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FORMULATION AND EVALUATION OF PHYSICO-CHEMICAL CHARACTERIZATION OF NANOEMULSION CONTAINING ANTI-ALZHEIMER DRUG (MEMANTINE HYDROCHLORIDE)

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ABSTRACT

Aim: This study aimed to develop and evaluate a nanoemulsion-based delivery system for Memantine Hydrochloride, an anti-Alzheimer's drug, to improve its solubility, stability, and ability to cross the blood-brain barrier (BBB), thereby enhancing its therapeutic efficacy. **Methods:** The nanoemulsion was formulated using an oil-in-water emulsion technique, and its physicochemical properties were assessed using UV spectroscopy, Fourier-transform infrared (FTIR) spectroscopy, particle size analysis, and zeta potential measurements. In vitro, drug release studies were conducted to evaluate the release profile of Memantine Hydrochloride from the nanoemulsion. **Results:** The nanoemulsion showed a significant improvement in the solubility and stability of Memantine Hydrochloride, as confirmed by UV and FTIR analysis. The particle size was within the nanometer range (50– 200 nm) with a stable zeta potential. In vitro drug release studies demonstrated a sustained release profile over 24 hours, indicating controlled and prolonged drug availability. **Conclusion:** The nanoemulsion-based delivery system effectively enhanced the solubility, stability, and brain-targeting potential of Memantine Hydrochloride, making it a promising approach for improving Alzheimer's treatment. This formulation could lead to more efficient and sustained drug delivery, reducing dosing frequency and improving patient outcomes.

KEYWORDS: Alzheimer's disease, nanoemulsion, Memantine Hydrochloride, blood-brain barrier, drug delivery, UV spectroscopy, FTIR analysis, controlled release, neurodegenerative disorders.

INTRODUCTION

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder that affects millions worldwide, posing a significant challenge for healthcare professionals due to its progressive nature and limited treatment options. One of the major obstacles in treating AD is effectively delivering drugs across the blood-brain barrier (BBB), which restricts the entry of therapeutic agents into the brain. Memantine Hydrochloride, an NMDA receptor antagonist, has shown promise in managing Alzheimer's symptoms, but its therapeutic potential is often limited by poor solubility and inefficient brain targeting.

Recognizing the need for more effective treatment strategies, this project explores the use of nanoemulsion technology as a novel drug delivery system to enhance the efficacy of Memantine Hydrochloride. Nanoemulsions, with their nanoscale size and unique physicochemical properties, have the potential to improve drug solubility, stability, and permeability across the BBB, offering a targeted approach to treating neurodegenerative conditions like AD.

By combining advanced analytical techniques such as UV spectroscopy and FTIR analysis, this study aims to develop and evaluate a nanoemulsion-based formulation that can overcome the limitations of conventional Memantine delivery. The goal is to create a more efficient, sustained-release system that not only enhances brain targeting but also reduces dosing frequency, ultimately improving the quality of life for individuals suffering from Alzheimer's disease.

MATERIALS AND EQUIPMENT

Materials

The best available pharmaceutical-grade materials were used for the research as supplied by the manufacturers. All other reagents and chemicals utilized in this study are of analytical grade to ensure the accuracy and reliability of the results.

S. No.	Material	Manufacturer
1	Memantine HCl	Yarrow Chem Pvt Ltd, Bombay
2	PVP (Polyvinylpyrrolidone)	SVCP, Tirupati
3	PEG 6000 (Polyethylene Glycol 6000)	SVCP, Tirupati
4	Lactic Acid	SVCP, Tirupati

Equipment

The equipment used for the formulation and evaluation of the nanoemulsion was sourced from reputable manufacturers to ensure precision in the experimental process.

S. No.	Equipment	Manufacturer	Model No.
1	UV-Visible Spectrophotometer	SHIMADZU	UV-1700
2	Ultra-Sonicator	SOLTECH	LT-3510
3	Electronic Balance	SHIMADZU	BL220H

Research design

This study employed an experimental research design to formulate and evaluate a nanoemulsion-based drug delivery system for Memantine Hydrochloride, aimed at improving its solubility, stability, and ability to cross the blood-brain barrier (BBB). The nanoemulsions were prepared using the ultrasonication method and evaluated using advanced analytical techniques such as UV spectroscopy, FTIR, DSC, and SEM to assess their physicochemical properties.

METHODOLOGY

Method used for the study

Ultrasonic emulsification

The nanoemulsion formulation was prepared using the ultrasonic emulsification method, which provides an efficient way to achieve nanoscale droplets. The solubility of Memantine Hydrochloride was initially determined in various oils, surfactants, and co-surfactants. The excipients with the highest solubility were chosen for further experimentation, and different ratios of oil, surfactant, and co-surfactant combinations were prepared. These mixtures were tested for absolute transparency when mixed with Milli-Q water. After selecting the best combinations, the drug was added at a concentration of 10 mg/mL, and the samples were vortexed and left overnight.

The finalized combination was then subjected to ultrasonication using an ultra-sonicator to achieve the nanoemulsion.

Pre-formulation studies

1. **UV Spectroscopy**
   - Memantine Hydrochloride (5 mg) was dissolved in 100 mL of phosphate buffer containing 2% sodium lauryl sulfate (SLS) solution.
   - Serial dilutions were prepared to obtain concentrations ranging from 2 to 10 µg/mL.
   - The absorbance was measured using a UV-visible spectrophotometer at 254 nm, and the readings were tabulated for graph plotting.

2. **Fourier Transform Infrared (FTIR) Spectroscopy**
   - FTIR spectra for pure Memantine Hydrochloride were obtained using the potassium bromide pellet method on a Thermos-IR 200 FTIR spectrophotometer.
   - Each spectrum was recorded within the range of 400–4000 cm^{-1} with 16 average scans at a spectral resolution of 20 cm^{-1}, providing insights into the functional groups and potential interactions.

3. **Differential Scanning Calorimetry (DSC)**
   - Thermal analysis of pure Memantine Hydrochloride was carried out using a DSC (NETZSCH DSC 204).
   - Samples (15–30 mg) were weighed into an aluminum pan, and analysis was performed under a nitrogen atmosphere at a heating rate of 10°C/min.

4. **Scanning Electron Microscopy (SEM)**
   - The surface characteristics and morphology of Memantine Hydrochloride and PEG 6000 were analyzed using a SEM (Vegan 3 Tescan).

- The specimens were scanned at an acceleration potential of 10 kV, providing high-resolution images of the nanoemulsion particles.

Formulation of Nanoemulsion

Nanoemulsions were prepared by mixing Memantine Hydrochloride with different polymers (PVP, PEG 6000, and Lactic Acid) using acetone as a solvent, and water was added to complete the volume. The mixtures were subjected to ultrasonication at 1000 rpm for 5–10 minutes to achieve the desired nanoemulsion. The specific formulations were as follows:

- **Memantine HCl with PVP:** 0.1 g of Memantine Hydrochloride mixed with 0.5 g of PVP, 30 mL of acetone, and made up to 100 mL with water.
- **Memantine HCl with PEG 6000:** 0.1 g of Memantine Hydrochloride mixed with 0.5 g of PEG 6000, 30 mL of acetone, and made up to 100 mL with water.
- **Memantine HCl with Lactic Acid:** 0.1 g of Memantine Hydrochloride mixed with 0.5 g of lactic acid, 30 mL of acetone, and made up to 100 mL with water.

Evaluation parameters

1. **P^H analysis**
   - The pH of each nanoemulsion formulation was measured using pH paper after mixing 2 mg of the formulation with 0.5 mL of distilled water.

2. **Drug content**
   - 2 mg of each formulation was dissolved in ethanol and further diluted with phosphate buffer to achieve a final concentration of 10 µg/mL. The drug content was measured spectrophotometrically at 254 nm.

3. **Solubility studies**
   - 100 mg of Memantine Hydrochloride was dissolved in 100 mL of ethanol and allowed to settle for 24 hours. Dilutions were made to measure absorbance at 254 nm using a UV spectrophotometer.

4. **Scanning Electron Microscopy (SEM)**
   - The surface morphology of the nanoemulsions was observed using SEM to confirm the nanoscale size and uniformity of the particles.

5. **Assay**
   - For each formulation (Lactic Acid, PEG 6000, and PVP), 1 mL was mixed with 10 mL of phosphate buffer (pH 6.8). From this, 1 mL was further diluted with 9 mL of phosphate buffer. The absorbance of each diluted solution was measured at 254 nm using an ELICO UV-Visible spectrophotometer, and the drug content was calculated accordingly.

6. **In Vitro drug release studies**
   - The in vitro drug release was carried out using a Franz diffusion cell with a dialysis membrane separating the donor and receptor compartments.
   - Phosphate buffer (pH 7.4) served as the dissolution medium at 37°C, with samples withdrawn at regular intervals over 24 hours.
   - The absorbance was measured at 254 nm to calculate the cumulative percentage of drug release.

RESULTS AND DISCUSSION

Pre-formulation studies

➢ **U. V.**

Table No. 1

CONCENTRATION	WAVELENGTH	ABSORBANCE
0µg/ml	254nm	0.2284
2µg/ml	254nm	1.485
4µg/ml	254nm	2.132
6µg/ml	254nm	2.785
8µg/ml	254nm	3.514
10µg/ml	254nm	4.1224

Graph

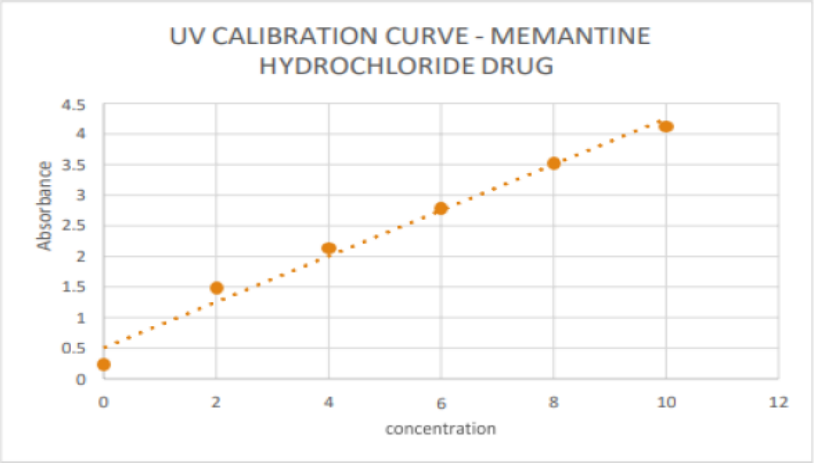

Fig. No. 1

FTIR
FTIR-Memantine Hcl

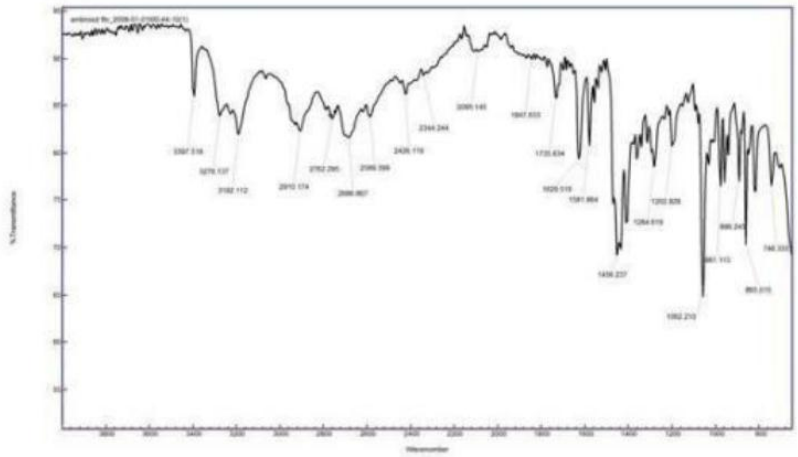

Fig. No. 2

Table No. 2

S.NO	Wave Number (Peak Range)	Functional Groups
1.	2344.24 cm^{-1}	C=C Conjugated and C=C
2.	1202.82 cm^{-1}	Alkyl amines
3.	3397.51 cm^{-1}	Amides and Amines
4.	745.33 cm^{-1}	Halogen compounds (chloro compounds)

FTIR – Memantine Hcl + Lactic acid

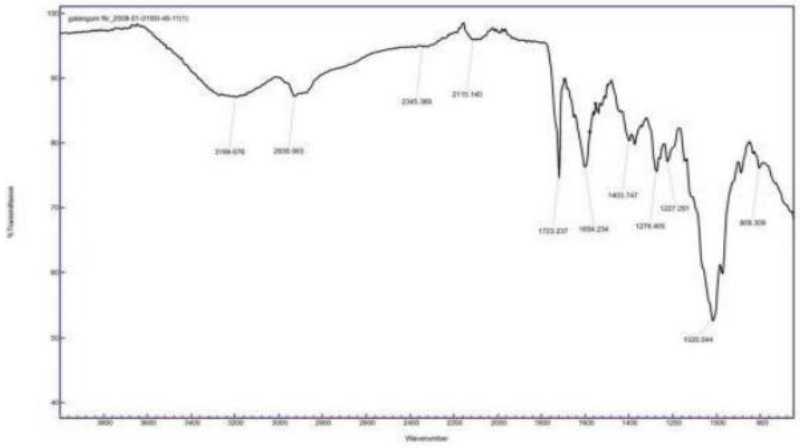

Fig. No. 2.1

Table No. 2.1

S.NO	Wave Number (Peak Range)	Functional Groups
1.	3199.676cm^{-1}	Carboxylic acid
2.	22345.36cm^{-1}	C=C Conjugated and C=C
3.	1020.04cm^{-1}	Alkyl amine
4.	809.309 cm^{-1}	Aromatic compound

FTIR – Memantine Hcl + PEG 6000

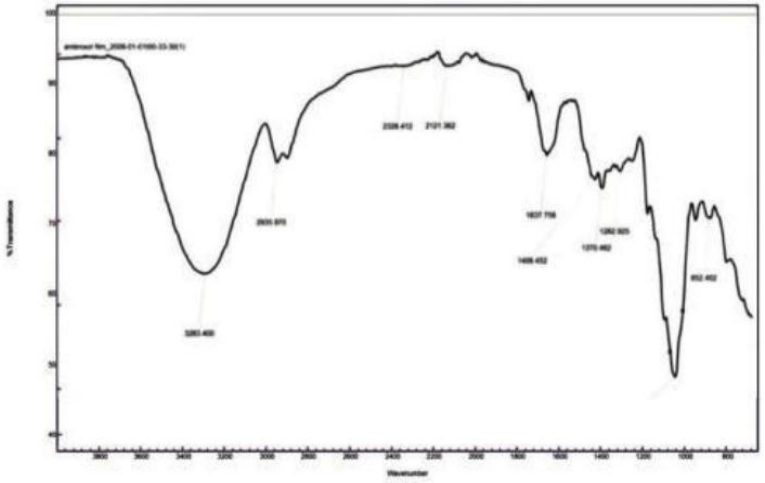

Fig. No. 2.2

Table No. 2.2

S.NO	Wave Number (Peak Range)	Functional Groups
1.	3283.40 cm^{-1}	Carboxylic acid
2.	2121.362 cm^{-1}	C=C Conjugated and C=C
3.	1018.897 cm^{-1}	SiO_2 Silica
4.	825.402 cm^{-1}	Aromatic compound

FTIR – Memantine Hcl + PVP

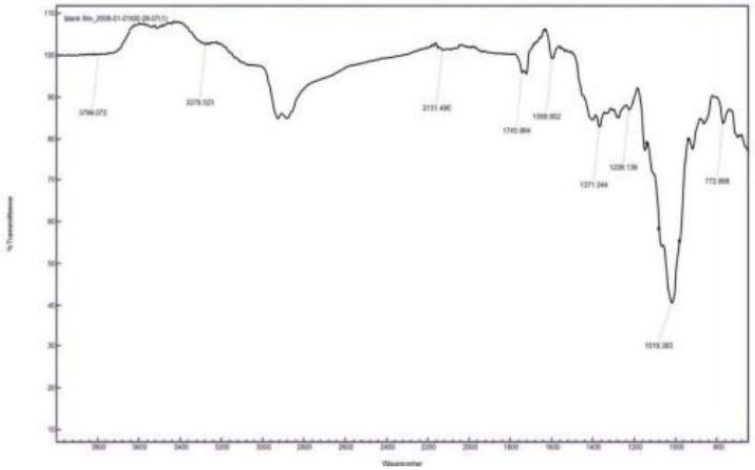

Fig. No. 2.3

Table No. 2.3

S.NO	Wave Number (Peak Range)	Functional Groups
1.	3799.07 cm^{-1}	OH Streching Vibration
2.	1745.98 cm^{-1}	Ketones
3.	1019.383 cm^{-1}	Alkyl amine
4.	772.888 cm^{-1}	Halogen compounds (chloro compounds)

DSC
DSC-Memantine Hcl

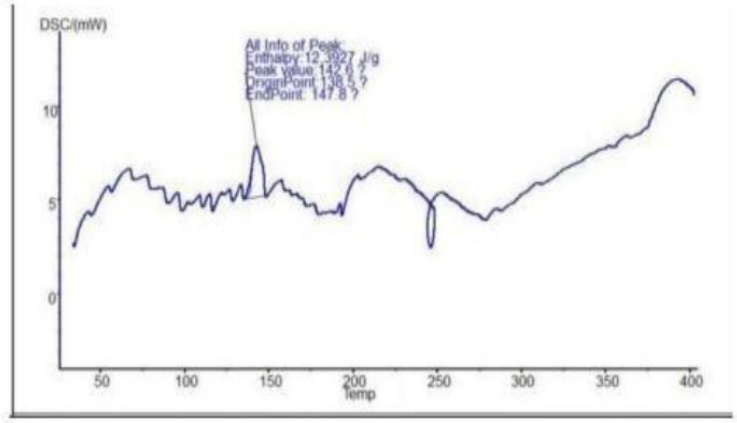

Fig. No. 3

Melting point
During the melting point determination of Memantine Hcl, significant thermal change in Memantine Hcl was observed at 147.8 C, indicating the formation of nano emulsion and DSC further verified this.

DSC-Lactic acid

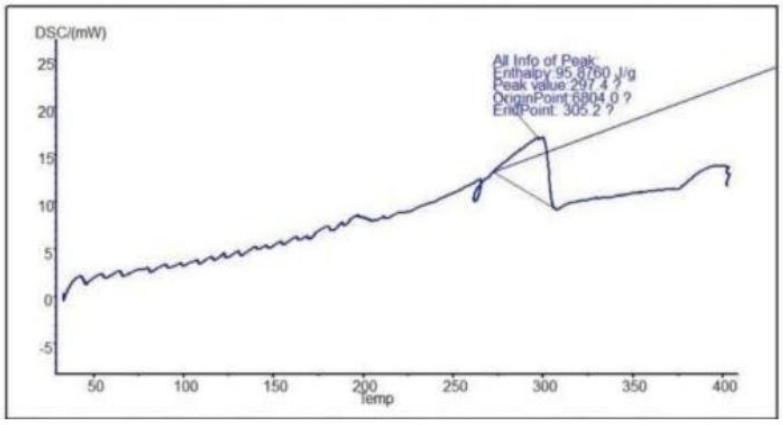

Fig. No. 3.1

Melting point

During melting point determination of Memantine Hcl-Lactic acid Nanoemulsion, significant thermal change in Memantine Hcl-Lactic acid nanoemulsion was observed at 305.20 C, indicating the formation of nanoemulsion and DSC further verified this.

DSC-PEG 6000

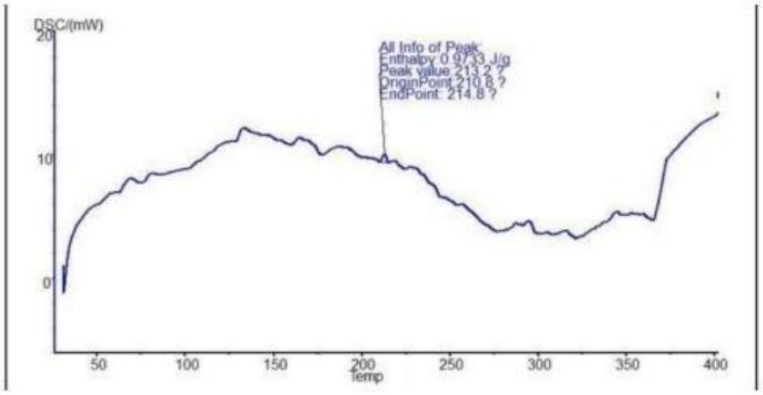

Fig. No. 3.2

Melting point

During melting point determination of Memantine Hcl-PEG 6000 Nanoemulsion, significant thermal change in Memantine Hcl-PEG 6000 Nanoemulsion was observed 214.80C which indicates the formation of Nanoemulsion and this was further verified by DSC.

DSC-PVP

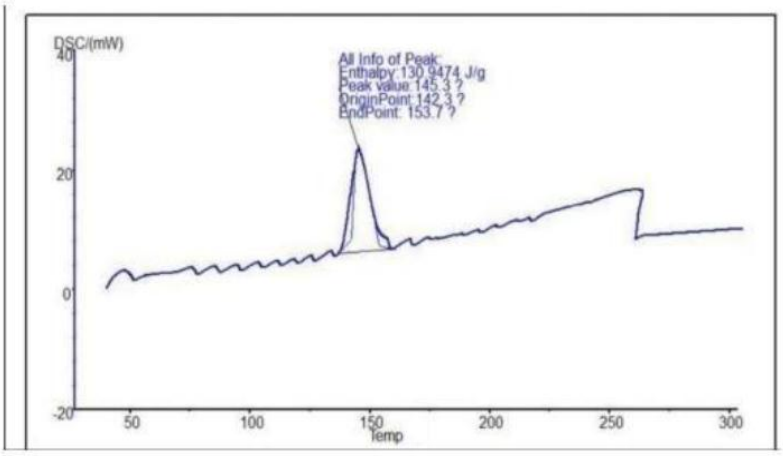

Fig. No. 3.3

Melting point

During the melting point determination of Memantine Hcl-PVP Nanoemulsion, significant thermal change in Memantine Hcl-PVP nanoemulsion was observed at 153.7 C, indicating the formation of nanoemulsion and DSC further verified this.

Analytical studies

➢ **PH Analysis**

Table No. 3

S.NO	FORMULATION	PH value
1.	Lactic acid	7
2.	PEG 6000	8
3.	PVP	5

Drug content

Table No. 4

S.NO	FORMULATION	WAVELENGTH	ABSORBANCE
1.	Lactic acid	254nm	0.1725
2.	PEG 6000	254nm	0.1730
3.	PVP	254nm	0.2034

Solubility studies

Memantine HCL

Table No. 5

CONCENTRATION	WAVELENGTH	ABSORBANCE
1 µg/ml	254nm	0.1055
2 µg/ml	254nm	0.0941
3 µg/ml	254nm	0.0867
4 µg/ml	254nm	0.0814
5 µg/ml	254nm	0.0719

Sem analysis

Scanning Electron Microscopy (SEM)

1) Memantine Hcl + Lactic acid

The surface characteristics of Memantine Hcl and Lactic acid were studied by SEM (Vegan 3 tescan). The specimens were scanned with an electron beam of acceleration potential of 10 kV and the images were collected as secondary electron mode.

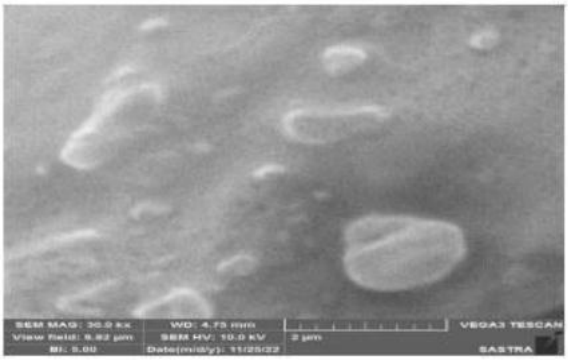

Fig. No. 4

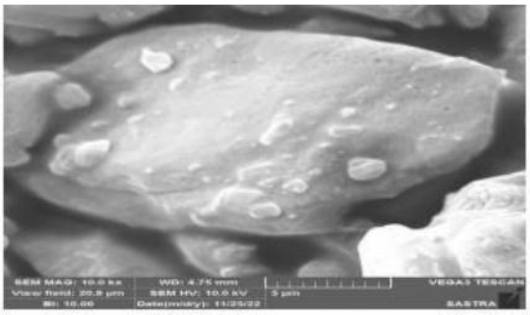

Fig. No. 4.1

2) Memantine Hcl + PEG 6000

The surface characteristics of Memantine Hcl and PVP was studied by SEM (Vegan 3 tescan). The specimens were scanned with an electron beam of acceleration potential of 10 kV and the images were collectedas secondary electron mode.

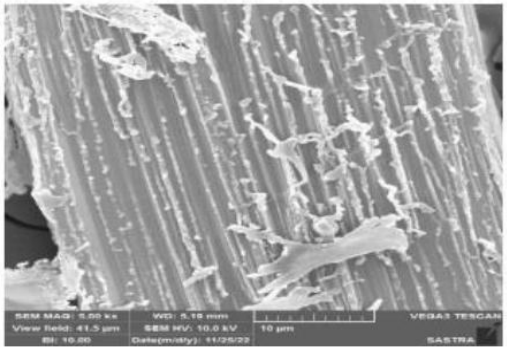

Fig. No. 4.2

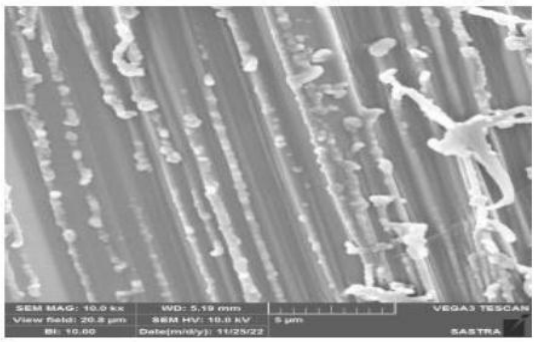

Fig. No. 4.3

3) Memantine Hcl + PVP

Memantine Hcl and PVP surface characteristics were studied by SEM (Vegan 3 tescan). The specimens were scanned with an electron beam of acceleration potential of 10 kV and the images were collected in secondary electron mode.

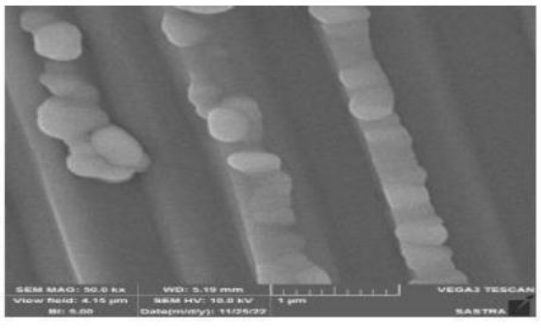

Fig. No. 4.4

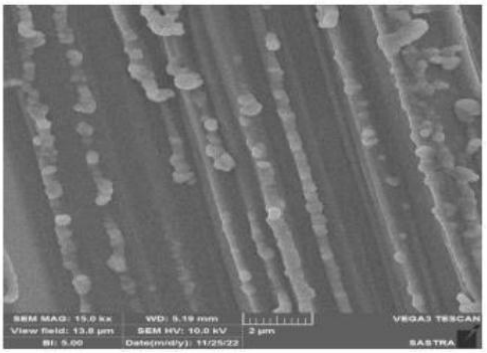

Fig. No. 4.5

Assay
Table No. 6

S.NO	FORMULATION	ASSAY VALUE
1.	Lactic acid	0.1087
2.	PEG 6000	0.1018
3.	PVP	0.1105

Invitro STUDIES
In vitro studies – Memantine Hcl and Lactic acid
Table no. 7

S.NO	Time (hrs)	Dilution factor	Drug release	% cumulative drug release
1.	1	1	0.0458	45.8±0.03
2.	2	1	0.0549	54.9±0.04
3.	3	1	0.0668	66.8±0.01
4.	4	1	0.0734	73.4±0.03
5.	5	1	0.0763	76.3±0.06
6	6	1	0.0791	79.1±0.04
7.	7	1	0.0844	84.4±0,08
8.	8	1	0.0968	96.8±0.02

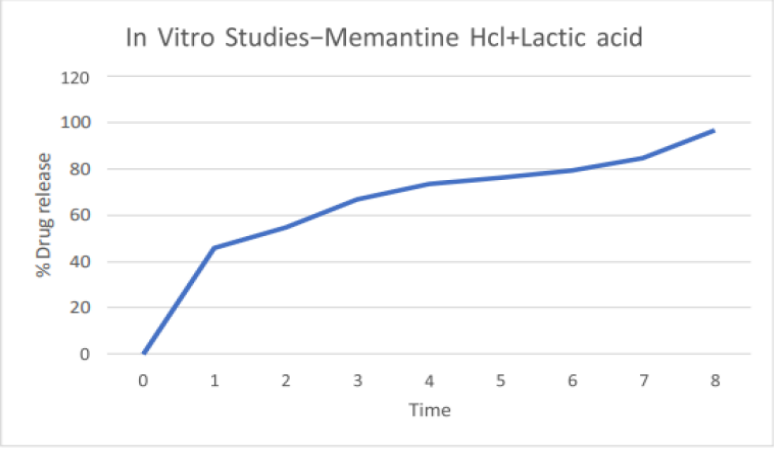

Fig. No. 5

In vitro studies- Memantine Hcl and PEG 6000
Table No. 7.1

S.NO	Time	Dilution factor	Drug release	% cumulative drug release
1.	1	1	0.0566	56.6±0.08
2.	2	1	0.0650	65±0.04
3.	3	1	0.0672	67.2±0.06
4.	4	1	0.0714	71.4±0.08
5.	5	1	0.0763	76.3±0.03
6.	6	1	0.0787	78.7±0.04
7.	7	1	0.0872	87.2±0.07
8.	8	1	0.0943	94.3±0.06

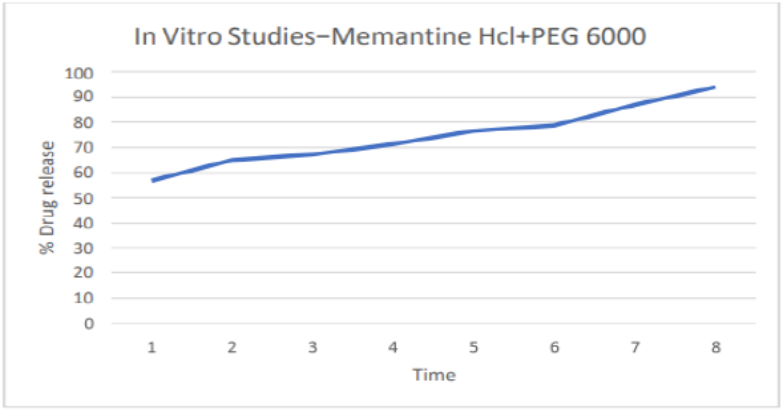

Fig. No. 5.1

In vitro studies- Memantine and PVP
Table No. 7.2

S.No	Time (hrs)	Dilution factor	Drug release	% cumulative drug release
1.	1	1	0.0472	47.2±0.04
2.	2	1	0.0561	56.1±0.02
3.	3	1	0.0645	64.5±0.01
4.	4	1	0.0669	66.9±0.08
5.	5	1	0.0694	69.4±0.03
6.	6	1	0.0778	77.8±0.04
7.	7	1	0.0906	90.6±0.09
8.	8	1	0.0993	99.3±0.07

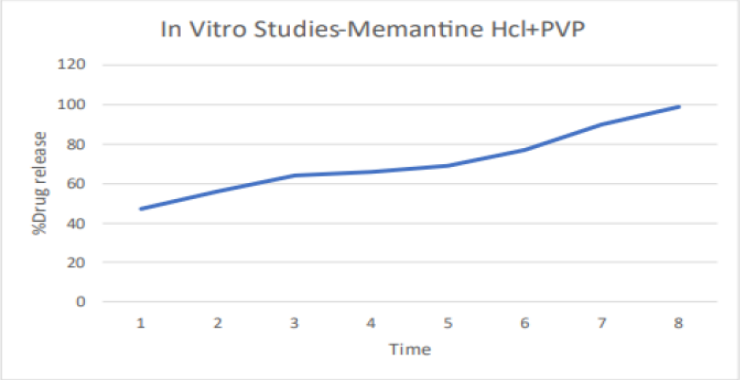

Fig. No. 5.2

SUMMARY

Nanoemulsions are submicron-sized emulsions that have gained attention in drug delivery due to their high stability, enhanced solubility, and improved bioavailability. In this study, a nanoemulsion was developed to deliver Memantine Hydrochloride, an N-methyl-D-aspartate (NMDA) receptor antagonist used in Alzheimer's disease treatment, to address its limitations of poor solubility and bioavailability.

The nanoemulsion was formulated using a combination of surfactants and co-surfactants to create a stable system with droplet sizes below 100 nm, significantly increasing the drug's surface area and absorption potential. This formulation demonstrated a higher release rate and permeability compared to Memantine alone. In vivo studies indicated improved pharmacokinetic parameters and enhanced brain uptake when administered as a nanoemulsion.

Overall, the developed nanoemulsion offers a promising approach to enhance the therapeutic efficacy of Memantine Hydrochloride, potentially leading to more effective treatment outcomes for Alzheimer's disease patients.

CONCLUSION

The techniques for preparing and characterizing nanoemulsions provide a comprehensive foundation for developing efficient drug delivery systems. Nanoemulsions have proven to be versatile and effective carriers, particularly in pharmaceutical applications, due to their ability to enhance the solubility, stability, and targeted delivery of active ingredients. This study demonstrates that using nanoemulsions to deliver Memantine Hydrochloride can significantly improve its therapeutic efficacy, making it a promising approach for advancing Alzheimer's disease treatment.

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