RESEARCH PAPER

Enhancing Risperidone Delivery through Optimized Niosomal Formulation Using Central Composite Design

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ABSTRACT

Objective: The research was planned to make Risperidone Niosomes made through the film hydration method and optimized using a central composite design (CCD).**Materials and Methods:**Niosome formulations were optimized using a three-level, two-factor CCD. The input factors were the concentrations of Brij 58 (X_1) and Brij 72 (X_2), and the response variable was the entrapment of Risperidone (Y_1). The optimized niosomes were assessed and served as the foundation for subsequent elastic vesicle development.**Results:**The optimal niosome formulation, containing 150 mg each of Brij 58 and Brij 72, exhibited enhanced entrapment efficiency (85.6 ± 2.12%). These niosomes demonstrated a desirable particle size of 215 ± 5.87 nm (RN-5) and zeta potential values ranging from -39.00 ± 0.82 mV to -52.36 ± 1.56 mV. However, the polydispersity index (PDI) of the prepared niosomes varied considerably, with values ranging from 0.378 ± 0.01 (RN-6) to 0.80 ± 0.02 (RN-1).**Conclusion:**The study successfully developed niosomes using the CCD, a statistical method that optimizes formulation parameters like surfactant concentration, cholesterol content, and hydration time. This approach enabled the identification of optimal conditions for niosome formation, resulting in desirable assets viz., particle size and encapsulation. The findings demonstrate the effectiveness of CCD in optimizing pharmaceutical formulations and elevate the importance of niosomes as drug delivery carters.

Keywords: Central Composite Design, Drug delivery, Entrapment, Niosomes, Risperidone

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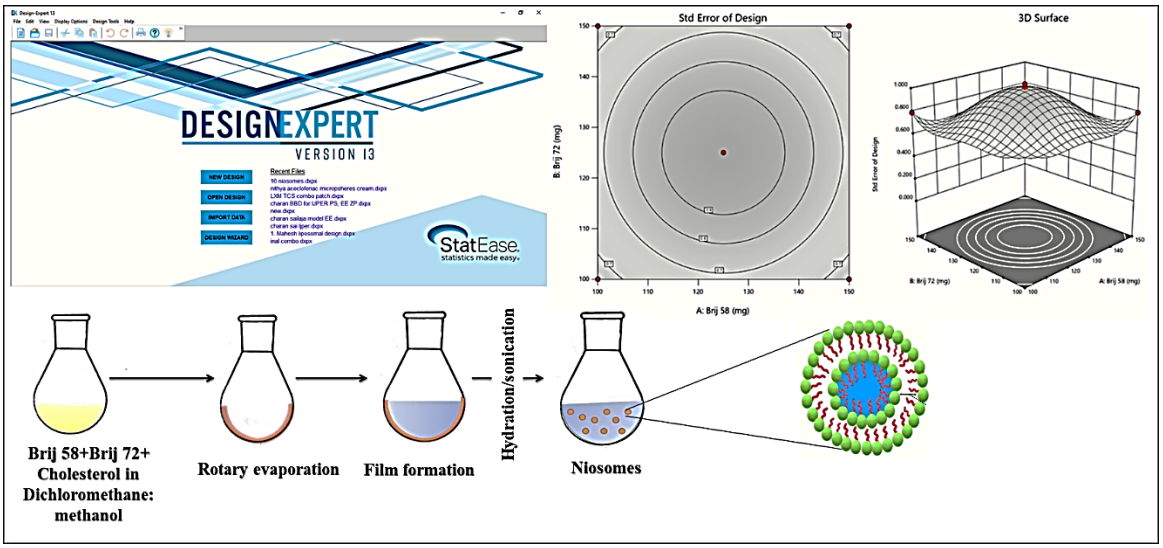
GRAPHICAL ABSTRACT

Enhancing Risperidone Delivery through Optimized Niosomal Formulation Using Central Composite Design



INTRODUCTION

Niosomes, non-ionic surfactant-based vesicles composed of a bilayer membrane enclosing an aqueous core, have appeared as a captivating podium for drug delivery systems (DDS).Their biocompatibility, stability, and ease of production render them attractive alternatives to liposomes. The versatility of niosomes lies in their ability to encapsulate both hydrophilic and hydrophobic drugs, enabling their application across a spectrum of therapeutic areas. By manipulating the composition of the niosomal membrane, controlled drug release can be achieved, enhancing drug bioavailability and efficacy. Oral administration benefits from niosomes' ability to protect drugs from enzymatic degradation and improve absorption, while parenteral delivery can be tailored for sustained release and slashed dosing frequency.[1] Their potential extends to ocular DDS, where they can improve bioavailability and prolong residence time, as well as pulmonary delivery, enabling targeted DDS to the respiratory system. In cancer therapy, niosomes offer the prospect of targeted DDS to tumor cells, augmenting efficacy while mitigating systemic toxicity. While challenges such as optimization for specific applications, ensuring long-term stability, and rigorous preclinical and clinical evaluation persist, the potential of niosomes is undeniable. Future research endeavors should concentrate on refining targeting capabilities, exploring combination DDS techniques, and investigating their suitability for gene and vaccine delivery. The convergence of these factors positions niosomes as a promising avenue for the development of innovative therapeutic formulations with improved efficacy and safety profiles.[2, 3]

Risperidone is prescribed for bipolar disorder, schizophrenia, and autism-related irritability, and exhibits key pharmacokinetic properties that influence its therapeutic efficacy. Risperidone is well-absorbed orally and reaches peak blood levels within 2 hours, with 70% reachability. It is extensively metabolized in the liver by CYP2D6, forming the active metabolite 9-hydroxy risperidone, which significantly contributes to its therapeutic effects. The drug has a variable elimination half-life, ranging from 3 to 20 hours for risperidone and 20 to 30 hours for its metabolite. It is primarily excreted through the urine. Genetic variability in CYP2D6 activity, along with factors like age, renal, and hepatic function, can significantly impact risperidone's pharmacokinetics, necessitating dose adjustments in certain populations.

Quality by Design (QbD) is a critical framework in formulation development, particularly in the formulation of drug-loaded Niosomal vesicles used in DDS. QbD is centered on the belief that quality is constructedintothe product by understanding and controlling formulation and manufacturing processes. In the context of niosome preparation, QbD involves a thorough understanding of the formulation components and their interactions, as well as the processes used to create the niosomes. CQAs are identified from the QTPP, representing the many properties that must be controlled to ensure the final inventionencounters its envisioned quality. For niosomes, CQAs might include particle size (PS), zeta potential (ZP), encapsulation efficiency (EE), and drug loading capacity. These

attributes are crucial because they influence the niosome's ability to deliver drugs effectively and safely. The CPPs are the variables within the manufacturing process that have a significant impact on CQAs. In niosome preparation, CPPs could include the temperature, hydration time, surfactant concentration, and homogenization speed. By identifying and controlling these parameters, QbD ensures that the niosomes are consistently produced with the desired quality attributes. The application of QbD in niosome formulation not only optimizes the product's performance but also enhances the understanding of the process itself. This deeper process knowledge facilitates the development of robust formulations that are less susceptible to variability, leading to more consistent DDS. Moreover, the QbD framework supports continuous improvement, as it encourages ongoing monitoring and adjustment of the manufacturing process to address any sources of variability. By integrating QbD principles, the development of niosomalDDS becomes more efficient, minimizing the period and expenditure linked with carrying new drugs. Additionally, QbD enhances regulatory compliance by providing a clear rationale for the design and control of the manufacturing process, which is essential for gaining approval from regulatory agencies. Overall, QbD is a powerful tool in the development of advanced DDS like niosomes, ensuring that they are safe, effective, and reliable for patient use.

To optimize the formulation, a statistical experimental design called central composite design (CCD) was employed. This involved varying two key components: the amount of Brij 58 (a surfactant) and Brij 72 in the niosomal structure. The primary goal was to achieve the highest possible entrapment efficiency of risperidone within the niosomes. Once the optimal niosome formulation was determined based on entrapment efficiency, it was further characterized to understand its properties.

MATERIALS AND METHODS

Materials

Risperidone wasgifted from AurobindoPharma, Hyderabad, India. Cholesterol, Brij 58, Brij 72, buffer tablets, methanol, and dichloromethane were procured from Fischer Scientific Co. All other chemicals used were of AR grade.

Making of niosomes

Risperidone (RPD)-loaded niosomes were produced using the film hydration method. A mixture of Brij 58, Brij 72, and cholesterol was dissolved in a dichloromethane-methanol solvent system containing RPD. This organic solution was evaporated under reduced pressure at 60°C to form a thin lipid film. Subsequently, the film was hydrated with phosphate buffer (pH 7.4) and subjected to heat and agitation to form a niosomal dispersion. To minimize PS, the dispersion underwent ultrasound sonication. Finally, the niosomes were stored at 4°C for equilibration.[4, 5]

Compatibility studies using FTIR

The compatibility study of RPD with excipients using FTIR spectroscopy through the KBr pellet method involves preparing a mixture of the RPD (1.752 mg) and KBr in a 1:100 ratio, grinding it finely, and compressing it under high pressure to form a transparent pellet. The pellet is then analyzed using FTIR spectroscopy over a suitable wavelength range (4000 to 400 cm^{-1}). The resulting spectrum is compared with that of the pure RPD to identify any changes in peak positions, intensity, or the appearance of new peaks, which could indicate potential interactions between the drug and excipients. If no significant differences are observed, it suggests compatibility, while any notable changes warrant further investigation.

The CCD

A three-level, two-factor CCD was utilized to statistically optimize RPD-loaded niosomes. Design-Expert® software (Version 13) generated the experimental design and established the mathematical association between independent variables (IVs) and output constraints. Various RPD-loaded niosome formulations were prepared according to the CCD design. Brij 58 (X_1) and Brij 72 (X_2) were selected as IVs and adjusted at three levels (low, medium, and high) based on preliminary trials. The (% EE) (Y_1) served as the dependent variable.[6, 7]

Table 1: Various formulations of LN

Factors	**Levels**		
	-1	**0**	**+1**
X_1= Brij 58 (mg)	100	125	150
X_2= brij 72 (mg)	100	125	150
Responses scrutinized	**Requirement**		
Y_1= EE (%)	Maximize		

Finding of PS, PDI and ZP

The study utilized dynamic light scattering (DLS) with a Zetasizer Nano ZS to characterize the mean PS, PDI, and ZP of the RPD-loaded niosomes. DLS is a sophisticated technique that measures the variations in light scattering caused by the Brownian motion of particles within a dispersion.[8] The Zetasizer Nano ZS, equipped with a helium-neon laser operational at a wavelength of 633 nm, was set to analyze these fluctuations at a controlled temperature of 25°C. Before the measurement, the niosomal dispersions were diluted appropriately to optimize the intensity of light scattering, ensuring accurate and reliable data. The PDI, a dimensionless number derived from DLS data, indicates the distribution of particle sizes within the sample. It provides insight into the uniformity of the niosome population, with a lower PDI value suggesting a more uniform size distribution.

The ZP, another crucial parameter, reflects the surface charge of the niosomes and their suspension stability. The ZP was measured using a grouping of laser Doppler velocimetry (LDV) and phase analysis light scattering (PALS). LDV assesses the velocity of particles moving under an applied electric field, while PALS enhances the sensitivity of this measurement by analyzing the phase shift in scattered light. The electrophoretic mobility, determined from these measurements, was then converted into ZP using the Smoluchowski equation.[9]

This completeexamination provided a detailed sympathetic of the physical features of the RPD-loaded niosomes, including their size distribution, stability, and potential behavior in biological systems.

%EE

The % EEof RPD was determined through centrifugation. This indirect method calculated the difference between the total RPD added and the amount remaining unencapsulated in the aqueous medium (Eq.1). Niosomes were separated from free RPD by centrifuging at 20,000 rpm for one hour at 4°C. The free RPD concentration in the supernatant was quantified spectrophotometrically at the absorption maximum of 238 nm.[10, 11]

$$\% EE = \frac{(\text{Total amount of RPD} - \text{Amount of free RPD})}{\text{Total amount of RPD}} X100 \text{---} (1)$$

Niosomoal optimization

Desirability values were calculated using Design-Expert® software as part of a systematic approach to identify the optimal niosome formulation through response surface analysis. This method involved applying a desirability function, which integrates multiple response variables into a single metric, to pinpoint the formulation that achieved the highest % EE. The desirability function evaluates each response by assigning a value between 0 (completely undesirable) and 1 (fully desirable), allowing for a comprehensive comparison across different formulations. The formulation with the highest desirability value was considered optimal, as it balanced the various factors influencing the niosome's performance. To validate the predictive accuracy of the model, the optimal niosome formulation suggested by the software was physically prepared and subjected to experimental evaluation. The key performance metrics, such as PS, EE, and stability, were then compared to the predictions made by Design-Expert® software. This step ensured that the theoretical model accurately reflected real-world outcomes, confirming the robustness and reliability of the design process. In addition to validating the niosome formulation, elastic vesicles were produced using the same method and components as those used for the optimal niosome formulation.[11] These elastic vesicles, which are known for their flexibility and ability to traverse biological barriers more effectively, were created to provide a comparative analysis. By evaluating both the optimal niosomes and the elastic vesicles, the study aimed to assess the advantages and potential applications of each type of vesicle in DDS, offering insights into their respective performances under similar conditions.[12]

RESULTS

FTIR spectral results

The FTIR spectral analysis revealed that the specific peaks of the pure drug, RPD, were consistently observed in the spectra of the drug-excipient mixtures. There were no significant shifts or changes in the intensity of these peaks, indicating that the structural integrity of the drug was maintained even when combined with the excipients.

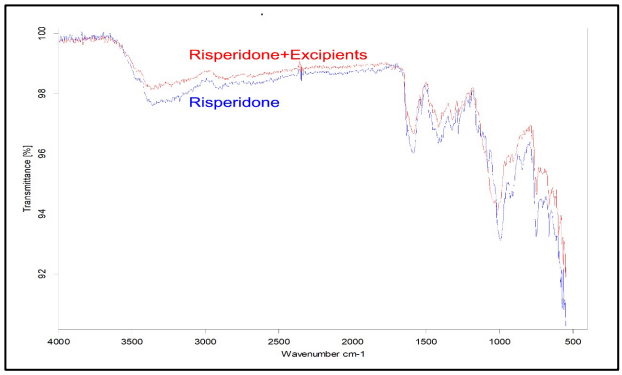


Figure 1. FTIR spectra of RPD and in combination with excipients

Physicochemical assets

The prepared niosomes exhibited a uniform PS ranging from 215 ± 5.87 nm to 402.02 ± 6.98 nm across different formulations (RN-5 to RN-4). The ZP values varied from -39.00 ± 0.82 mV to -52.36 ± 1.56 mV, indicating good stability of the niosomal systems. The % EE RPD within the niosomes ranged from 71.00 ± 0.71% to 85.60 ± 1.36%. The PDI of the prepared niosomes varied significantly, ranging from 0.378 ± 0.01 (RN-6) to 0.80 ± 0.02 (RN-1) (Figure 2).

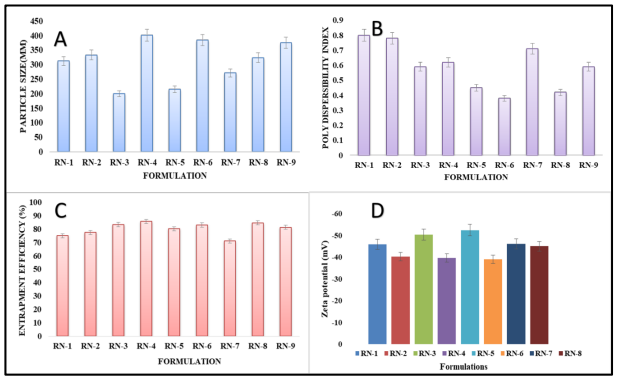


Figure 2. Physicochemical constraints of the niosomses

Optimization results

Statistical analysis using coded factors revealed significant correlations between the IVs, Brij 58 and Brij 72 concentrations, and the % EE. The generated equations effectively predicted EE% values based on varying levels of the IVs. The equations can be expressed as follows:

$EE = +81.27+1.09A+4.47B-0.02AB+0.2769A^2-1.56B^2$

The statistical summary of the quadratic responses for %EE revealed high values, indicating strong predictive capabilities of the models. These models can be reliably employed to forecast %EE values under new experimental conditions.

The statistical analysis undertaken to assess the quadratic responses about %EE yielded notably elevated values. This quantitative outcome signifies a robust correlation between the IVs under investigation and the dependent variable, %EE. These findings underscore the efficacy of the employed experimental design in capturing the intricate relationships between the factors influencing the EE.

Contour plots illustrate the relationships between the levels of Brij 58 and Brij 72 towards the responses (%EE). These plots provide a two-dimensional view of how changes in these factors influence the responses. The contour lines reveal regions where the response values remain constant, showing how varying one factor while holding others constant affects the response. The 3D plots offer a three-dimensional perspective on the interactions between the inputs with the response. These plots help visualize how changes in the levels of these factors influence the responses more comprehensively. By adjusting the levels of Brij-58 and Brij-72, the 3D plots highlight the combined effects of these factors on the response variables, showing areas where optimal responses can be achieved. Cubic plots display the relationships between the IVs (Brij-58 and Brij-72) and the responses through a three-dimensional surface. These plots provide insight into the non-linear interactions among the factors and their effects on %EE. The cubic plots illustrate how combinations of different levels of the factors affect the responses, helping to identify optimal conditions for achieving desired results. (Figure 3).

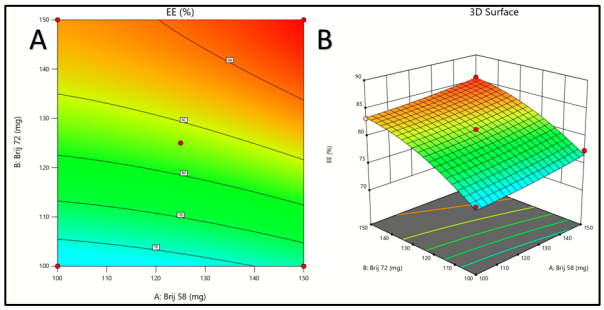


Figure 3. Contour plot (A) and 3D plot (B)indicate the effect of inputfactors on the % EE

Optimization

The contour plots, 3D plots, and cubic plots collectively illustrate the relationships between the levels of Brij 58 and Brij 72 and their impact on the response variable (%EE). The analysis reveals that the optimum concentrations of Brij 58 and Brij 72 required to achieve

the maximum %EE of 80% are 107.42 and 121.63, respectively (Figure 4).

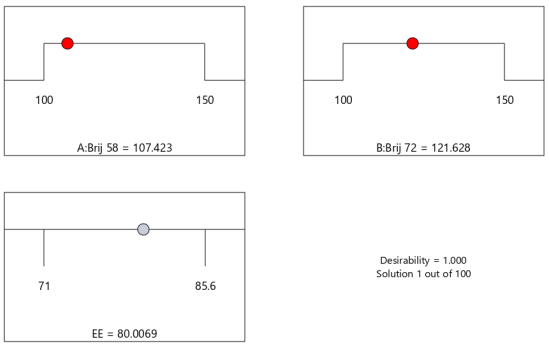


Figure 4. Ramps showing the optimum concentrations of Brij 58 and Brij 72 required for the maximum % EE

Standard error

Contour and 3D plots generated using Design Expert software effectively visualized the standard error across the experimental design space. Areas of higher standard error were represented by darker shades or elevated values on the plot. Conversely, regions with lower standard error exhibited lighter shades or lower values. This visual representation provided a clear indication of prediction precision within the experimental domain (Figure 5).

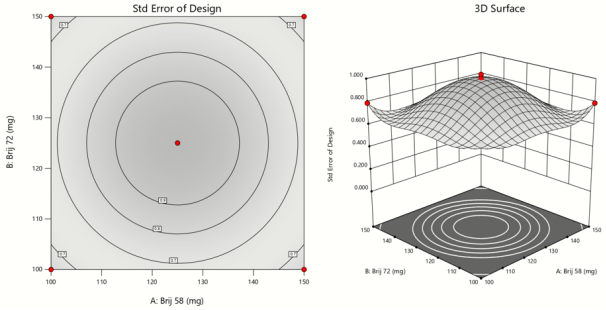


Figure 5. Contour and 3D plots showing the standard error of the design

DISCUSSION

The undisturbed distinctive peaks in the FTIR spectra of RPD in the presence of excipients suggest no significant interaction between the RPD and the excipients used in the niosomes. This compatibility is essential as it ensures that the excipients do not interfere with the drug's stability, efficacy, or safety. The findings support the suitability of the selected excipients for the formulation, allowing the drug to retain its intended therapeutic properties.

The obtained PS values suggest that the prepared niosomes fall within the nanometric range, which is desirable for enhancedRPD delivery. The relatively narrow PS distribution, as indicated by the consistent PS values, is crucial for achieving reproducible drug release and penetration. The negative ZP values observed for all formulations imply good stability of the niosomal systems, as the electrostatic repulsion between particles prevents aggregation. The EE% values demonstrate successful EE of RPD within the niosomes, which is essential for effective DDS. Variations in EE% among different formulations could be attributed to differences in lipid composition and preparation conditions.[13]

PDI is a crucial parameter indicating the heterogeneity of PS distribution within a sample. A lower PDI value, as observed in RN-6 (0.378 ± 0.01), signifies a more uniform PS distribution, suggesting that the niosomes in this formulation are relatively consistent in size and shape. Conversely, higher PDI values, such as that of RN-1 (0.80 ± 0.02), indicate a broader PS distribution, implying greater variation in niosome size and shape within the formulation.[14]

The mathematical models derived from the experimental data provided valuable insights into the influence of Brij 58 and Brij 72 on EE%. Positive coefficient values in the equations indicated a direct relationship between the factor and EE%, suggesting that increasing the concentration of the respective surfactant enhanced EE. Conversely, negative coefficients implied an inverse relationship, where higher surfactant concentrations led to decreased EE%. The inclusion of interaction terms in the model highlighted the complex interplay between Brij 58 and Brij 72, demonstrating that their combined effect on EE% was not simply additive. These interactions revealed synergistic or antagonistic effects, which significantly influenced the overall characteristics of the prepared niosomes. A deeper understanding of these interactions is crucial for optimizing niosome formulation and achieving desired drug delivery properties.[15]

The contour plots effectively demonstrate the influence of Brij 58 and Brij 72 on %EE, highlighting regions of constant response values. This visualization aids in understanding how each factor individually impacts the response when the other is held constant. The 3D plots offer a more comprehensive view by showcasing the interactions between Brij 58 and Brij 72. These plots reveal how simultaneous changes in both factors can lead to optimal response values, providing a clearer picture of the combined effects on %EE. Cubic plots further enhance this understanding by illustrating the

non-linear interactions between the factors. These plots are particularly useful in identifying the optimal conditions for achieving desired %EE values, as they show how different combinations of Brij 58 and Brij 72 levels influence the response. This detailed visualization helps in pinpointing the precise conditions needed for optimal results.[16]

The optimization analysis has determined that Brij 58 and Brij 72 concentrations of 107.42 and 121.63 units, respectively, yield a peak EE of 80%. This precise ratio suggests a delicate balance between the surfactants is crucial. To understand how these surfactants enhance %EE, further investigation into their interplay is necessary. Factors such as HLB, micelle formation, and solubility likely contribute to optimal performance. Characterizing the system's properties at these concentrations, including PS, ZP, and morphology, can provide insights into the underlying mechanisms. Additionally, studying the interactions between the surfactants, encapsulated material, and other components will help elucidate their roles. Ensuring the system's robustness under different conditions and scaling up the process for practical applications are essential next steps. The potential applications of this optimized formulation are promising. In fields like drug delivery, cosmetics, and food science, it could enhance product efficacy and stability. However, further research is needed to fully realize it's potential.[17]

The visualization of standard error through contour and 3D plots in Design Expert proved to be a valuable tool for experimental design and optimization. By identifying regions of high and low prediction precision, researchers could focus their efforts on areas with lower standard error to enhance the reliability of their findings. Furthermore, the ability to customize plot displays allowed for tailored analysis based on specific research objectives. These plots contributed significantly to informed decision-making by providing a visual representation of experimental uncertainty. It is recommended that researchers utilize these plots as a standard practice in experimental design to optimize resource allocation and maximize the accuracy of results.[18-34]

CONCLUSION

The successful optimization of niosome formulation using a three-level, three-factor central composite design highlighted the critical role of Brij 58 and Brij 72 in enhancing %EE. The formulation incorporating the maximum permissible levels of both surfactants demonstrated superior EE. These optimized niosomes, characterized for their properties, serve as a promising foundation for developing elastic vesicles. This research contributes to the advancement of noisome-based drug delivery systems by providing insights into formulation parameters that significantly impact EE. Further studies exploring the correlation between surfactant concentration, niosome characteristics, and drug release profiles are warranted to fully elucidate the potential of this delivery system.

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FUNDING

Self-funding

ETHICAL STATEMENT

Not applicable

CONFLICT OF INTEREST

Declared none.

ABBREVIATIONS

CYP2D6: Cytochrome P450 2D6; QbD: Quality by Design; QTPP: Quality Target Product Profile; CQAs: Critical Quality Attributes; CPPs: Critical Process Parameters; CCD: Central Composite Design; RPD: Risperidone; FTIR: Fourier Transform Infrared Spectroscopy; DLS: Dynamic Light Scattering; PDI: Polydispersity Index; ZP: Zeta Potential; LDV: Laser Doppler Velocimetry; PALS: Phase Analysis Light Scattering; AR: Analytical Reagent

SUMMARY

This research aimed to develop a niosomal drug delivery system for Risperidone using the film hydration method, with optimization achieved through central composite design (CCD). The study focused on adjusting the concentrations of Brij 58 and Brij 72 to enhance the entrapment efficiency of Risperidone. The optimal formulation of niosomes, incorporating specific amounts of Brij 58 and Brij 72, exhibited improved entrapment efficiency. The niosomes displayed desirable PS, ZP, indicating stability and effective drug encapsulation. Although the polydispersity index (PDI) varied among the formulations, the study successfully utilized CCD to identify optimal conditions for niosome formation. The findings highlight the effectiveness of CCD in optimizing pharmaceutical formulations and the potential of niosomes as efficient drug delivery carriers.

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