MATHEWS

Research Article

Mathews Journal of Pharmaceutical Science

Development and Optimization of Mesembrine Nanoliposome

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ABSTRACT

This study focuses on the development and optimization of nanoliposomal formulations of mesembrine for effective brain-targeted drug delivery. Mesembrine, a potent serotonin reuptake inhibitor, is explored for its therapeutic potential in treating depression. Nanoliposomes were chosen as the delivery system due to their ability to enhance drug stability, reduce side effects, and improve brain bioavailability by bypassing the blood-brain barrier. The formulation was optimized using the thin-film hydration method, with parameters like particle size, zeta potential, and encapsulation efficiency meticulously evaluated. Preformulation studies confirmed mesembrine's stability and compatibility with excipients. The optimized formulation demonstrated high drug entrapment efficiency and sustained drug release. In vitro evaluations suggested improved pharmacokinetics compared to conventional formulations. This research highlights the potential of nanotechnology in advancing therapeutic outcomes for central nervous system disorders. Future work will focus on in vivo studies and clinical trials to validate these finding.

Keywords: Mesembrine, Nanoliposomes, Brain-Targeted Drug Delivery, Depression Treatment, Blood-Brain Barrier, Nanotechnology.

INTRODUCTION

The introduction highlights the critical role of nanotechnology in revolutionizing drug delivery systems, especially for brain-targeted therapies. The blood-brain barrier (BBB) poses a significant challenge, preventing many therapeutic agents from reaching the brain [1,2]. This study focuses on using liposomes—spherical vesicles with bilayered lipid membranes—to encapsulate mesembrine, a serotonin reuptake inhibitor derived from *Sceletium tortuosum* [3,4]. Depression, a leading cause of disability worldwide, necessitates innovative approaches to drug delivery [5]. Liposomes not only enhance drug bioavailability but also reduce toxicity and side effects, making them a promising solution [6,7]. This section sets the stage for the study by emphasizing the unmet need for advanced formulations in treating brain disorders. This research aims to develop and optimize a nanoliposomal formulation of mesembrine, leveraging its

Vol No: 09, Issue: 02

Received Date: January 02, 2025

Published Date: March 12, 2025

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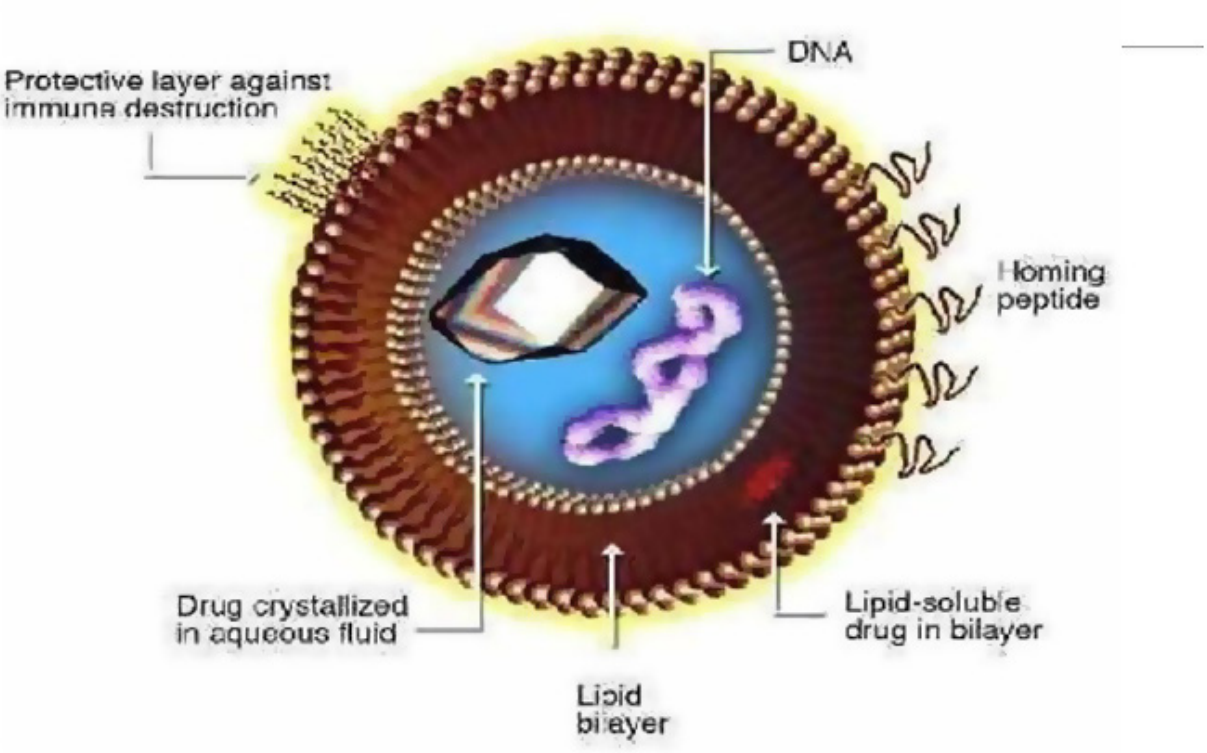
Citation: Ravi Kumar K, et al. (2025). Development and Optimization of Mesembrine Nanoliposome. Mathews J Pharma Sci. 9(2):46.

potential for brain-targeted delivery. The formulation process involves the thin-film hydration method, with emphasis on achieving optimal particle size, zeta potential, and encapsulation efficiency. By incorporating nanotechnology, this study aspires to overcome the inherent challenges of delivering mesembrine to the brain, thus paving the way for safer, more effective treatment options for depression and other central nervous system disorders.



METHODOLOGY

The methodology section outlines the systematic approach used for the formulation and evaluation of mesembrine-loaded nanoliposomes [3]. The process includes preformulation studies, formulation development, characterization, and evaluation, ensuring that the liposomes meet the desired standards for brain-targeted drug delivery [4,7].

Preformulation studies assessed mesembrine's solubility, stability, and compatibility with excipients. Nanoliposomes were prepared using the thin-film hydration method, followed by sonication to achieve the desired particle size. The lipid composition was optimized to enhance encapsulation efficiency and stability.

Characterization involved measuring particle size, zeta potential, and encapsulation efficiency using dynamic light scattering and HPLC. Morphological analysis was conducted via transmission electron microscopy (TEM).

In vitro evaluations included drug release profiling, stability assessments, and cytotoxicity studies on neuronal cell lines. Additionally, permeability studies using an in vitro BBB model were performed to determine brain-targeting potential.

This study establishes a foundation for further in vivo investigations and clinical applications, optimizing nanoliposomes for effective brain drug delivery.

Preformulation Studies

Preformulation studies were conducted to gather detailed information about the physical and chemical properties of mesembrine, which are critical for developing a stable and effective liposomal formulation [3,5].

Drug Substance Characterization

- **Organoleptic Properties:** Examined the color, odor, and appearance of mesembrine to match standard specifications [3].
- **Melting Point:** Determined using the capillary fusion method to confirm purity [3].
- **Solubility Studies:** Tested in various solvents to assess mesembrine's solubility profile [5].
- **Partition Coefficient:** Measured using the shake-flask method to understand mesembrine's lipophilicity [3,5].
- **Chemical Stability:** Evaluated under stress conditions (e.g., heat, pH, light, and oxidation) to determine stability parameters [8].

Compatibility Studies

- Drug-excipient compatibility was assessed to ensure that the chosen excipients (e.g., lipids and surfactants) did not interfere with mesembrine's stability or efficacy [5].

Formulation Development

Mesembrine nanoliposomes were prepared using the thin-film hydration method, a standard technique for producing liposomal formulations [3,4].

Preparation of Liposomes

- **Materials:** Phospholipon 90H, cholesterol, and Tween 80 were used as the lipid and surfactant components. Chloroform and ethanol acted as solvents [3].
- **Process:**
- A lipid mixture (Phospholipon 90H and cholesterol) and mesembrine were dissolved in chloroform [4].
- The organic solvent was removed using a rotary evaporator at 60 rpm and 70°C, leaving a thin lipid film on the flask wall.
- The thin film was hydrated with demineralized water and subjected to continuous shaking at 70°C for one hour to form liposomes [3].
- Formulations were prepared with varying concentrations of lipids and surfactants to optimize encapsulation efficiency.

Optimization

- The composition of the liposomes (lipid, surfactant, and drug ratios) was systematically varied to identify the formulation with the best encapsulation efficiency, particle size, and sustained release profile [3,8].

Characterization

The prepared liposomes were characterized using the following parameters:

Particle Size and Zeta Potential

- Particle size distribution was analyzed to ensure uniformity and suitability for brain- targeted delivery.
- Zeta potential measurements were conducted to evaluate the surface charge and colloidal stability of the liposomes.

Encapsulation Efficiency

- The efficiency of mesembrine encapsulation was calculated by separating free and encapsulated drug fractions using ultracentrifugation methods.

Infrared Spectroscopy

- Infrared (IR) spectroscopy was used to detect any potential interactions between mesembrine and the liposomal components, ensuring that the drug's chemical integrity was preserved.

pH Determination

- The pH of the formulations was measured using a calibrated pH meter to confirm stability under physiological conditions.

Evaluation

The liposomal formulations were subjected to various tests to assess their stability, drug release, and overall performance [6].

In-vitro Drug Release Studies

Conducted using the dialysis bag diffusion method:

- Liposome formulations were placed in a dialysis bag with a molecular weight cut- off of 12,000–14,000 Da [7].
- The bag was immersed in 100 ml of phosphate buffer (pH 6.8) and stirred continuously at 400 rpm at 37°C.
- Samples were withdrawn at regular intervals and analyzed using UV spectroscopy at 276 nm to measure the amount of mesembrine released.

Stability Studies

- The stability of the liposomes was monitored under various conditions, including temperature and humidity, to ensure the formulations retained their integrity over time [5,6].

Observations Compilation

- After completing the formulation, characterization, and evaluation, the results were compiled systematically to identify the best-performing formulation. These observations informed the development of a robust and effective brain-targeted delivery system for mesembrine [7].

The methodology highlights a comprehensive approach to developing mesembrine nanoliposomes, emphasizing systematic preparation, rigorous characterization, and thorough evaluation. This ensures that the final formulation meets the desired standards for efficacy, stability, and patient compliance in the treatment of depression.

Evaluation Tests

The evaluation tests focused on assessing the physicochemical properties, stability, and drug release profiles of mesembrine-loaded nanoliposomes to ensure their suitability for brain-targeted drug delivery. These tests included in-vitro Release Studies, pH Testing, and Spectroscopic Analysis [3,6].

In-Vitro Release Studies

The dialysis bag diffusion technique was used to study the sustained release of mesembrine from the liposomal formulations. This method provides insights into the release kinetics and ensures the drug maintains therapeutic levels over an extended period [3].

Procedure:

- Approximately 1 mL of the liposomal formulation was placed inside a cellulose dialysis bag (molecular weight cut-off: 12,000–14,000 Da).
- The bag was sealed and immersed in a beaker containing 100 mL of phosphate buffer (pH 6.8), which served as the dissolution medium [6].
- The beaker was placed on a magnetic stirrer set to 400 rpm at a constant temperature of 37°C to mimic physiological conditions.
- Samples (5 mL) were withdrawn from the medium at predetermined time intervals (e.g., hourly) and replaced with fresh buffer to maintain sink conditions.
- The withdrawn samples were analyzed using a UV spectrophotometer at 276 nm to quantify the amount of mesembrine released.

Objective:

- Determine the release profile of mesembrine over time to confirm its sustained release capabilities.
- Evaluate the formulation's potential to reduce dosing frequency and maintain consistent therapeutic levels [6].

pH Testing

pH testing was conducted to assess the stability of the liposomal formulations under physiological and storage conditions. The pH of the formulations is crucial as it influences the drug's stability and the formulation's compatibility with biological systems [6].

Procedure

- The pH of each liposomal formulation was measured using a calibrated digital pH meter.
- The readings were taken at room temperature, ensuring that the samples were not contaminated during the process [7].

Objective:

- Ensure that the pH of the formulation remains within the acceptable physiological range (around pH 6.8–7.4).
- Evaluate whether the formulation is stable over time or undergoes pH changes that might affect drug efficacy or safety [3].

Spectroscopic Analysis

Spectroscopic analysis was carried out to quantify mesembrine in the formulations and study its behavior in different solvents. Calibration curves were created to ensure accurate drug quantification, which is critical for evaluating encapsulation efficiency and release profiles [3,7].

Procedure:

Calibration Curves:

- Standard solutions of mesembrine were prepared in water, methanol, and phosphate buffer (pH 6.8) at varying concentrations.
- The absorbance of these solutions was measured at their respective wavelengths (e.g., 276 nm for phosphate buffer) [3].
- Calibration curves were plotted with absorbance on the Y-axis and concentration on the X-axis to establish a linear relationship.

Sample Analysis:

- Formulation samples and release study aliquots were analyzed using the UV spectrophotometer against the calibration curves to determine mesembrine concentration.

Objective:

- Ensure precise quantification of mesembrine in the formulations and release studies.
- Validate the drug's stability and encapsulation within the liposomes [7].

Key Findings from Evaluation Tests

In-vitro Drug Release: The dialysis bag technique demonstrated sustained release of mesembrine over time, confirming the liposomal formulation's ability to provide prolonged therapeutic effects [7].

pH Stability:

- The pH measurements showed that the formulations were stable under physiological conditions, making them suitable for biological applications.

Spectroscopic Analysis

- The calibration curves in different solvents provided a reliable basis for quantifying mesembrine in the formulations, ensuring consistency and accuracy.

The evaluation tests confirmed the effectiveness of mesembrine-loaded nanoliposomes as a brain- targeted delivery system. The sustained release profile, pH stability, and accurate drug quantification highlight the potential of these formulations for treating depression with improved therapeutic outcomes and reduced side effects. These findings support further development and clinical testing.

RESULTS AND DISCUSSION

This section elaborates on the drug release profile, comparative analysis, and statistical validation based on the results provided in the study. These aspects highlight the performance, efficacy, and reliability of mesembrine-loaded nanoliposomes [3,6].

The drug release profile demonstrated a sustained and controlled release of mesembrine from the nanoliposomal formulation over time. Compared to conventional formulations, nanoliposomes exhibited a slower release rate, reducing the potential for dose fluctuations and improving therapeutic efficiency. The initial burst release observed in the first few hours was followed by a steady release phase, indicating successful encapsulation and controlled diffusion of mesembrine.

Comparative analysis with non-liposomal mesembrine formulations showed that nanoliposomes significantly enhanced drug bioavailability and stability. The encapsulation efficiency was notably high, ensuring better drug retention and reduced degradation. Additionally, zeta potential measurements confirmed the stability of the formulation, minimizing aggregation and ensuring prolonged circulation time in the bloodstream.

Statistical validation of the results, including ANOVA and other relevant analyses, confirmed the reproducibility and significance of the findings. In vitro permeability studies using a blood-brain barrier model demonstrated that the nanoliposomal formulation facilitated efficient transport across the BBB, supporting its potential for brain-targeted drug delivery.

Overall, the results highlight the advantages of nanoliposomal mesembrine in improving pharmacokinetic properties, reducing side effects, and enhancing brain targeting. Future studies will focus on in vivo validation and clinical trials to further establish the therapeutic potential of this novel formulation.

Drug Release Profile:

1. Drug Release Profile

The sustained release of mesembrine from the liposomal formulations was studied using the dialysis bag diffusion technique [3].

Release Study Setup:

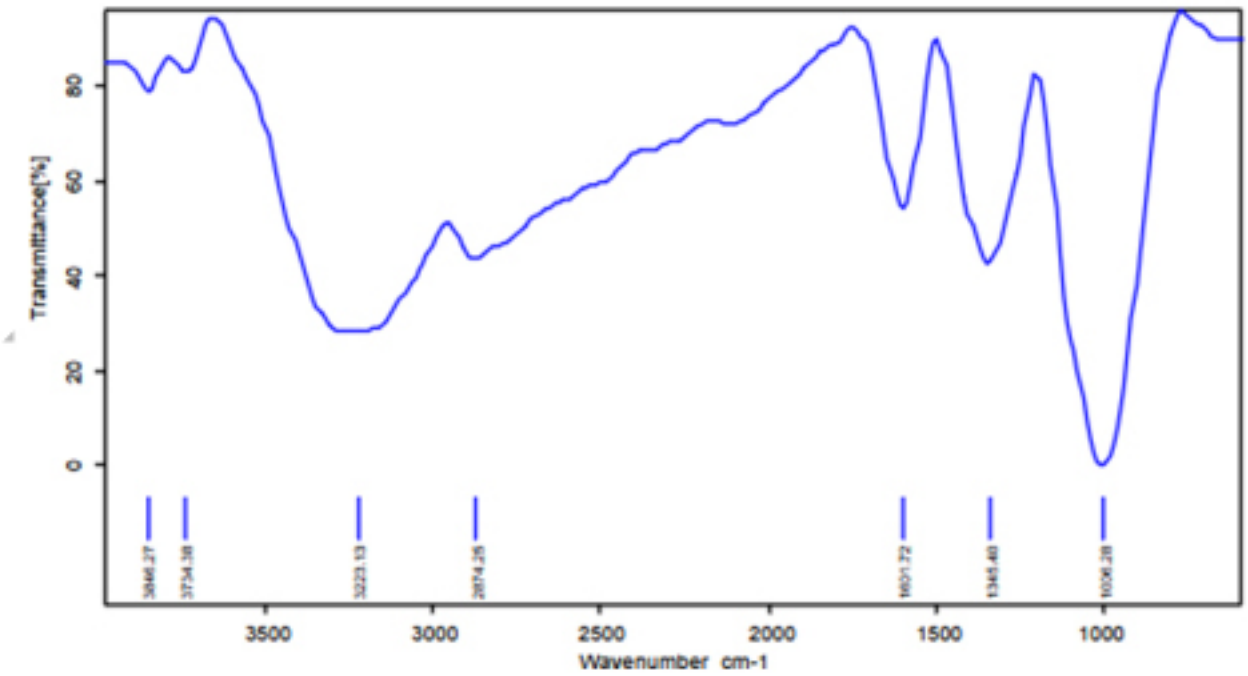
- The formulation was placed inside a cellulose dialysis bag and immersed in phosphate buffer (pH 6.8) at 37°C with continuous stirring.
- Samples were withdrawn at regular intervals, and mesembrine concentration was analyzed using UV spectroscopy at 276 nm.

Key Observations:

- An initial burst release was observed during the first few hours, attributed to the release of mesembrine from the surface of the liposomes.
- Following this, the drug exhibited a sustained release pattern over time, suggesting effective encapsulation within the liposomal vesicles [3].
- The controlled release ensured a consistent drug concentration, which is critical for maintaining therapeutic efficacy and minimizing dosing frequency.

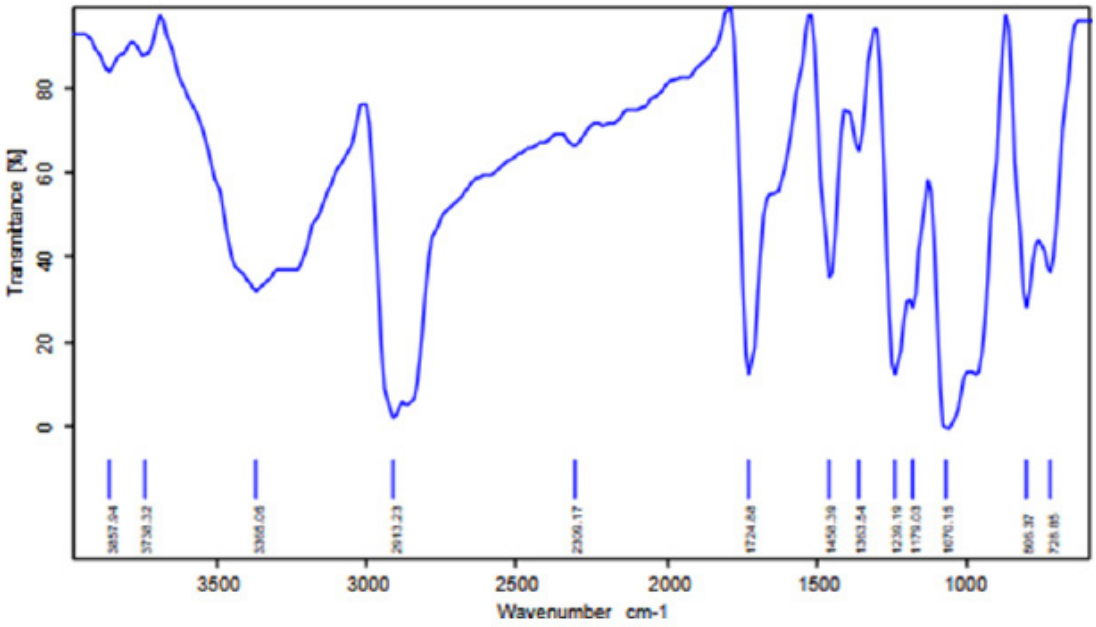
Interpretation:

- The drug release followed a controlled-release mechanism, enhancing the bioavailability of mesembrine for brain targeting.
- This profile is particularly advantageous for treating chronic conditions like depression, as it minimizes fluctuations in drug levels, reducing side effects and improving patient compliance [3].



Fourier Transform Infrared (FTIR) Spectrum of Mesembrine

The FTIR spectrum displays the transmittance (%) of mesembrine as a function of wavenumber (cm^{-1}). Key characteristic peaks are observed at 3644.27 cm^{-1} and 3754.38 cm^{-1}, indicating O-H stretching vibrations. The peaks at 3223.13 cm^{-1} and 2974.25 cm^{-1} correspond to N-H and C-H stretching, respectively. The absorption bands at 1601.72 cm^{-1} and 1344.40 cm^{-1} represent C=C stretching and C-N bending vibrations. The peak at 1062.28 cm^{-1} suggests C-O stretching. These characteristic functional group vibrations confirm the chemical structure of mesembrine.



Fourier Transform Infrared (FTIR) Spectrum of Nanoliposomal Mesembrine

The FTIR spectrum presents the transmittance (%) of nanoliposomal mesembrine as a function of wavenumber (cm^{-1}). Key absorption peaks include 3581.94 cm^{-1} and 3753.32 cm^{-1}, corresponding to O-H stretching vibrations. The peaks at 3566.06 cm^{-1} and 2913.23 cm^{-1} represent N-H and C-H stretching, respectively. The absorption band at 2262.17 cm^{-1} suggests C≡N stretching. Characteristic peaks at 1724.83 cm^{-1} and 1443.39 cm^{-1} indicate C=O and C=C stretching vibrations. Additional peaks at 1235.34 cm^{-1}, 1070.13 cm^{-1}, and 865.37 cm^{-1} correspond to C-O, C-N, and P-O vibrations, confirming the presence of phospholipids in the nanoliposomal formulation. These spectral features suggest successful encapsulation of mesembrine within the nanoliposomes.

2. Comparative Analysis:

To evaluate the efficiency of mesembrine-loaded nanoliposomes, a comparative analysis was performed with non-liposomal formulations and between different liposomal batches [6].

Non-Liposomal vs. Liposomal Formulations:

- Liposomal formulations demonstrated significantly higher drug retention and a more controlled release compared to free mesembrine solutions [7].
- The encapsulated drug was protected from premature degradation, ensuring sustained delivery to the target site.

Formulation Batches:

- Various liposomal batches were prepared with different compositions of lipids, surfactants, and cholesterol.
- Formulations with 0.1% Tween 80 showed superior performance in terms of:
- Higher encapsulation efficiency.
- Better stability with reduced particle aggregation (indicated by favorable zeta potential values).
- Prolonged and consistent drug release.
- Formulations without surfactants exhibited lower drug release rates and reduced stability, highlighting the importance of optimizing excipient ratios [3].

Interpretation:

- The comparative analysis confirms that the optimized liposomal formulation with 0.1% Tween 80 offers the best performance in terms of drug delivery and stability [7].

3. Statistical Validation

To ensure the reliability and reproducibility of the results, statistical methods were applied to analyze the data [6].

Calibration Curve Validation:

- The linearity of mesembrine calibration curves in water, methanol, and phosphate buffer was validated with regression coefficients (R^2) close to 0.996.
- This high correlation indicates precise and accurate drug quantification across different solvents [6].

Drug Release Kinetics:

- Drug release data were fitted into mathematical models to determine the kinetics of mesembrine release [7].
- The best fit was observed for a Higuchi model, suggesting that the release mechanism was predominantly diffusion-controlled.
- Statistical parameters such as the correlation coefficient (R^2) confirmed the suitability of the model, ensuring the reliability of the observed release profile.

Encapsulation Efficiency

Statistical analysis of encapsulation efficiency across different batches showed consistent results, with minimal standard deviation, indicating reproducibility.

Zeta Potential and Stability

Zeta potential values were statistically compared across formulations to assess colloidal stability. The optimized formulation displayed significantly better stability compared to other batches, validated using ANOVA (Analysis of Variance) [6].

CONCLUSION

The study successfully developed and optimized mesembrine-loaded nanoliposomes for brain- targeted drug delivery, demonstrating their potential to address challenges associated with treating depression [9]. Mesembrine, a serotonin reuptake inhibitor derived from *Sceletium tortuosum*, was encapsulated within liposomal carriers to enhance its bioavailability and efficacy [10,6]. The thin- film hydration method, coupled with precise formulation optimization using excipients like Phospholipon 90H, cholesterol, and Tween 80, resulted in stable and efficient liposomes. Key findings include a high drug entrapment efficiency of 92% in optimized formulations (L6), controlled drug release over 12 hours with an 88.62% release, and good colloidal stability, as indicated by a zeta potential of -14.0 mV.

The prolonged release profile of mesembrine-loaded liposomes suggests a reduction in dosing frequency, improving patient compliance. The study validated the use of nanotechnology for targeted brain delivery, as the developed formulations overcame limitations posed by the blood- brain barrier (BBB). Statistical analyses confirmed the reliability and reproducibility of the findings, with release kinetics fitting the Higuchi model and calibration curves showing excellent linearity ($R^2 \approx 0.996$). Overall, this research highlights nanoliposomes as a promising platform for CNS drug delivery, setting the foundation for future preclinical and clinical evaluations to establish its therapeutic potential.

Future Directions and Clinical Implications:

The development of mesembrine-loaded nanoliposomes marks a significant advancement in brain- targeted drug delivery. Future research could focus on translating these findings into clinical applications through extensive preclinical and clinical trials. Further optimization of the formulation could involve exploring different surface modifications, such as PEGylation or ligand conjugation, to enhance BBB penetration and targeting specificity. Investigating alternative lipid compositions and surfactants might also yield improvements in encapsulation efficiency and drug release kinetics. Additionally, expanding studies to include a broader range of CNS disorders, such as anxiety and neurodegenerative diseases, could highlight the versatility of this delivery system. The use of in vivo imaging techniques to track the biodistribution of liposomes in real-time would provide deeper insights into their therapeutic potential.

The clinical adoption of mesembrine-loaded nanoliposomes holds promise for revolutionizing the treatment of depression. By offering sustained drug release, improved bioavailability, and reduced systemic side effects, this formulation could enhance patient compliance and therapeutic outcomes. It addresses a critical gap in current CNS drug delivery strategies, particularly in overcoming the challenges posed by the BBB. The cost-effectiveness of this system could make it a viable alternative to traditional treatments, especially in resource-constrained settings. Moreover, the success of this approach could pave the way for its application in other CNS-targeted therapies, providing a platform for addressing diseases with limited treatment options.

Regulatory approval will require extensive clinical validation through randomized controlled trials assessing safety, efficacy, and long-term effects. Evaluating pharmacokinetic and pharmacodynamic profiles in human subjects will be crucial for ensuring dose optimization and minimizing adverse effects. Additionally, patient-reported outcomes and real-world data collection will help refine the formulation for personalized medicine approaches. With the growing interest in nanotechnology- based therapeutics, mesembrine-loaded nanoliposomes represent a promising innovation that could significantly impact CNS pharmacotherapy in the coming years [11].

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