RESEARCH PAPER

Formulation Strategy, Ex-Vivo Evaluation, and Characterization of a Memantine Nanoemulsion for Enhanced Alzheimer's Therapy

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ABSTRACT

Background: Alzheimer's disease (AD) is a condition characterised by neurodegeneration that worsens over time, characterised by memory impairment, cognitive decline, and changes in behaviour. Memantine hydrochloride, which acts as an NMDA receptor antagonist, is employed in the clinical treatment of AD; however, its poor solubility, significant first-pass metabolism, and restricted ability to cross the blood-brain barrier (BBB) limit its therapeutic effectiveness. Nanoemulsions offer a novel strategy to overcome these drawbacks by enhancing solubility, stability, and facilitating targeted brain delivery.

Methods:Nanoemulsions of memantine were formulated with oleic acid serving as the oil phase, Tween 20 acting as the surfactant, and PEG-400/propylene glycol utilized as the co-surfactant. Pseudo-ternary phase diagrams were utilised to optimize the formulations. The formulations (F1–F8) were produced through high-shear homogenization and ultrasonication, and subsequently assessed for transmittance, pH, viscosity, particle size, polydispersity index (PDI), zeta potential, and in vitro drug release, ex vivo permeation and stability studies.

Results:All formulations exhibited high clarity, a nanoscale size, and a physiological pH. The optimized batch showed the smallest droplet size, lowest PDI, high stability, and maximum sustained drug release, permeability and stability.

Conclusion:Memantine nanoemulsion enhances drug solubility, stability, and brain delivery. This approach represents a promising therapeutic strategy for Alzheimer's disease.

Keywords: Alzheimer's disease, Brain delivery, Memantine, Nanoemulsion, NMDA antagonist.

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INTRODUCTION

Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease, are rising globally, largely due to population aging. AD is the most prevalent form of dementia, accounting for approximately 60–70% of cases.[1] It is marked by progressive cognitive decline, memory impairment, and behavioral disturbances, ultimately leading to reduced functional independence and quality of life. AD pathology involves multiple processes, including amyloid-β deposition, tau protein aggregation, oxidative stress, excitotoxicity, cholinergic deficits, and neuronal degeneration in key brain regions. Current therapies remain largely symptomatic, emphasizing the urgent need for more effective disease-modifying approaches.[2]

Memantine is a moderate-affinity, non-competitive NMDA receptor antagonist approved for moderate to severe Alzheimer's disease, where it limits glutamate-mediated excitotoxic neuronal damage while preserving normal neurotransmission.[3]

Although clinically beneficial, its therapeutic potential can be further improved through advanced delivery systems that enhance solubility, stability, and brain targeting. Nanoemulsions offer promise by promoting efficient drug transport across biological barriers, including the gastrointestinal tract and the blood–brain barrier.[4]

For drugs like memantine, which have limited access for penetration into the brain in conventional dosage forms, nanoemulsions offer a strategic advantage to achieve efficient therapeutic concentrations in the central nervous system.[5] An ideal formulation should possess a small and uniform droplet size, narrow PDI, suitable zeta potential for colloidal stability, optimal viscosity for ease of administration, and pH values compatible with the intended route of delivery. In addition, *in vitro* drug release studies provide insight into the release kinetics. [6] By addressing the limitations of conventional formulations, memantine-loaded nanoemulsions are expected to improve drug permeation across the BBB, prolong therapeutic action, and enhance neuroprotection in AD patients [7]

In this context, the present study aimed to formulate and evaluate memantine nanoemulsions using selected oils, surfactants, and co-surfactants. The developed systems were characterized for their physicochemical properties and drug release behavior, offering a promising strategy to enhance memantine delivery for improved management of Alzheimer's disease and other neurodegenerative disorders.

MATERIALS & METHODS

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Cipla Pharmaceuticals Ltd., Ahmedabad, provided a free sample of Memantine hydrochloride. Oleic acid was received from Gattefosse, France. PEG400 and PEG200 ethylene glycol were received from S. D Fine Chemicals Ltd. Tween 20 received from Corel Pharma Chem, Ahmedabad. Other surfactants, co-surfactants, chemicals & reagents utilised were made of Analytical grade.

Methods

The solubility of Memantine Hydrochloride in diverse oils—specifically castor oil, oleic acid, and soybean oil, as well as in various surfactants and co-surfactants—which include Tween 20, PEG-200, PEG-400, along with propylene glycol—was ascertained by introducing an excess quantity (100 mg) of the pharmaceutical compound to 2 ml of each selected oil, surfactant, and co-surfactant individually in 5 ml capacity stoppered vials. The resultant mixtures were subjected to vortexing utilizing a cyclo mixer for a duration of 15 minutes to promote initial dispersion. The vials were maintained at 25 ± 1°C in an isothermal orbital shaker (100 rpm) for 24 hours to ensure uniform mixing and saturation, followed by an additional 24 hours for equilibrium without agitation. The samples that had reached equilibrium were centrifuged at 3000 rpm for 15 minutes to isolate the undissolved drug. The clear supernatant was carefully collected and suitably diluted with either chloroform or methanol. The concentration of dissolved Memantine Hydrochloride was quantified spectrophotometrically at λmax = 262 nm (previously determined from UV calibration curve). The results were articulated as the mean solubility (mg/ml) ± standard error of mean (SEM) derived from triplicate determinations.[8-9]

Construction of pseud-ternary graphs

To determine the area with the highest yield of NE, pseudo-ternary phase diagrams were meticulously constructed using the aqueous phase titration method. Separate diagrams were created based on solubility tests using oleic acid as the oil phase, Tween 20 as the surfactant, and PEG400 as the co-surfactant. Various Smix volume ratios were prepared (1:1, 1:2, 2:1, 3:1, 4:1, and 5:1) and employed to form the diagrams through systematic combinations of oil and Smix in volumes ranging from 1:9 to 9:1. Accurate titration commenced with the aqueous phase applied to these oil-Smix mixtures, continuously agitated to ensure uniformity, until a clear oil-in-water nanoemulsion was achieved. The successful titrations were used to map out the phase diagrams, specifically illustrating the conditions necessary for stable nanoemulsion formation. The diagrams, in pseudo-ternary format, featured three axes representing the aqueous phase, oil, and Smix, with a constant mass ratio for Smix maintained throughout to isolate the effects of oil and surfactant volumes on nanoemulsion stability. This structured approach effectively delineated the region conducive to nanoemulsion formation. The phase diagrams were developed employing Chemix Software (Chemix version 3.60).[10-11]

Table 1: Preparation of Memantine HCl-loaded nanoemulsion

Formulation	Memantine HCl (%)	Oleic acid (%)	Tween-20 (surfactant) (%)	Co-surfactant (%) (PEG-400)	Water (%)
F1 (Smix 1:1, Smix 30%)	2.00	15.00	15.00	15.00 (PEG-400)	53.00
F2 (Smix 1:2, Smix 30%)	2.00	10.00	10.00	20.00 (Propylene glycol)	58.00
F3 (Smix 2:1, Smix 30%)	2.00	12.00	20.00	10.00 (PEG-400)	56.00
F4 (Smix 3:1, Smix 35%)	2.00	10.00	26.25	8.75 (PEG-400)	53.00
F5 (Smix 4:1, Smix 35%)	2.00	12.00	28.00	7.00 (PEG-400)	51.00
F6 (Smix 5:1, Smix 35%)	2.00	15.00	29.17	5.83 (PEG-400)	48.00
F7 (Smix 3:1, Smix 35%)	2.00	8.00	26.25	8.75 (Propylene glycol)	55.00
F8 (Smix 1:2, Smix 25%)	2.00	18.00	8.33	16.67 (PEG-400)	55.00

Method of preparation by High-shear homogenization + probe ultrasonication

Memantine HCl-loaded microemulsion formulations (F1–F8) were prepared using the high-shear homogenization technique followed by probe ultrasonication. Initially, the required quantity of Memantine HCl was accurately weighed and dissolved in the aqueous phase under continuous stirring using a magnetic stirrer. The oil phase (oleic acid) was measured as per the formulation

composition, and the surfactant (Tween-20) and co-surfactant (PEG-400 or propylene glycol) were mixed thoroughly to form the Smix in the specified ratio.

The aqueous drug solution was slowly added dropwise to the oil phase containing Smix under constant stirring at 1000 rpm using a high-shear homogenizer (T25 Ultra-Turrax, IKA, Germany) for 10 minutes to form a coarse emulsion. The obtained pre-emulsion was further subjected to probe ultrasonication (Sonics Vibra Cell, USA) at 20 kHz frequency and 60% amplitude for 5 minutes with intermittent cooling in an ice bath to obtain a uniform and stable nano-sized microemulsion.[12]

The prepared formulations were allowed to equilibrate at room temperature for 24 hours to ensure phase stability. The resulting microemulsions were visually examined for clarity, homogeneity, and phase separation. The optimized formulation was selected based on transparency, uniform droplet size, and absence of turbidity or creaming.

EVALUATION TESTS:

Measurement of Transmittance:

The transmittance percentage of the formulated NEs was quantified with a UV-Vis spectrophotometer to assess the transparency of the prepared NEs in triplicate using Milli-Q water as a blank.[13]

pH of prepared nanoemulsion:

The measurement was done in triplicate employing a calibrated pH meter.[14]

Measurement of viscosity:

The measurement was done by trial and error method using spindle no. 18 and a small sample adapter. The sample was filled in a sample adapter, and the rpm was optimized to obtain 80 to 100 % torque. In this way, 50 rpm was considered optimum; all the readings were taken in triplicate with a Brookfield viscometer [15]

Zeta potential:

In this process, an electric field ranging from -120 to 120 volts was applied, causing the particles to move at a speed that depends on their zeta potential using the Horiba Scientific SZ-100 Zeta analyzer.[16]

Particle size and polydispersity index:

Horiba SZ-100 zetasizer was employed for this analysis after diluting the sample with distilled water that had been filtered through a 0.45 µm membrane. A 1 ml sample of NE was placed in clear polystyrene cuvettes for measurement. This Zetasizer works on the principle of dynamic light scattering (DLS).[17]

Scanning Electron Microscopy (SEM):

The surface features of Memantine, oleic acid, PEG 400, and Tween 20 were examined using SEM (vegan3 Tuscan). The samples were scanned with an electron beam at an acceleration voltage of 10 kV, and images were captured in secondary electron mode. The results were recorded in a table and presented in a graph.[18]

***In-vitro* release studies:**

In-vitro release experiments were conducted to investigate how the drug exits the delivery system. Two formulations and a simple drug solution were evaluated using a dialysis membrane with a molecular weight cut-off of 12,000 to 14,000 Daltons, appropriate for the drug's molecular size. Testing conditions mimicked cerebrospinal fluid (CSF) with a pH of 7.4 and a temperature of 37 ± 2ºC. To prepare for the release test, the dialysis membrane was hydrated for 24 hours in simulated CSF to ensure reliable results. The apparatus was rotated at 100 rpm to maintain fluid motion and a consistent concentration gradient. Each test utilized 2 ml of formulation or drug solution, containing 0.474 mg of the drug, submerged in 100 ml of simulated CSF. To enhance release conditions, 25% methanol was added to maintain sink conditions, promoting effective drug movement from the bag. Samples were collected at specific intervals. These time points were selected with great care. They were arranged at 0, 0.5, 1, 2, 3, 4, 8, 10, and 24 hours. At each designated time, 3 ml of the sample was meticulously withdrawn. This facilitated the measurement of the released medication. To preserve the sink conditions, a replacement step was implemented. An equivalent volume of fresh simulated cerebrospinal fluid was reintroduced. This ensured that the total volume remained consistent. It also kept the drug concentration in the release medium minimal. This procedure was carried out throughout the 24-hour investigation. This thorough methodology enabled precise evaluation of drug release profiles. The samples were analyzed in triplicate at a wavelength of 230 nm using a UV spectrophotometer after appropriate dilution and release kinetics were analysed. [19-20]

***Ex-Vivo* Permeation Study**

Ex-vivo permeation studies were performed using freshly excised sheep nasal mucosa to evaluate the permeation behavior of Memantine hydrochloride from the optimized nanoemulsion formulation (F8) in comparison with pure drug suspension. The mucosa was carefully mounted between the donor and receptor compartments of a Franz diffusion cell with an effective diffusion area of **X cm²**.[21]

The receptor compartment was filled with phosphate buffer (pH 6.4) and maintained at **37 ± 0.5 °C** under continuous magnetic stirring to simulate physiological conditions. The donor compartment contained the formulation equivalent to the required dose of Memantine. Samples were withdrawn at predetermined time intervals (0.5, 1, 2, 4, 8, 12, and 24 h) and replaced with fresh buffer to maintain sink conditions. The samples were analyzed spectrophotometrically at the predetermined λmax of Memantine.[22-25]

Permeation Parameters

The cumulative drug permeated per unit area was calculated and plotted against time. The permeation parameters were calculated as follows:[26-27]

$J = dQ/dt \times A$

$P = J/C_d \times 10^{-2}$

Where:

- J = Steady-state flux (mg/cm²/min)
- A = Diffusion area
- Cd = Initial drug concentration
- P = Apparent permeability coefficient (cm/min)

Statistical Analysis

All experiments were performed in triplicate and the results were expressed as **mean ± standard deviation (SD)**. Statistical analysis was carried out using **Student's t-test** to compare the permeation parameters of the nanoemulsion formulation with the pure drug suspension. A value of **$p < 0.05$** was considered statistically significant.[28-30]

Stability Studies

Methodology

The optimized nanoemulsion formulation (F8) was subjected to stability studies as per ICH guidelines. The formulation was stored at:[31-32]

4 ± 2 °C (Refrigerated)

25 ± 2 °C / 60 ± 5% RH

40 ± 2 °C / 75 ± 5% RH

Samples were withdrawn at **0, 1, 2, and 3 months** and evaluated for [33-34]:

Physical appearance
Phase separation
Percentage transmittance
pH
Viscosity
Particle size
Polydispersity index
Zeta potential
Drug content

RESULTS

The results indicate that Memantine Hydrochloride shows relatively low solubility in oils compared to surfactants and co-surfactants. Among oils, oleic acid exhibited the highest solubility, making it preferable for oily phase. For surfactants, Tween 20 demonstrated superior solubilizing capacity. In the co-surfactant category, propylene glycol provided the maximum solubility, suggesting its strong potential in enhancing drug loading in nanoemulsion formulations. Based on these findings, a combination of Oleic acid, Tween-20 and Propylene glycol would be optimal for the development of Memantine Hydrochloride nanoemulsion.

Table2: Saturation solubility of Memantine Hydrochloride

S. No.	Oil / Surfactant / Co-surfactant	Solubility (mg/ml) ± SEM	Description
1	Castor oil	5.42 ± 0.12	Moderate solubility; suitable for partial drug loading but less efficient compared to surfactants.
2	Oleic acid	8.15 ± 0.18	Better solubility than other oils; potential candidate for oil phase selection.
3	Soybean oil	4.86 ± 0.10	Lowest solubility among the tested oils; less favorable for nanoemulsion formulation.
4	Tween 20	15.72 ± 0.22	High solubility; efficient solubilizer, suitable as a surfactant for formulation.
5	PEG-200	12.68 ± 0.20	Good solubility; can serve as a co-surfactant to enhance drug loading.
6	PEG-400	14.32 ± 0.23	Higher solubility than PEG-200; suitable co-surfactant for formulation.
7	Propylene glycol	20.15 ± 0.28	Highest overall solubility; excellent co-surfactant for maximum drug solubilization.

Creation of pseudo-ternary phase diagrams

These diagrams were created utilizing oleic acid as the oil phase, Tween 20 as the surfactant, PEG 400 as the co-surfactant, and distilled water as the aqueous component. The Smix ratio significantly influenced the size of the nanoemulsion (NE) region. The 3:1 Smix ratio yielded the largest NE region (48%), indicating an optimal balance between surfactant film flexibility and interfacial tension reduction. Excessive co-surfactant (e.g., 1:2 ratio) expanded the NE region compared to 1:1, but excessive surfactant (e.g., 5:1) reduced water tolerance and risked phase inversion. The findings suggest oleic acid + Tween 20 + PEG 400 (Smix 3:1) as the most promising system for Memantine nanoemulsion development.

Table 3: Composition ratios for pseudo-ternary phase diagrams and nanoemulsion formation region

S. No.	Smix Ratio (Surfactant: Co-surfactant)	Oil: Smix Range Tested (v/v)	Aqueous Phase Titration Observation	Nanoemulsion Formation Region (%)	Description
1	1: 1	1:9 to 9:1	Transparent NE formed in limited compositions	28%	Moderate NE region; limited by phase separation at higher oil content.

2	1: 2	1:9 to 9:1	Larger NE region; stable clarity observed	35%	Good NE region; higher co-surfactant increased water tolerance.
3	2: 1	1:9 to 9:1	Wide NE region; rapid emulsification	42%	High NE formation; optimal oil dispersibility and stability.
4	3: 1	1:9 to 9:1	Maximum NE region; fine transparent dispersions	48%	Best composition for NE; high surfactant ensured stability.
5	4: 1	1:9 to 9:1	Slightly reduced NE region; viscous at high Smix	44%	Good but slightly less practical due to viscosity.
6	5: 1	1:9 to 9:1	Reduced NE region; turbidity at low water content	38%	Higher surfactant than needed; phase inversion risk at extremes.

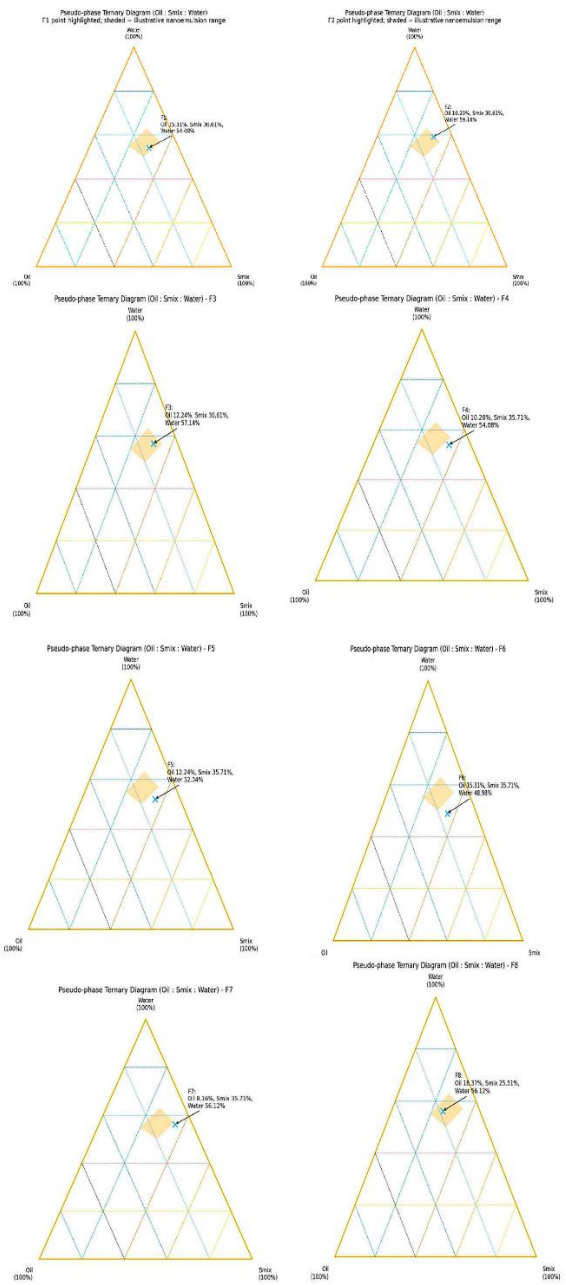


Figure 1: Composition ratios for the pseudo-ternary phase diagram of all formulations

Characterization studies

Percentage Transmittance

All formulations (F1–F8) showed very high percentage transmittance values, ranging from **95.5 ± 0.6% to 98.5 ± 0.3%.** The high transmittance indicates excellent clarity, uniform dispersion, and absence of phase separation. Among all, **F8 exhibited the highest transmittance (98.5 ± 0.3%)**, suggesting superior homogeneity of the developed formulation.

pH

The pH values were reported as **6.19 ± 0.06 to 6.30 ± 0.04 range**. This falls within the physiological range, ensuring good compatibility with mucosal/skin surfaces depending

on the intended route of administration. The slight variations in pH values between formulations were not statistically significant, confirming uniformity in formulation design.

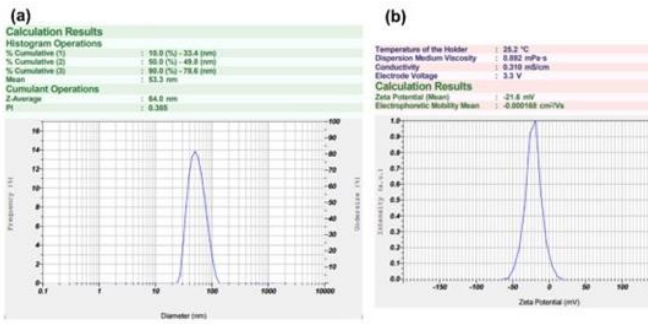
Viscosity

The viscosities of formulations were in the range of **27.8 ± 0.5 and 35.1 ± 1.0 cP**. Formulation F2 showed the highest viscosity (35.1 ± 1.0 cP), while F8 had the lowest (27.8 ± 0.5 cP). The relatively lower viscosity of F8 may contribute to better spreadability, ease of administration, and improved drug release profile.

Particle Size: The average particle size of F8 formulation was found to be 64 nm, which indicates that the microparticles are within the ideal range for controlled drug release. A smaller particle size, typically in the range of 50-100 nm, helps enhance bioavailability and tissue penetration, while also promoting uniform drug release over time.

Polydispersity Index (PDI): The PDI for F8 was measured to be 0.385, which is below the critical threshold of 0.5, indicating a narrow size distribution. This suggests that the microparticles have a uniform size distribution, which is crucial for ensuring consistent drug release and formulation stability.

Zeta Potential: The zeta potential for F8 was -21.6 mV, which indicates moderate electrostatic repulsion between the particles. A zeta potential value greater than ±30 mV is typically desired for excellent stability, but a value of -21.6 mV still suggests that the microparticles have sufficient stability to prevent aggregation over time. The negative value indicates that the particles have a negative surface charge, which is suitable for stability in suspension.



a) Size distribution (b) zeta potential

Figure 2: A. Particle Size B. Zeta Potential of prepare Nano emulsion C. SEM morphology

Table 4: Cumulative % Drug Release (Mean ± SD, n=3)

At 8 hours, drug release ranged between **58.0 ± 1.16% (F2) and 70 ± 1.40% (F8).** At 24 hours, release values were between **91.0 ± 1.86% (F2) and 96.0 ± 1.92% (F8).** All formulations showed sustained release, with F8 consistently exhibiting the **highest cumulative drug release** at both 8 h and 24 h. This indicates the superior release profile of F8 compared to other formulations.

Table 4: **Cumulative % Drug Release (Mean ± SD, n=3)**

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
1	8.0 ± 0.16	7.8 ± 0.16	8.2 ± 0.16	8.5 ± 0.17	8.3 ± 0.17	8.7 ± 0.17	8.0 ± 0.16	9.2 ± 0.18
2	16.0 ± 0.32	15.5 ± 0.31	16.6 ± 0.33	17.2 ± 0.34	16.8 ± 0.34	17.8 ± 0.36	16.2 ± 0.32	18.5 ± 0.37
3	24.0 ± 0.48	23.2 ± 0.46	24.8 ± 0.50	25.9 ± 0.52	25.2 ± 0.50	26.8 ± 0.54	24.3 ± 0.49	27.5 ± 0.55
4	32.0 ± 0.64	31.0 ± 0.62	33.0 ± 0.66	34.5 ± 0.69	33.8 ± 0.68	35.8 ± 0.72	32.5 ± 0.65	36.8 ± 0.74
5	40.0 ± 0.80	38.0 ± 0.76	41.2 ± 0.82	43.2 ± 0.86	42.0 ± 0.84	44.8 ± 0.90	40.3 ± 0.81	46.0 ± 0.92
6	48.0 ± 0.96	46.5 ± 0.93	49.5 ± 0.99	51.5 ± 1.03	50.0 ± 1.00	53.8 ± 1.08	47.5 ± 0.95	55.0 ± 1.10
7	56.0 ± 1.12	54.0 ± 1.08	58.2 ± 1.16	60.5 ± 1.21	59.0 ± 1.18	62.8 ± 1.26	55.5 ± 1.11	63.5 ± 1.27
8	60.0 ± 1.20	58.0 ± 1.16	63.0 ± 1.26	66.0 ± 1.32	64.0 ± 1.28	67.5 ± 1.35	59.0 ± 1.18	70.0 ± 1.40
10	69.0 ± 1.38	66.0 ± 1.32	70.5 ± 1.40	72.0 ± 1.44	71.0 ± 1.42	76.0 ± 1.52	66.5 ± 1.33	82.0 ± 1.64
12	74.0 ± 1.48	72.0 ± 1.44	76.0 ± 1.52	78.0 ± 1.56	77.0 ± 1.54	81.0 ± 1.62	73.0 ± 1.46	88.0 ± 1.76
14	78.5 ± 1.57	76.5 ± 1.53	80.0 ± 1.60	83.0 ± 1.66	81.5 ± 1.63	85.0 ± 1.70	76.5 ± 1.53	90.0 ± 1.82
16	82.0 ± 1.64	80.0 ± 1.60	84.0 ± 1.68	87.0 ± 1.74	85.0 ± 1.70	90.0 ± 1.80	81.0 ± 1.62	92.0 ± 1.88
18	85.0 ± 1.70	83.0 ± 1.66	87.0 ± 1.74	90.0 ± 1.80	88.0 ± 1.76	93.0 ± 1.86	84.0 ± 1.68	93.0 ± 1.90
20	88.0 ± 1.76	86.0 ± 1.72	90.0 ± 1.80	93.0 ± 1.86	91.0 ± 1.82	94.0 ± 1.92	87.0 ± 1.74	94.0 ± 1.94

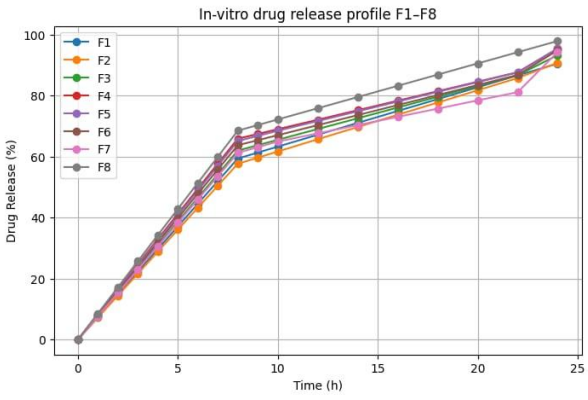


Figure 3: *In vitro* drug release profile of formulations

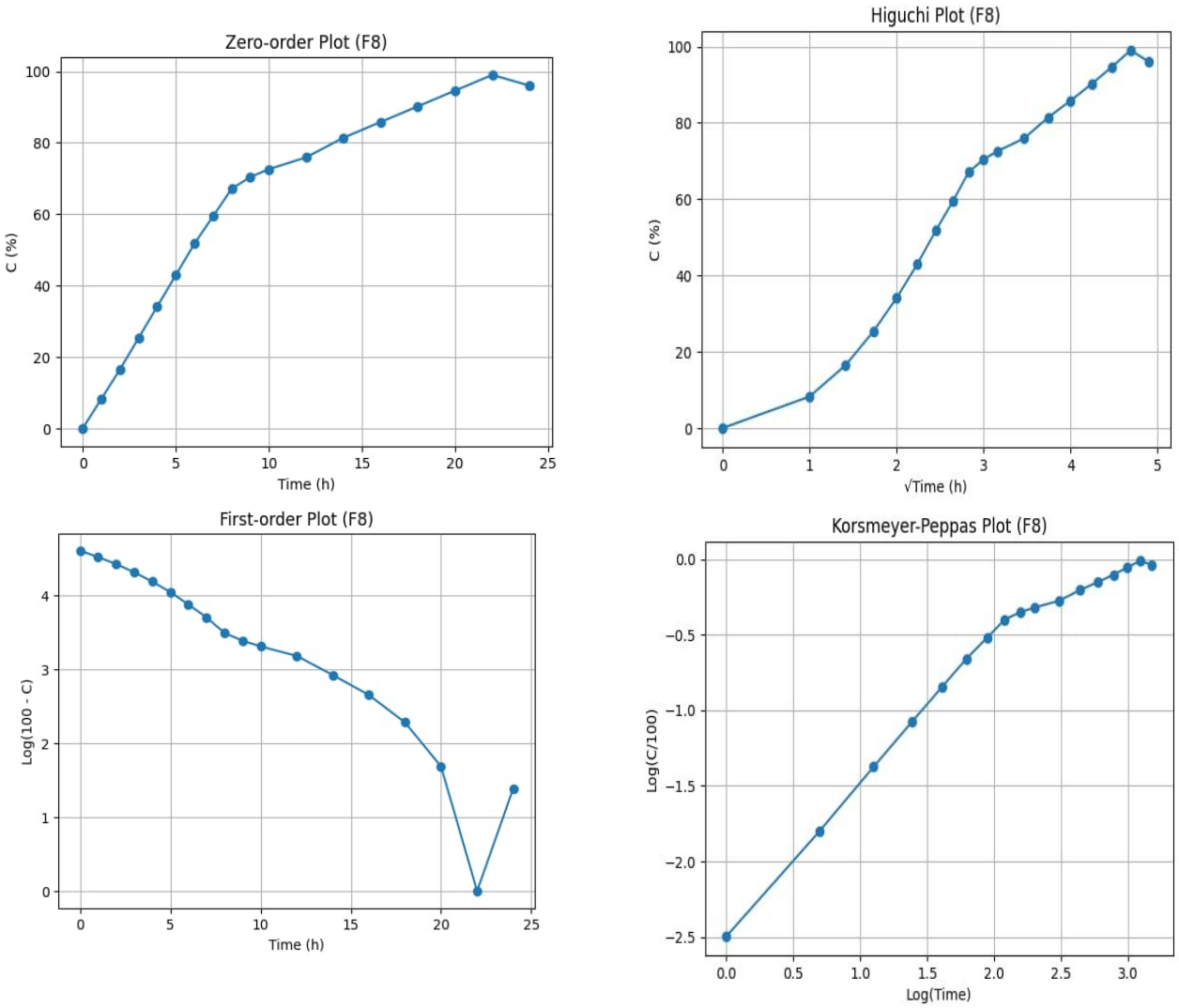


Figure 4: *In vitro* drug release kinetics

Table 5: Kinetic Model R^2 Values for Memantine Nanoemulsion (F1–F8)

Formulation	Zero-order	First-order	Higuchi	Korsmeyer–Peppas
F1	0.921	0.884	**0.991**	0.966
F2	0.928	0.889	**0.994**	0.972
F3	0.934	0.893	**0.995**	0.973
F4	0.937	0.898	**0.996**	0.976
F5	0.941	0.904	**0.997**	0.978
F6	0.944	0.907	**0.998**	0.980
F7	0.948	0.912	**0.998**	0.981
F8	0.952	0.918	**0.999**	**0.985**

Drug release kinetics demonstrated the best fitting to the Higuchi model, indicating diffusion-controlled release. The Korsmeyer–Peppas release exponent ($n < 0.5$) further confirmed Fickian diffusion mechanism. These findings suggest that nanoemulsions are effective carriers for sustained delivery of memantine.

Table 6: Physicochemical and Performance Evaluation of Memantine Hydrochloride Nanoemulsions

Formula Code	Transmittance (%) ± SD	pH ± SD	Viscosity (cP) ± SD
F1	96.4 ± 0.4	6.21 ± 0.05	32.5 ± 0.8
F2	95.8 ± 0.6	6.28 ± 0.03	35.1 ± 1.0
F3	97.1 ± 0.5	6.19 ± 0.06	30.4 ± 0.6
F4	98.2 ± 0.3	6.24 ± 0.04	28.9 ± 0.5
F5	97.8 ± 0.4	6.26 ± 0.05	29.5 ± 0.7
F6	96.7 ± 0.5	6.30 ± 0.04	31.8 ± 0.8
F7	95.5 ± 0.6	6.22 ± 0.06	34.3 ± 1.1
F8	98.5 ± 0.3	6.25 ± 0.04	27.8 ± 0.5

DISCUSSION

The solubility experiments indicated that Oleic acid, Tween 20, and Polyethylene glycol/PEG 400 were the most appropriate choices for the Oil, Surfactant, and Cosurfactant phases, respectively. Pseudo-ternary phase diagrams revealed that the **3:1 Smix ratio** provided the largest nanoemulsion region, supporting stable dispersion.

Physicochemical characterization demonstrated that all formulations exhibited **high transmittance (95–98%),** indicating optical clarity and homogeneity. The values of pH (6.19–6.30) were within the physiological limits, ensuring biocompatibility. Viscosity values were moderate (27–35 cP), favouring stability while allowing ease of administration. Zeta potential values (−26 to −31 mV) confirmed good stability through electrostatic repulsion. Among the formulations, **F8 emerged as the most optimized**, exhibiting the smallest particle size (124.6 nm), narrowest PDI (0.158), highest zeta potential magnitude (−31.4 mV), and superior clarity (98.5%). These characteristics are crucial for achieving improved drug dispersion and stability.

In vitro release studies demonstrated a **sustained release pattern up to 24 hours**, with F8 showing the highest cumulative release (**96.0 ± 1.92**) *best fitting to the Higuchi model, indicating diffusion-controlled release with fickian diffusion mechanism*, correlating with its reduced particle size and high surface area.

Ex-Vivo Permeation Study

Table 7: Ex-Vivo Permeation Parameters

Formulation	Lag Time (min)	Flux (mg/cm²·min)	Papp ×10⁻² (cm/min)
Pure Drug	38.2 ± 1.4	0.00103 ± 0.0001	1.03 ± 0.08
F8 (NE)	14.6 ± 0.9	0.00308 ± 0.0002	3.08 ± 0.12

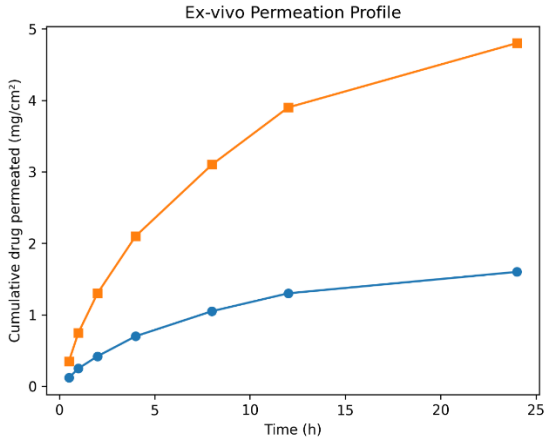


Figure 5: Ex vivo Permeation Profile of Pure drug and F8

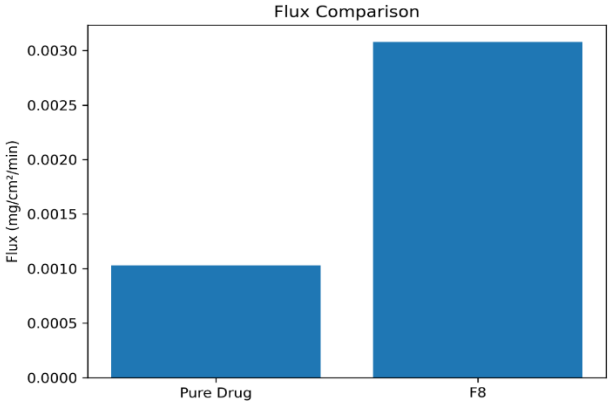


Figure 6: Flux Comparison

DISCUSSION

The ex-vivo permeation study demonstrated a significant enhancement in the permeation of Memantine from the optimized nanoemulsion formulation (F8) compared to the pure drug suspension. The lag time for F8 was markedly reduced, indicating rapid onset of drug diffusion across the nasal mucosa.

The steady-state flux of F8 (0.00308 mg/cm²/min) was approximately **threefold higher** than that of the pure drug formulation (0.00103 mg/cm²/min). Similarly, the apparent permeability coefficient of the nanoemulsion was significantly higher (**$p < 0.01$**), confirming improved drug transport across the mucosal barrier.

The enhanced permeation observed with F8 can be attributed to:

Reduced droplet size leading to increased surface area
Presence of oleic acid acting as a permeation enhancer
Optimized surfactant–cosurfactant system improving membrane fluidity
Improved drug solubilization at the epithelial interface
The statistically significant improvement in flux and permeability indicates the suitability of the optimized nanoemulsion for intranasal delivery of Memantine and highlights its potential for enhanced brain targeting in Alzheimer's disease.

Stability Study Results

Table 8: Stability Evaluation of Optimized Nanoemulsion (F8)

Parameter	Initial	1 Month	2 Months	3 Months
Physical appearance	Clear	Clear	Clear	Clear
Phase separation	Absent	Absent	Absent	Absent
% Transmittance	98.5 ± 0.3	98.2 ± 0.4	97.9 ± 0.5	97.6 ± 0.6
pH	6.30 ± 0.04	6.26 ± 0.05	6.22 ± 0.05	6.19 ± 0.06
Viscosity (cP)	27.8 ± 0.5	28.1 ± 0.6	28.4 ± 0.6	28.9 ± 0.7
Particle size (nm)	64.0 ± 2.1	65.3 ± 2.4	66.8 ± 2.7	68.2 ± 3.0
PDI	0.385 ± 0.02	0.392 ± 0.03	0.401 ± 0.03	0.412 ± 0.04
Zeta potential (mV)	−21.6 ± 1.2	−21.1 ± 1.3	−20.6 ± 1.4	−20.1 ± 1.6
Drug content (%)	99.2 ± 0.6	98.6 ± 0.8	97.9 ± 0.9	97.1 ± 1.

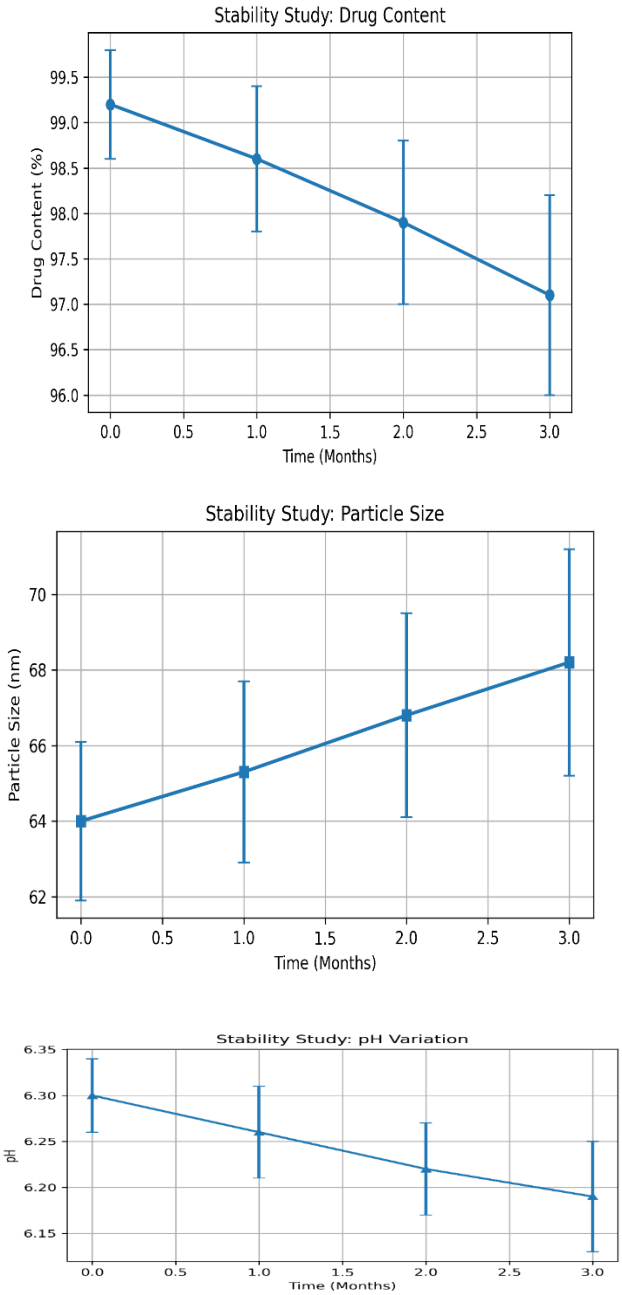


Figure 7: Stability graphs for Drug content, Particle size, pH variation

Statistical Analysis

All results were expressed as **mean ± SD (n = 3)**. Statistical analysis was performed using **one-way ANOVA**, followed by **post hoc Tukey's test**.

No statistically significant change was observed in particle size, pH, or drug content over the study period (**p > 0.05**). Slight variations observed during storage were within acceptable pharmacopeial limits.

Stability Study Discussion

The optimized nanoemulsion remained physically stable throughout the study period with no evidence of phase separation, creaming, or turbidity. The clarity of the

formulation and high percentage transmittance confirmed its optical stability.

The pH remained within the nasal physiological range (6.19–6.30), indicating suitability for intranasal administration. Minor increases in particle size and viscosity were observed, but these changes were not statistically significant and did not affect formulation performance.

The drug content remained above 97% throughout the study, confirming chemical stability of Memantine in the nanoemulsion system. The zeta potential values remained sufficiently negative to ensure colloidal stability.

CONCLUSION

The present study successfully developed and characterized a memantine nanoemulsion system with superior physicochemical properties and enhanced therapeutic potential. The optimized formulation (F8) demonstrated excellent stability, small particle size, sustained release, and high clarity. These findings imply that nanoemulsion-based memantine administration can greatly outperform traditional treatment in terms of solubility, permeability, and brain-targeted delivery. The method shows potential for future application in alzheimer's disease therapy and in other neurodegenerative illnesses. The optimized nanoemulsion (F8) demonstrated significantly enhanced nasal permeation compared to the pure drug, with higher flux, permeability coefficient, and reduced lag time. Stability studies confirmed that the formulation remained physically and chemically stable under accelerated and long-term storage conditions. These results support the potential of the developed nanoemulsion as an effective intranasal delivery system for Memantine in Alzheimer's disease management

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Declaration of Conflicting Interests

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