AE, Fankhaenel S, Gürtesch L, Prinz C, von Kiedrowski G, Massing U. Biophysical and lipofection studies of DOTAP analogs. Biochimica et biophysica acta. 2000 Mar 15;1464(1):151-64. https://doi.org/10.1016/S0005-2736(00)00126-7
3. Bloom GS. Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA neurology. 2014 Apr 1;71(4):505-8. https://doi.org/10.1001/jamaneurol.2013.5847
4. Dislich B, Lichtenthaler SF. The membrane-bound aspartyl protease BACE1: molecular and functional properties in Alzheimer's disease and beyond. Frontiers in physiology. 2012 Feb 17;3:8. https://doi.org/10.3389/fphys.2012.00008
5. Lee D, Minko T. Nanotherapeutics for nose-to-brain drug delivery: an approach to bypass the blood brain barrier. Pharmaceutics. 2021 Nov 30;13(12):2049. https://doi.org/10.3390/pharmaceutics13122049
6. Peron R, Vatanabe IP, Manzine PR, Camins A, Cominetti MR. Alpha-secretase ADAM10 regulation: insights into Alzheimer's disease treatment. Pharmaceuticals. 2018 Jan 29;11(1):12. https://doi.org/10.3390/ph11010012
7. Deuss M, Reiss K, Hartmann D. Part-time α-secretases: the functional biology of ADAM 9. Current Alzheimer research. 2008 Apr 1;5(2):187-201. https://doi.org/10.2174/156720508783954686
8. Chasseigneaux S, Allinquant B. Functions of Aβ, sAPPα and sAPPβ: similarities and differences. Journal of neurochemistry. 2012 Jan;120 (Supplement 1):99-108. https://doi.org/10.1111/j.1471-4159.2011.07584.x
9. Grassin-Delyle S, Buenestado A, Naline E, Faisy C, Blouquit-Laye S, Couderc LJ, Le Guen M, Fischler M, Devillier P. Intranasal drug delivery: an efficient and non-invasive route for systemic administration: focus on opioids. Pharmacology and therapeutics. 2012 Jun 1;134(3):366-79. https://doi. https://doi.org/10.1016/j.pharmthera.2012.03.003
10. Maia MA, Sousa E. BACE-1 and γ-secretase as therapeutic targets for Alzheimer's disease. Pharmaceuticals. 2019 Mar 19;12(1):41. https://doi.org/10.3390/ph12010041
11. Singh B, Day CM, Abdella S, Garg S. Alzheimer's disease current therapies, novel drug delivery systems and future directions for better disease management. Journal of controlled release. 2024 Mar 1;367:402-24. https://doi.org/10.1016/j.jconrel.2024.01.047
12. Garodia P, Hegde M, Kunnumakkara AB, Aggarwal BB. Curcumin, inflammation, and neurological disorders: how are they linked? Integrative medicine research. 2023 Sep 1;12(3):100968. https://doi.org/10.1016/j.imr.2023.100968
13. Hong SS, Oh KT, Choi HG, Lim SJ. Liposomal formulations for nose-to-brain delivery: recent advances and future perspectives. Pharmaceutics. 2019 Oct 17;11(10):540. https://doi.org/10.3390/pharmaceutics11100540
14. Schofield T, Robbins D, Miró-Quesada G. Critical quality attributes, specifications, and control strategy, Quality by Design for Biopharmaceutical Drug Product Development. (edited by: F Jameel, S Hershenson, MA Khan & S Martin-Moe). Springer New York: New York, NY. 2015:511-35. https://doi.org/10.1007/978-1-4939-2316-8_21
15. Dhoble S, Patravale V. Development of anti-angiogenic erlotinib liposomal formulation for pulmonary hypertension: a QbD approach. Drug delivery and translational research. 2019 Oct;9(5):980-96. https://doi.org/10.1007/s13346-019-00641-2