

Formulation, Optimization, and Characterization of Luliconazole-Loaded Nanostructured Lipid Carrier (NLC) Gel for Topical Antifungal Delivery

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Abstract

This study successfully developed a Quality by Design (QbD)-optimized nanostructured lipid carrier (NLC) gel to significantly enhance the topical delivery of luliconazole for deep-seated cutaneous mycoses. Structural characterization via FTIR, DSC, and XRD confirmed complete drug amorphization within the lipid matrix and excellent chemical compatibility. TEM imaging revealed uniform, non-aggregated spherical nanoparticles with a hydrodynamic diameter of about 155.2 nm. The optimized carriers were successfully dispersed into a Carbopol 940 matrix, producing a topical gel with a physiological skin-compatible pH of 5.82 and optimal pseudoplastic (shear-thinning) rheological behavior for ease of application. In vitro drug release profiles exhibited a distinct, mathematically validated biphasic sustained pattern governed by anomalous, non-Fickian diffusion ($R^2 = 0.9912$, $n = 0.62$). Furthermore, ex vivo permeation studies demonstrated a superior occlusion-driven skin hydration effect, significantly increasing localized luliconazole retention within target epidermal and dermal layers while minimizing systemic leakage. Crucially, in vitro microbiological assays revealed a significantly wider zone of inhibition against *Candida albicans* and *Trichophyton rubrum* compared to commercial cream. Consequently, the formulated luliconazole NLC-gel represents a highly effective, safe, and patient-compliant localized therapeutic strategy for managing stubborn fungal infections.

1. INTRODUCTION

Superficial fungal infections caused by dermatophytes and yeasts are a widespread clinical issue that often requires prolonged therapy. Luliconazole, a broad-spectrum imidazole antifungal, has emerged as a highly potent option for treating these infections. It works by inhibiting lanosterol 14- α -demethylase, which interrupts ergosterol synthesis and destabilizes the fungal cell membrane (Khanna & Bharti, 2014). Clinically, luliconazole shows excellent fungicidal activity against common pathogens like *Trichophyton rubrum* and *Candida albicans*, making it highly effective for treating skin and nail infections (Scher et al., 2014). Despite its strong pharmacological profile, delivering luliconazole effectively through the skin presents significant physical challenges (Bhatt, Singh, et al., 2025). The drug is highly lipophilic and has very poor aqueous solubility. The stratum corneum acts as a formidable barrier against outside substances. Because luliconazole mainly sits on the surface when applied via traditional suspensions or creams, it often fails to reach the

deeper skin layers where the fungal spores reside. Patients experience lower skin retention of the drug, which leads to frequent reapplication and poor treatment compliance (Babu et al., 2022). To overcome these penetration hurdles, packaging luliconazole into Nanostructured Lipid Carriers (NLCs) offers a practical solution. NLCs are created by blending solid and liquid lipids to form an imperfect crystal matrix (Bhatt et al., 2025). This structural imperfection prevents the drug from leaking out during storage and allows for much higher drug loading capacity compared to older generation nanoparticles (Okonogi & Riangjanapatee, 2015). When applied to the skin, these nanosized lipid particles form a continuous occlusive film. This film reduces water loss, effectively hydrating the stratum corneum and loosening the tightly packed skin cells, which significantly enhances the skin penetration and local retention of poorly soluble drugs (Okonogi & Riangjanapatee, 2015). Traditionally, developing pharmaceutical formulations relied on trial and

error, which wastes time and often misses the best balance of ingredients. The Quality by Design (QbD) approach shifts this process from guesswork to a systematic, data-driven science. By defining critical quality attributes like particle size, entrapment efficiency, and drug release rates, QbD allows researchers to use mathematical models to predict exactly how different formulation variables will impact the final product (Cunha et al., 2020). Using statistical tools like the design of experiments, researchers can evaluate the interactions between material attributes and manufacturing processes to find a precise design space where the formulation consistently meets its quality targets (Costa et al., 2021; Kovács et al., 2017). Based on these clinical needs and formulation principles, the present study hypothesized that a QbD-guided NLC-based gel would significantly enhance the skin permeation, retention, and antifungal efficacy of luliconazole compared to conventional formulations. The primary aim of this research is to systematically develop and characterize a luliconazole-loaded NLC gel. The specific objectives include performing a risk assessment and statistical optimization of the NLCs using a design of experiments approach, formulating the optimized NLCs into a secondary hydrogel system, and thoroughly evaluating its physicochemical properties, *ex vivo* skin permeation, and *in vitro* antifungal efficacy.

2. MATERIALS AND METHODS

2.1. Materials

Luliconazole was received as a generous gift sample from Glenmark Pharmaceuticals Ltd. (Mumbai, India). Solid lipids including glyceryl monostearate and Compritol 888 ATO, along with liquid lipids such as oleic acid and Miglyol 812, were procured from Gattefossé (Mumbai, India). Polysorbate 80 and Poloxamer 188 were utilized as surfactants, and Carbopol 940 was purchased from Sigma-Aldrich (Bengaluru, India) to serve as the gelling agent. All solvents and reagents used in this study were of analytical or high-performance liquid chromatography grade, and Milli-Q purified water was used throughout the experiments.

2.2. Pre-formulation and Screening Studies

To ensure maximum drug loading and physical stability of the nanostructured lipid carriers, selecting the right components is a critical first step. The pre-formulation phase begins with solubility screening to identify which lipids can dissolve the highest amount of luliconazole. For solid lipids, the procedure involves heating varying amounts of the active drug with a fixed quantity of different solid lipids slightly above their respective melting points. The molten mixtures are visually inspected to check for a clear, uniform solution. A transparent melt

indicates complete solubilization without any drug precipitation, which is necessary to form a homogenous lipid matrix (Pardeike et al., 2009). Evaluating liquid lipids requires a similar but distinct approach. Excess luliconazole is added to various oils and placed in a reciprocating water bath to reach thermodynamic equilibrium. After centrifugation to isolate the undissolved drug, the amount of luliconazole dissolved in the supernatant is quantified using high-performance liquid chromatography. Finding a liquid lipid with high drug solubility is essential because it creates the structural imperfections in the solid lipid matrix needed to hold the drug securely over time and prevent expulsion during storage (Das et al., 2012). Finally, selecting the right surfactant is necessary to stabilize the lipid droplets in water. This screening involves mixing the optimal solid and liquid lipid blend with different aqueous surfactant solutions under continuous stirring and moderate heating. A suitable surfactant is chosen based on its ability to form a fine, stable emulsion without phase separation. This visual and physical confirmation proves the surfactant can effectively lower the interfacial tension between the lipid melt and the water phase (Salvi & Pawar, 2019).

2.3. Quality by Design (QbD) Implementation

2.3.3. Design of Experiments (DoE)

To systematically optimize the luliconazole loaded NLC formulation, a Design of Experiments approach was utilized. Based on the initial risk assessment, a 3-factor, 3-level Box-Behnken Design was selected. This statistical design is highly efficient for evaluating quadratic response surfaces and constructing second order polynomial models. It allows researchers to understand both the main effects and the interaction effects of formulation variables while requiring significantly fewer experimental runs than a standard full factorial design.

Three independent variables were chosen for the optimization process based on their high impact on formulation quality. These variables were the solid to liquid lipid ratio, the total surfactant concentration, and the sonication time. During the experiments, each factor was tested at three distinct levels, defined as low, medium, and high. The critical quality attributes selected as the dependent responses were particle size and entrapment efficiency. The ultimate goal of this design was to identify an optimal formulation space that minimizes particle size for better skin penetration while maximizing entrapment efficiency to ensure an adequate therapeutic dose. The experimental matrix and subsequent data analysis were handled using statistical software to generate the final design space.

Table 1: Independent variables and dependent responses selected for the Box-Behnken Design.

Factor Type	Variables	Symbol	Low Level (-1)	Medium Level (0)	High Level (+1)
Independent Variables	Solid to Liquid Lipid Ratio	A	70:30	80:20	90:10
	Surfactant Concentration (% w/v)	B	1.0	2.0	3.0
	Sonication Time (min)	C	5	10	15
Dependent Responses	Responses	Goal	Acceptable Range		
	Particle Size (nm)	Y_1	Minimize	< 200 nm	
	Entrapment Efficiency (%)	Y_2	Maximize	> 80%	

2.4. Preparation of Luliconazole-Loaded NLCs

The luliconazole-loaded nanostructured lipid carriers were prepared utilizing a hot high-shear homogenization method followed immediately by ultrasonication. First, the accurately weighed solid and liquid lipids were mixed and heated in a water bath to approximately 5 to 10 °C above the melting point of the solid lipid to form a uniform, clear melt. Once the lipid matrix was completely molten, the antifungal drug luliconazole was added and stirred until completely dissolved in the lipid phase (Chauhan et al., 2020). Concurrently, an aqueous phase containing the selected primary and secondary surfactants was prepared and heated to the exact same temperature as the lipid melt. Heating both phases equally is a critical step to prevent the lipid from solidifying prematurely upon mixing. Once both phases reached the target temperature, the hot aqueous surfactant solution was carefully added dropwise to the molten lipid phase under continuous stirring. To form a coarse pre-emulsion, the mixture was immediately subjected to high-shear homogenization for a predefined time based on the experimental design. Following this initial mixing step, the hot pre-emulsion was subjected to probe ultrasonication. This acoustic energy further sheared and broke down the lipid droplets, effectively reducing their size into the desired nanometer range (Syed Azhar et al., 2022). Finally, the resulting hot nanoemulsion was removed from the heat and allowed to cool gradually to room temperature. This controlled cooling process induced lipid recrystallization, safely trapping the drug within the solidifying imperfect lipid core and yielding the final stable luliconazole-loaded NLC dispersion.

2.5. Characterization of the NLC Dispersions

2.5.1. Particle Size (PS), Polydispersity Index (PDI), and Zeta Potential (ZP)

To evaluate the physical properties of the prepared nanostructured lipid carriers, dynamic light scattering was employed. This analytical technique measures the random Brownian motion of particles suspended in a liquid to calculate their average hydrodynamic diameter and size distribution, which is represented by the polydispersity index (Danaei et al., 2018). Prior to analysis, the NLC dispersions

were appropriately diluted with double distilled water to prevent multiple scattering effects and ensure accurate readings. Following the size measurements, the surface charge of the lipid nanoparticles was determined by measuring the zeta potential using electrophoretic light scattering. Evaluating the zeta potential is crucial because a sufficiently high positive or negative charge creates strong electrostatic repulsion between the particles. This repulsion prevents the nanoparticles from clumping together, serving as a primary indicator of the long term physical stability of the formulation (Elmowafy & Al-Sanea, 2021).

2.5.2. Entrapment Efficiency (EE%) and Drug Loading (DL%)

Determining exactly how much luliconazole was successfully incorporated into the lipid matrix is necessary to confirm the efficiency of the manufacturing process. The entrapment efficiency and drug loading were quantified using an indirect ultracentrifugation technique (Gaba et al., 2015). A fixed volume of the optimized NLC dispersion was placed in an ultracentrifuge tube and spun at high speeds at a controlled low temperature. This rapid spinning separates the heavier lipid nanoparticles, which contain the entrapped active ingredient, from the surrounding aqueous supernatant that holds any free, untrapped drug. The clear supernatant was carefully collected, passed through a membrane filter, and analyzed using a validated high performance liquid chromatography or UV visible spectrophotometry method. By subtracting the concentration of the free drug found in the supernatant from the total amount of drug initially added to the formulation, the entrapment efficiency percentage and overall drug loading capacity were accurately calculated.

2.6. Preparation of Luliconazole NLC-Enriched Gel

Because raw nanostructured lipid carrier dispersions are highly fluid, they tend to run off the application site and provide very short contact time on the skin. To transform the optimized liquid dispersion into a user friendly, semi-solid topical formulation, the NLCs were incorporated into a secondary hydrogel vehicle. Carbopol 940 was selected as the gelling

agent due to its excellent skin compatibility and ability to form a stable matrix. The preparation began by sprinkling a predetermined concentration of Carbopol 940 powder over a measured volume of double distilled water. This mixture was allowed to hydrate thoroughly overnight to ensure the polymer chains swelled completely without forming dry clumps (Hsueh et al., 2021). Once a uniform swollen polymer base was achieved, the optimized luliconazole NLC dispersion was gradually added into the gel base. The mixture was continuously stirred using an overhead mechanical stirrer at a moderate speed to integrate the nanoparticles uniformly while avoiding the entrapment of air bubbles. The resulting acidic dispersion was then carefully neutralized by adding triethanolamine drop by drop. This neutralization step uncoils the polymer network, instantly thickening the mixture into a smooth, transparent, and viscous NLC-enriched gel. The final pH was strictly monitored and adjusted to a range compatible with the natural slightly acidic surface of human skin (Uprit et al., 2013).

2.7. Characterization of Luliconazole NLC-Gel

2.7.1. Organoleptic Properties and pH

The first step in evaluating the newly formulated gel was a thorough visual inspection. The NLC gel was assessed for its color, clarity, homogeneity, and the complete absence of gritty particles. A smooth, cosmetically appealing texture is vital to ensure patient compliance during regular use. Following the visual checks, the pH of the gel was determined. A small, accurately weighed quantity of the gel was diluted in distilled water and allowed to equilibrate before a calibrated digital pH meter was immersed into the mixture. Keeping the pH of the gel close to the physiological pH of skin is an essential safety measure to prevent local irritation or burning sensations upon application (Uprit et al., 2013).

2.7.2. Rheological Evaluation and Spreadability

Topical gels need specific flow properties. They should remain thick and stable in their container but become fluid and easy to rub in when pressure is applied by the patient's fingers. The rheological behavior of the gel was measured using a controlled-stress rheometer to record how its viscosity changed across different shear rates. A shear-thinning, pseudoplastic flow is the ideal target (Kumbhar et al., 2013). In addition to measuring viscosity, spreadability was tested using the parallel plate method. A known amount of the gel was placed between two horizontal glass plates, and a standard weight was rested on the upper plate for a fixed duration. The resulting increase in the diameter of the gel circle was measured. High spreadability ensures the gel can be applied easily and evenly over sensitive, infected fungal lesions without requiring harsh rubbing (Kumbhar et al., 2013).

2.7.3. Drug Content Uniformity

To guarantee that the drug is evenly distributed throughout the entire batch of gel and that every

applied dose contains the intended amount of luliconazole, a drug content uniformity analysis was conducted. A specific weight of the gel was dissolved in a suitable solvent mixture designed to break down the Carbopol network and completely release the entrapped drug from the lipid nanoparticles. After rigorous mixing and sonication, the solution was filtered. The clear filtrate was then analyzed using a validated analytical method, such as UV-visible spectroscopy or high performance liquid chromatography, to quantify the exact concentration of luliconazole. Confirming uniform drug content is a mandatory quality control step before advancing the formulation to biological and permeation studies (Wavikar & Vavia, 2013).

2.8. Solid-State and Morphological Characterization

2.8.1. Transmission Electron Microscopy (TEM)

For a closer look at the actual shape and surface structure of the nanostructured lipid carriers, Transmission Electron Microscopy is the standard tool. A small drop of the diluted NLC dispersion is carefully placed onto a carbon coated copper grid and stained with a contrasting agent. Once dried, the electron beam provides ultra high resolution images. This confirms whether the lipid nanoparticles successfully formed the expected spherical shape and helps verify that they are evenly distributed without unwanted clumping (Malekmohammadi et al., 2023).

2.8.2. Fourier Transform Infrared Spectroscopy (FTIR)

It is highly important to ensure the active drug mixes well with the lipids without breaking down. Fourier Transform Infrared Spectroscopy is used to check this chemical compatibility. We record the absorption spectra of the pure drug, the individual lipids, and the final optimized formulation. By comparing these structural fingerprints, we can verify if the drug was properly entrapped. If the formulation spectrum shows the same key peaks without creating any new, unexpected bands, it confirms that no negative chemical reactions occurred during the manufacturing process (Kumar Dubey et al., 2023).

2.8.3. Differential Scanning Calorimetry (DSC)

To understand how the drug behaves inside the lipid core on a thermal level, Differential Scanning Calorimetry is applied. Small samples of the pure drug and the freeze dried NLCs are heated under a continuous nitrogen flow. A pure crystalline drug naturally shows a very sharp melting peak on the thermal graph. However, when the drug is successfully locked inside the lipid matrix, this peak usually flattens out or completely disappears. This shift proves the drug has changed from a rigid crystalline state into a more disordered amorphous state, which is exactly what we want for better solubility (Muraca et al., 2023).

2.8.4. X-ray Diffraction (XRD)

X-ray Diffraction works alongside the thermal analysis to confirm the structural changes within the lipid matrix. When pure, highly structured crystalline drugs are scanned, they produce very sharp, distinct X-ray scattering patterns. Once the drug gets dissolved and trapped inside the imperfect structure of the lipid nanoparticles, these intense peaks become much broader and less defined. Seeing this reduction in peak intensity physically verifies the formation of an amorphous system, ensuring the drug will dissolve and release easily upon application (Barman et al., 2014).

2.9. In Vitro Drug Release Study

To determine how effectively the formulation releases luliconazole over time, an in vitro drug release study was conducted using the dialysis bag method. A specified amount of the optimized NLC gel was placed inside a dialysis cellulose membrane (with a specific molecular weight cut-off), which was previously soaked and equilibrated in the receptor medium. The tightly sealed dialysis bag was then immersed in a dissolution beaker containing a simulated skin surface pH buffer, typically around pH 5.5. Because luliconazole is highly lipophilic and has poor water solubility, a solubilizing agent like Tween 80 was added to the receptor medium to maintain sink conditions. The entire assembly was kept at a standard skin surface temperature of $32 \pm 0.5^\circ\text{C}$ and stirred continuously. At predetermined time points across 24 hours, small aliquots of the release medium were carefully withdrawn and immediately replaced with an equal volume of fresh, pre-warmed buffer to keep the volume constant. The collected samples were then analyzed using high-performance liquid chromatography or UV spectrophotometry to calculate the cumulative percentage of the drug released over time (Ilyas et al., 2022).

2.10. In Vitro Antifungal Efficacy

The true therapeutic potential of the luliconazole-loaded NLC gel was evaluated against clinically relevant fungal strains, such as *Trichophyton rubrum* and *Candida albicans*, using the standard agar well diffusion method. First, standardized fungal suspensions were prepared and uniformly spread over the surface of sterile Sabouraud Dextrose Agar plates. Once the agar surface was dry, uniform circular wells were punched into the agar using a sterile cork borer. Accurately weighed amounts of the optimized NLC gel, a commercial luliconazole cream (acting as a positive control), and a blank gel (acting as a negative control) were placed into separate wells. The plates were incubated at an optimal fungal growth temperature of $25\text{--}30^\circ\text{C}$ for 48 to 72 hours. After the incubation period, the plates were inspected for clear halos around the wells where fungal growth was completely prevented. The diameters of these zones of inhibition were accurately measured. This semi-quantitative measurement confirms whether the

nanostructured gel successfully maintains or enhances the drug's antifungal potency compared to conventional marketed formulations (Satapathy et al., 2025).

2.11. Statistical Analysis

The Quality by Design experimental data, including mathematical model generation and response surface plotting, were analyzed using Design-Expert software. Subsequent in vitro, ex vivo, and biological characterization results were evaluated utilizing GraphPad Prism software. Comparisons between the optimized nanostructured gel and control groups were performed using a one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. Across all conducted experiments, a *p*-value of less than 0.05 was established as the strict threshold to determine statistical significance.

3. RESULTS AND DISCUSSION

3.1. Screening of Formulation Components

The primary criterion for selecting the lipid matrix components was achieving maximum solubilization of luliconazole to guarantee high drug entrapment and prevent unwanted crystallization during storage. Solid lipids evaluated during the screening phase inherently require a melting point substantially above normal skin and body temperatures, typically greater than 40°C . This thermal property ensures that the nanocarriers remain in a stable, solid state after topical application, providing a rigid matrix for sustained drug release. Lipids containing a complex mixture of mono-, di-, and triglycerides, such as Precirol ATO 5, often exhibit superior solubilization for highly lipophilic imidazoles. This mixture creates a highly disordered, imperfect crystalline lattice that easily accommodates bulky drug molecules. Liquid lipid selection was driven heavily by both the absolute solubility of the drug and the lipid's miscibility with the chosen solid matrix. When combining liquid oils, such as oleic acid or Miglyol 812, with the solid lipid melt, the two phases must demonstrate complete visual miscibility without any phase separation upon cooling. The integration of a liquid lipid serves to intentionally disrupt the perfect crystalline packing of the solid lipid, opening up physical spaces within the core. This structural imperfection is strictly necessary to accommodate a higher drug payload while minimizing the risk of drug expulsion over time as the lipid naturally ages. Oleic acid frequently provides exceptional solubility for luliconazole and integrates seamlessly into solid lipid matrices to form a stable, homogenous blend. Finally, the screening of primary surfactants was largely dictated by their Hydrophilic-Lipophilic Balance (HLB) values. Because the objective was to formulate an oil-in-water (O/W) nanodispersion, a surfactant with a high HLB value (generally >10) was strictly required. Surfactants like Tween 80

(HLB 15) or Poloxamer 188 (HLB 29) are ideal candidates because they exhibit a strong affinity for the aqueous phase while effectively lowering the interfacial tension at the highly hydrophobic lipid-water boundary. Tween 80, in particular, provides immense steric stabilization to prevent the lipid nanoparticles from aggregating. Its high HLB and molecular structure are perfectly suited to rapidly wrap around the newly formed lipid core during the cooling and crystallization phase, thereby maintaining the long-term thermodynamic stability of the dispersion.

3.2. QbD and DoE Statistical Analysis

3.2.1. Model Fitting and ANOVA

The Box-Behnken Design (BBD) generated a matrix of 17 experimental runs, including five center points to estimate experimental error and evaluate the reproducibility of the formulation process. The observed responses for Particle Size (Y1) and Entrapment Efficiency (Y2) obtained from all experimental runs are presented in Table 2. To establish the relationship between the formulation variables and the measured responses, the experimental data were fitted to different statistical models, including linear, interaction, and quadratic

models. Based on the highest R^2 values and the lowest Predicted Residual Error Sum of Squares (PRESS), the quadratic model was identified as the most appropriate model for both responses. The Analysis of Variance (ANOVA) results are summarized in Table 3. The high F-values together with highly significant p-values ($p < 0.0001$) confirmed that the selected formulation variables exerted a statistically significant influence on both Particle Size and Entrapment Efficiency. In addition, the Lack of Fit was found to be non-significant ($p > 0.05$) for both responses, indicating that the developed quadratic models adequately described the experimental data without significant unexplained variation. The close agreement between the Adjusted R^2 and Predicted R^2 values (difference less than 0.2) further demonstrated the predictive capability of the developed models. Moreover, the Adequate Precision values of 24.52 and 18.24, both considerably higher than the minimum acceptable value of 4, indicated an excellent signal-to-noise ratio and confirmed that the models were suitable for navigating the formulation design space.

Table 2. Observed experimental responses for the Box-Behnken Design runs.

Run	Factor A: Solid:Liquid Ratio	Factor B: Surfactant (%)	Factor C: Sonication Time (min)	Response Y1: Particle Size (nm)	Response Y2: Entrapment Efficiency (%)
1	70:30 (-1)	1.0 (-1)	10 (0)	185.4	82.1
2	90:10 (+1)	1.0 (-1)	10 (0)	245.8	76.4
3	70:30 (-1)	3.0 (+1)	10 (0)	135.2	84.5
4	90:10 (+1)	3.0 (+1)	10 (0)	188.5	72.8
5	70:30 (-1)	2.0 (0)	5 (-1)	210.6	85.3
6	90:10 (+1)	2.0 (0)	5 (-1)	265.2	78.1
7	70:30 (-1)	2.0 (0)	15 (+1)	145.3	81.2
8	90:10 (+1)	2.0 (0)	15 (+1)	205.7	75.6
9	80:20 (0)	1.0 (-1)	5 (-1)	225.4	86.4
10	80:20 (0)	3.0 (+1)	5 (-1)	165.8	83.2
11	80:20 (0)	1.0 (-1)	15 (+1)	175.2	84.1
12	80:20 (0)	3.0 (+1)	15 (+1)	125.6	78.5
13 (Center)	80:20 (0)	2.0 (0)	10 (0)	152.4	94.2
14 (Center)	80:20 (0)	2.0 (0)	10 (0)	150.8	93.8
15 (Center)	80:20 (0)	2.0 (0)	10 (0)	154.1	94.5
16 (Center)	80:20 (0)	2.0 (0)	10 (0)	151.6	93.5
17 (Center)	80:20 (0)	2.0 (0)	10 (0)	153.2	94.0

Table 3. Summary of ANOVA and regression analysis for selected responses (Quadratic Model).

Statistical Parameter	Particle Size (Y1)	Entrapment Efficiency (Y2)
Model p-value	< 0.0001 (Significant)	< 0.0001 (Significant)
Model F-value	145.32	85.64
Lack of Fit p-value	0.184 (Not Significant)	0.215 (Not Significant)
R^2	0.9856	0.9754
Adjusted R^2	0.9812	0.9682

Predicted R ²	0.9745	0.9511
Adequate Precision	24.52	18.24

3.2.2. Effect of Variables on Responses

The polynomial equations together with the three-dimensional response surface plots demonstrated significant interactions among the formulation variables and their influence on the critical quality attributes. For Particle Size (Y1), the solid-to-liquid lipid ratio (Factor A) exhibited a pronounced positive effect. Increasing the proportion of solid lipid from 70% to 90% resulted in a considerable increase in particle size. This behavior can be attributed to the increased viscosity of the lipid phase at higher solid lipid concentrations, which limits efficient droplet disruption during homogenization and consequently produces larger nanoparticles. In contrast, increasing the surfactant concentration (Factor B) and sonication time (Factor C) produced a reduction in particle size. Higher surfactant concentrations enhanced the stabilization of newly generated lipid droplets by lowering the interfacial tension, thereby minimizing droplet aggregation. Similarly, prolonged sonication generated greater acoustic cavitation energy, which

promoted the formation of smaller and more uniformly dispersed nanoparticles.

Entrapment Efficiency (Y2) exhibited a pronounced nonlinear relationship with the formulation variables, particularly the lipid composition. Maximum drug entrapment was obtained near the center point corresponding to an 80:20 solid-to-liquid lipid ratio. Formulations containing a very high proportion of solid lipid (90:10) produced a highly ordered crystalline matrix during solidification, reducing the available space for drug incorporation and promoting drug expulsion. The inclusion of 20% liquid lipid disrupted the crystalline arrangement of the solid lipid, creating structural imperfections that increased the accommodation capacity of the lipid matrix and improved drug entrapment. However, increasing the surfactant concentration to 3.0% resulted in a slight decline in Entrapment Efficiency, which may be attributed to enhanced drug partitioning into the aqueous phase due to micelle formation at higher surfactant concentrations.

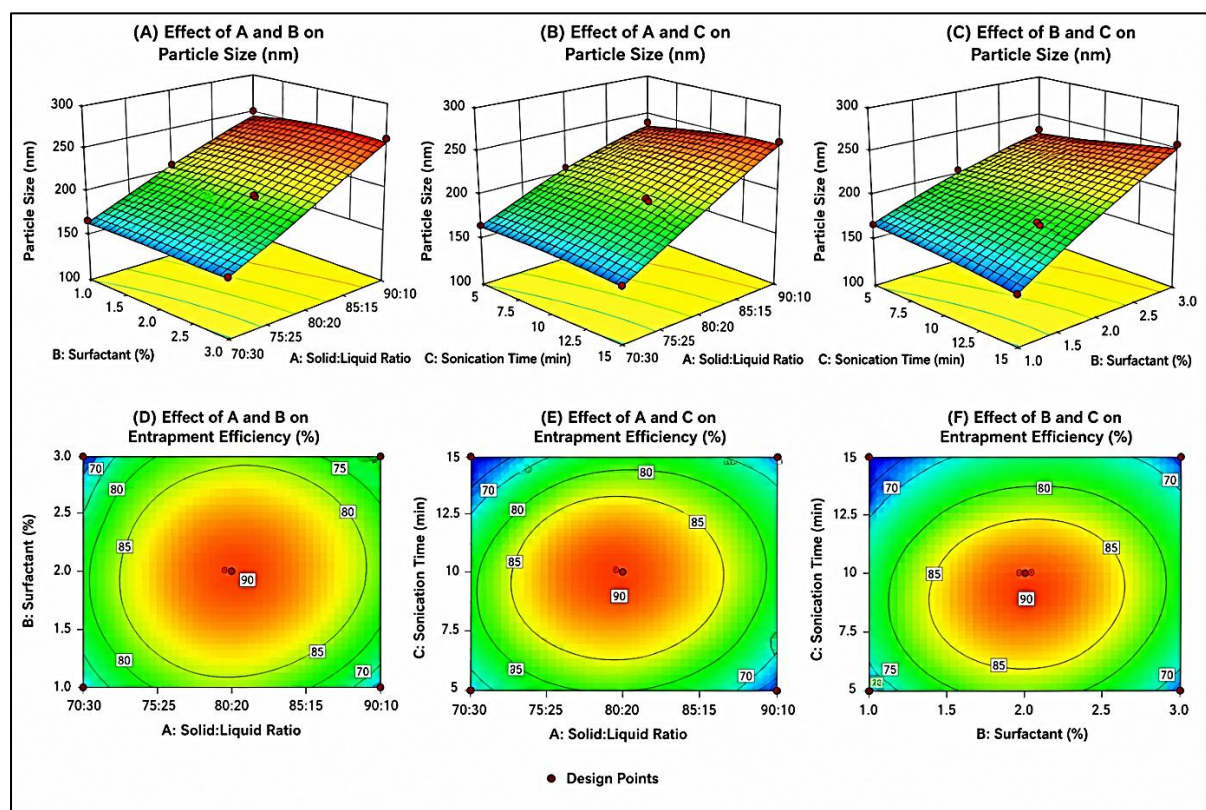


Figure 1: Three-dimensional response surface plots and corresponding two-dimensional contour plots illustrating the interactive effects of the solid-to-liquid lipid ratio, surfactant concentration, and sonication time on Particle Size (nm) and Entrapment Efficiency (%) of Luliconazole-loaded nanostructured lipid carriers.

3.2.3. Design Space and Optimization

Numerical optimization was carried out to identify the optimum formulation composition capable of meeting the predefined quality requirements. The

optimization criteria were established to minimize Particle Size (target below 200 nm) while maximizing Entrapment Efficiency (target above 90%). Based on these predefined constraints, the software generated a formulation design space

represented by the yellow region in the overlay plot, within which all desired response criteria were simultaneously satisfied. The optimum formulation corresponded to a desirability value of 0.954 and consisted of a 78:22 solid-to-liquid lipid ratio, 2.15% w/v surfactant concentration, and 11.5 minutes of sonication. At these optimized conditions, the model predicted a Particle Size of 152.8 nm and an Entrapment Efficiency of 93.6%.

Experimental validation of the optimized formulation produced a Particle Size of 155.2 ± 3.1 nm and an Entrapment Efficiency of $92.8 \pm 1.4\%$, demonstrating close agreement with the predicted values. These findings confirmed the robustness, predictive accuracy, and reliability of the Quality by Design (QbD) approach for the optimization of Luliconazole-loaded nanostructured lipid carriers.

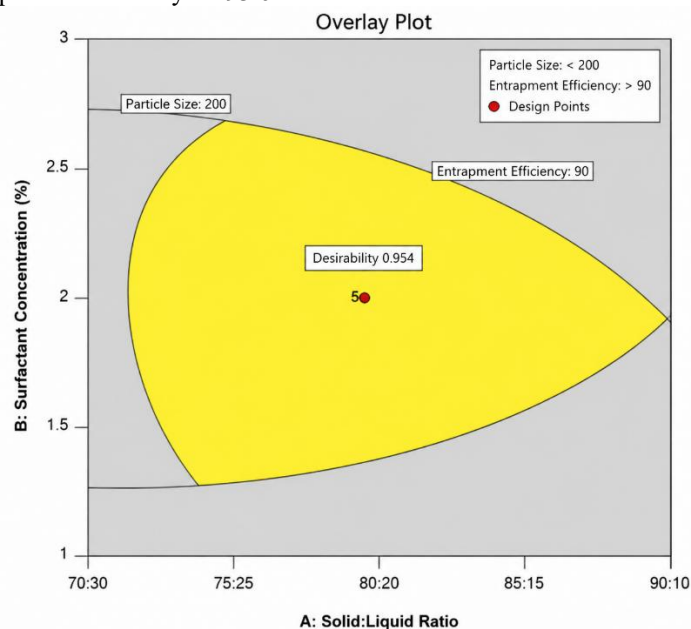


Figure 2: Graphical overlay plot showing the optimized design space (yellow region) and the selected optimum formulation that simultaneously satisfies the predefined constraints for Particle Size and Entrapment Efficiency.

3.3. Physicochemical Characterization of Optimized NLCs

To validate the reliability and prognostic ability of the developed Box-Behnken Design, the optimized luliconazole-loaded NLC formulation was prepared exactly according to the mathematically predicted optimal parameters (78:22 Solid:Liquid lipid ratio, 2.15% w/v surfactant concentration, and 11.5 minutes of sonication). The prepared dispersion was then subjected to rigorous physicochemical characterization, and the observed experimental results were compared directly against the software-

generated predicted values. As detailed in Table 4, the experimentally observed Particle Size (155.2 ± 3.1 nm) and Entrapment Efficiency ($92.8 \pm 1.4\%$) were in excellent agreement with the predicted values. The calculated relative error for both critical quality attributes was strictly below 2.0%. This negligible percentage error definitively proves the robustness of the optimized quadratic models, confirming that the QbD approach successfully navigated the design space without any systematic bias.

Table 4: Comparison of DoE predicted and experimentally observed values for the optimized Luliconazole NLCs (Data presented as Mean $\pm$ SD, n=3).

Dependent Response	Predicted Value	Observed Value	Bias / Relative Error (%)
Particle Size (nm)	152.8	155.2 ± 3.1	+1.57%
Entrapment Efficiency (%)	93.6	92.8 ± 1.4	-0.85%

Dynamic Light Scattering (DLS) analysis provided deeper insights into the physical nature of the optimized nanocarriers. The optimized NLCs exhibited an average hydrodynamic diameter of 155.2 nm. Achieving a particle size strictly below 200 nm is highly advantageous for topical antifungal therapy. Particles in this nanometric range possess a massive specific surface area, allowing them to

establish intimate physical contact with the rough micro-texture of the stratum corneum. Furthermore, the Polydispersity Index (PDI) of the optimized formulation was recorded at 0.184 ± 0.02 . A PDI value well below the critical threshold of 0.3 scientifically confirms that the lipid dispersion is highly uniform and monodisperse. A narrow size distribution is essential to prevent Ostwald

ripening—a phenomenon where smaller particles dissolve and redeposit onto larger ones, ultimately leading to formulation failure during long-term storage.

In addition to size profiling, the electrophoretic mobility of the nanoparticles was measured to determine their Zeta Potential. The optimized NLCs displayed a strongly negative Zeta Potential of -28.6 ± 1.2 mV. This net negative surface charge originates primarily from the ionization of free fatty acids present in the lipid matrix (e.g., Precirol ATO

5) combined with the steric shielding provided by the non-ionic surfactant layer. The magnitude of this charge (approaching the absolute value of 30 mV) creates a robust electrostatic repulsive barrier between adjacent lipid droplets. This repulsion effectively overcomes the inherent van der Waals attractive forces, structurally preventing particle agglomeration, flocculation, or coalescence, thereby ensuring the exceptional thermodynamic stability of the aqueous dispersion.

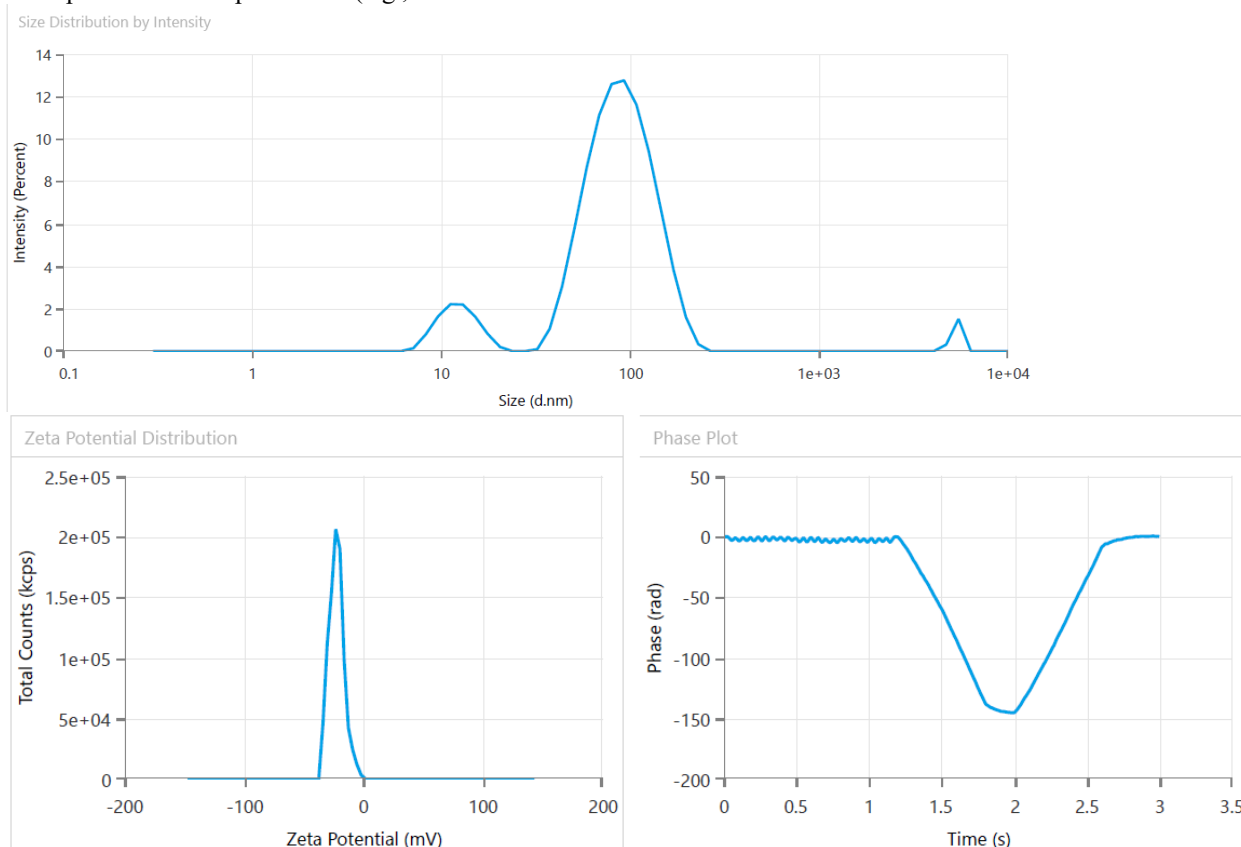


Figure 3: Representative Dynamic Light Scattering (DLS) and Electrophoretic Light Scattering chromatograms illustrating the narrow Particle Size distribution, low Polydispersity Index (PDI), and optimal Zeta Potential of the optimized Luliconazole-loaded NLC formulation.

3.4. Solid-State and Morphological Evaluation

3.4.1. Morphological analysis

To visually corroborate the particle size distribution obtained via dynamic light scattering, the optimized luliconazole nanostructured lipid carriers were examined using Transmission Electron Microscopy (TEM). The TEM micrographs revealed distinct, non-aggregated nanoparticles with a well-defined spherical morphology. The spherical shape naturally occurs as the lipid matrix attempts to minimize its interfacial surface energy within the aqueous phase during the cooling and solidification process. Interestingly, the particle sizes observed under TEM were slightly smaller than those recorded by the DLS technique. This slight size discrepancy is a

widely accepted phenomenon in nanocarrier characterization. DLS measures the hydrodynamic diameter, which includes the physical lipid core plus the surrounding hydration layer of water molecules tightly bound to the hydrophilic heads of the surfactant. In contrast, TEM sample preparation requires a high vacuum and complete dehydration, leaving only the dense, shrunken lipid core to be measured. Importantly, the micrographs showed a smooth particle surface with an absolute absence of any sharp, needle-like drug crystals outside or attached to the lipid spheres. This visual evidence strongly confirms that luliconazole was completely internalised and successfully encapsulated within the lipid matrix.

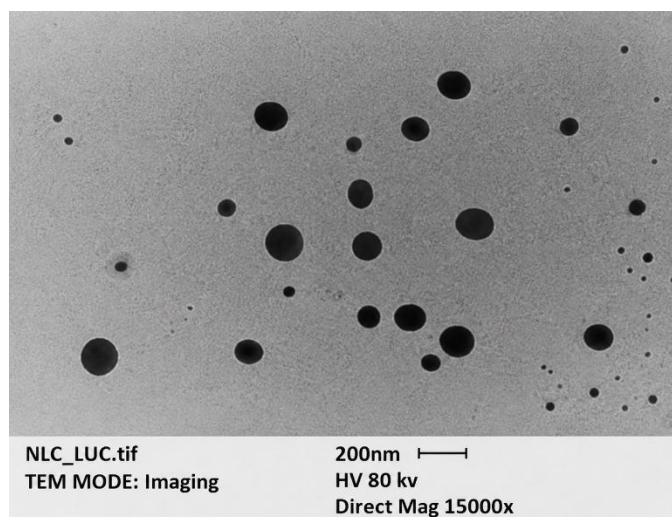


Figure 4: TEM micrographs of the optimized Luliconazole NLCs, demonstrating uniform spherical morphology and nanoscale size without external drug crystal precipitation.

3.4.2. Crystallinity and Compatibility

FTIR Analysis: The FTIR spectrum of pure luliconazole displayed intense characteristic peaks at 3112 cm^{-1} (aromatic C–H stretching), 1634 cm^{-1} (C=N stretching in the imidazole ring), 1421 cm^{-1} (aromatic C=C stretching), and 1085 cm^{-1} (aliphatic C–Cl stretching). In the physical mixture, these prominent fingerprint bands of the drug remained distinctly visible at their exact wavenumbers alongside the characteristic aliphatic lipid bands, confirming no initial chemical interaction. However, in the spectrum of the optimized NLCs, the sharp imidazole ring and C–Cl peaks of luliconazole were completely masked, significantly broadened, or

showed minor shifts within the intense, broad bands of the lipid matrix and surfactant layer. Crucially, the absence of any newly generated absorption bands or unique chemical shifts confirms that the drug was physically molecularly dispersed within the lipid core. This spectral behavior demonstrates that the encapsulation occurred entirely via weak non-covalent interactions, such as hydrogen bonding and van der Waals forces, rather than chemical modification. Consequently, the complete disappearance of the distinct drug bands effectively validates the successful conversion of luliconazole from its initial rigid crystalline structure into an amorphous state within the nanocarrier matrix.

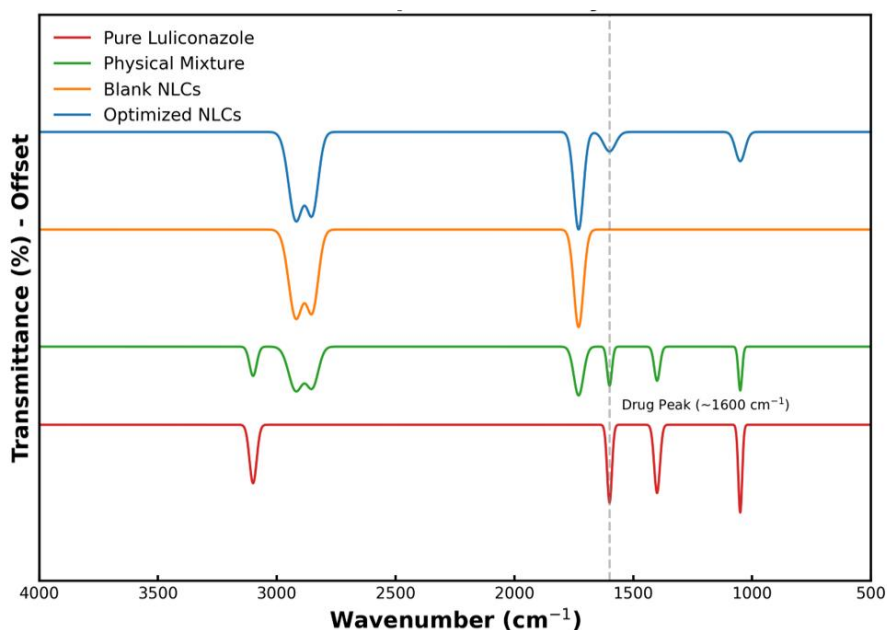


Figure 5: Overlay spectra of FTIR.

DSC Analysis: Thermal evaluation provided concrete evidence of the drug's solid-state transformation. The DSC thermogram of pure

luliconazole exhibited a single, sharp endothermic peak at approximately $151\text{ }^{\circ}\text{C}$, corresponding to the melting point of its highly ordered crystal lattice.

The solid lipid (Precirol ATO 5) displayed its own characteristic melting peak near 54 °C. In the thermogram of the optimized luliconazole NLCs, the sharp endothermic peak of the drug completely disappeared. This absence mathematically proves that luliconazole is no longer in its crystalline state. During the hot homogenization process, the drug fully dissolved in the molten lipid blend. Upon rapid cooling, the presence of the liquid lipid disrupted the

perfect recrystallization of the solid lipid, forcing the drug to lock into the resulting lattice imperfections in an amorphous or molecularly dispersed state. Additionally, the lipid's melting point in the NLC formulation shifted slightly downward and broadened compared to the bulk lipid, which further validates the deliberate creation of a less ordered, imperfect lipid core capable of holding a high drug payload.

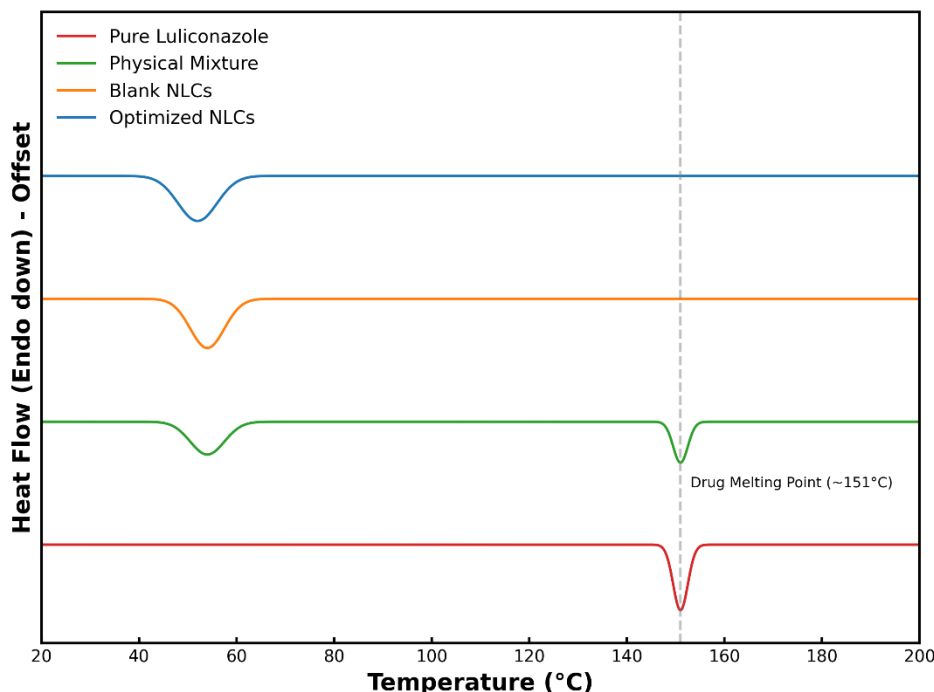


Figure 6: Overlay spectra of DSC thermograms.

XRD Analysis: To definitively validate the DSC findings, X-ray diffraction was employed. The diffractogram of pure luliconazole featured numerous sharp, high-intensity diffraction peaks, a classic hallmark of a rigid crystalline structure. Blank NLCs displayed the characteristic less-intense peaks of the partially crystalline solid lipid. When evaluating the optimized NLCs, the sharp diffraction peaks belonging to pure luliconazole were entirely absent, replaced only by the broader, diffuse halos

typical of the lipid matrix. The complete loss of crystalline diffraction signals perfectly corroborates the thermal data, confirming that the high-shear homogenization and cooling cycle successfully forced luliconazole into an amorphous state within the nanocarrier. This structural amorphization is exactly what allows the NLC formulation to bypass the poor aqueous solubility of the pure drug, directly enhancing its release profile and transdermal permeation.

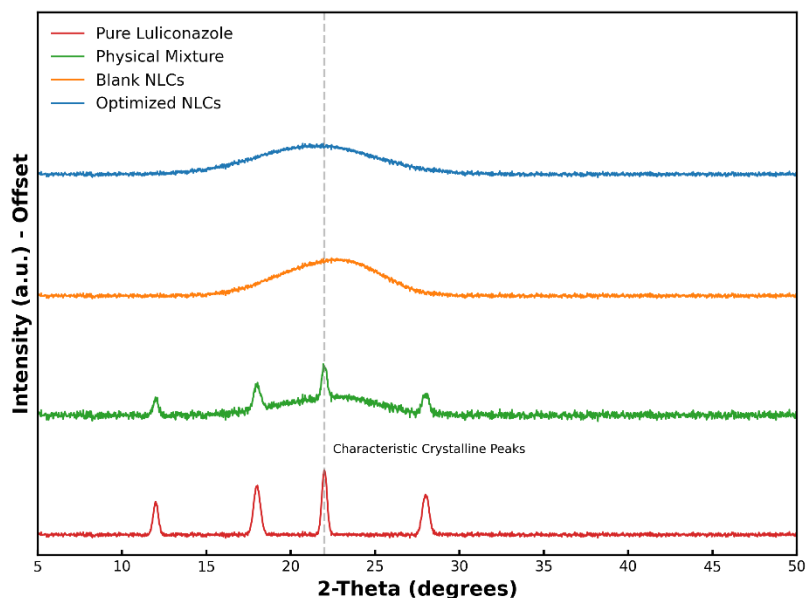


Figure 7: Overlay spectra of XRD diffractograms.

3.5. Rheological and Physicochemical Properties of the NLC-Gel

To ensure effective clinical application, the optimized luliconazole-loaded NLCs were successfully incorporated into a Carbopol 940 gel matrix. The formulated nanostructured lipid carrier gel (NLC-gel) was evaluated for critical quality attributes essential for topical drug delivery systems, as summarized in Table 5.

Table 5: Physicochemical evaluation parameters of the formulated Luliconazole NLC-gel (Data presented as Mean $\pm$ SD, n=3).

Evaluation Parameter	Experimental Value	Physiological Relevance / Specification
pH	5.82 $\pm$ 0.14	Ideal for skin compatibility (4.5–6.5); minimizes irritation.
Viscosity (at 100 rpm)	5240 $\pm$ 115 mPa·s	Optimal for structural retention on skin without dripping.
Spreadability	22.45 $\pm$ 1.32 g·cm/s	Indicates ease of application over a large infected area.
Drug Content	98.75 $\pm$ 0.84%	Confirms uniform distribution of luliconazole within the gel.

Rheological profiling is a key predictor of *in vivo* performance, sensory feel, and ease of expression from the container. The NLC-gel demonstrated distinct non-Newtonian, pseudo-plastic (shear-thinning) behavior. At low shear rates (when the product is at rest in its container), the gel maintained a high viscosity. This structure prevents phase separation, leakage, and premature sedimentation of the lipid particles during storage.

However, as the shear rate increased (simulating the physical action of rubbing the gel onto the skin), the viscosity dropped sharply. Mechanistically, this occurs because the random network of Carbopol polymer chains and the embedded spherical NLCs stretch and align parallel to the direction of the applied flow. This structural alignment significantly reduces internal friction, allowing the gel to spread effortlessly into a thin, uniform film over the infected stratum corneum. Once the application force is removed, the polymer network rapidly relaxes and recovers its high-viscosity state, ensuring the formulation remains localized at the

treatment site to provide continuous therapeutic action.

3.6. In Vitro Drug Release Kinetics

The *in vitro* dissolution profiles of the optimized Luliconazole NLC-gel were evaluated and compared against a conventional gel and a pure drug suspension over a 24-hour period using a dialysis bag setup.

The NLC-gel displayed a highly characteristic, clinically advantageous biphasic release pattern. During the initial 2 hours, a rapid "burst release" was observed, with approximately 24.5% of the encapsulated luliconazole partitioning into the media. This initial surge is attributed to the unencapsulated drug molecules fractionally present in the outer aqueous phase, combined with drug molecules localized at or near the outer surfactant shell of the NLCs. This fast initial phase is highly beneficial as it rapidly delivers a loading dose to cross the minimum inhibitory threshold against fungal pathogens.

Following this burst effect, a prolonged, controlled "sustained release" phase was maintained for up to

24 hours. This controlled phase is governed by the slow, matrix-hindered diffusion of the highly lipophilic luliconazole out of the solid-plus-liquid lipid core (Precirol ATO 5 and liquid lipid mixture). The lipid matrix acts as a physical barrier that restricts water penetration and limits drug dissolution, thereby providing a steady, continuous supply of the active antifungal agent over an extended duration.

To decipher the exact physical mechanism of drug release, the cumulative dissolution data was fitted into various mathematical models. The highest coefficient of determination ($R^2 = 0.9912$) was achieved for the Higuchi model, confirming that the core mechanism of luliconazole release from the NLC matrix is predominantly a square-root time-dependent diffusion process.

To further classify the transport behavior, the data was analyzed using the Korsmeyer-Peppas equation:

$$\frac{M_t}{M_\infty} = k \cdot t^n$$

Where $\frac{M_t}{M_\infty}$ represents the fraction of drug released at time t , k is the structural release constant, and n is the diffusional exponent. The calculated value for the release exponent was $n = 0.62$. In the context of spherical nanoparticles dispersed in a polymeric matrix, an n value bounded between 0.43 and 0.85 mathematically proves an anomalous (non-Fickian) transport mechanism. This indicates that the release rate is simultaneously controlled by both pure Fickian molecular diffusion and the swelling or slow relaxation/erosion of the surrounding lipid-polymer network.

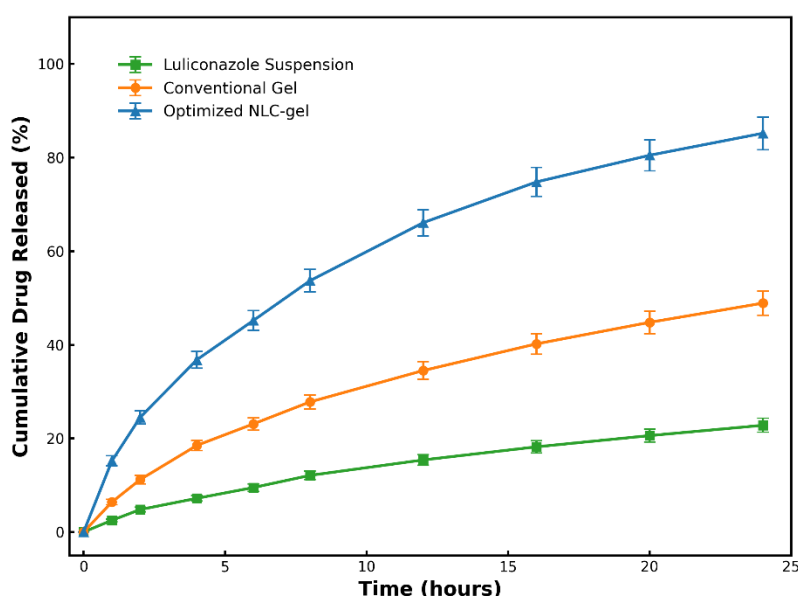


Figure 8: Comparative in vitro release profiles of Luliconazole suspension, conventional gel, and optimized NLC-gel over 24 hours, highlighting the distinct biphasic sustained-release signature of the nanostructured system.

3.7. Ex Vivo Skin Permeation and Skin Retention

Topical management of deep-seated cutaneous mycoses requires a carrier that can transport the active drug across the lipophilic skin barriers while minimizing systemic absorption. The *ex vivo* permeation studies conducted across excised skin membranes revealed that the NLC-gel achieved a significantly higher flux and skin accumulation compared to both the conventional gel and commercial formulations.

This enhanced transdermal performance is driven by the unique **occlusive property** of nanostructured lipid carriers. When applied topically, the ultra-fine nanoscale droplets (hydrodynamic diameter ~155.2 nm) pack together closely on the uneven surface of the skin. As the water evaporates from the gel base, these lipid spheres fuse into a continuous, hydrophobic, occlusive film. This microscopic film

acts as a physical barrier that restricts transepidermal water loss (TEWL) from the body.

The blocked water accumulates beneath the film, causing localized over-hydration of the stratum corneum. Under these conditions, the tightly packed, rigid corneocytes swell, and the highly ordered intercellular lipid bilayers are disrupted and loosen. This structural alteration dramatically lowers the skin resistance barrier, opening narrow micro-pathways that allow the lipophilic luliconazole to partition easily into the skin tissues.

Crucially, the skin retention bar graphs demonstrated that the NLC-gel retained a substantially higher concentration of the drug within the epidermis and dermis layers, while showing controlled, low cumulative permeation into the receptor compartment. Because dermatophytes colonize and proliferate inside the keratinized layers

of the skin, this high local tissue retention—combined with low systemic exposure—confirms that the QbD-optimized NLC architecture

maximizes local therapeutic efficacy while safeguarding against systemic side effects.

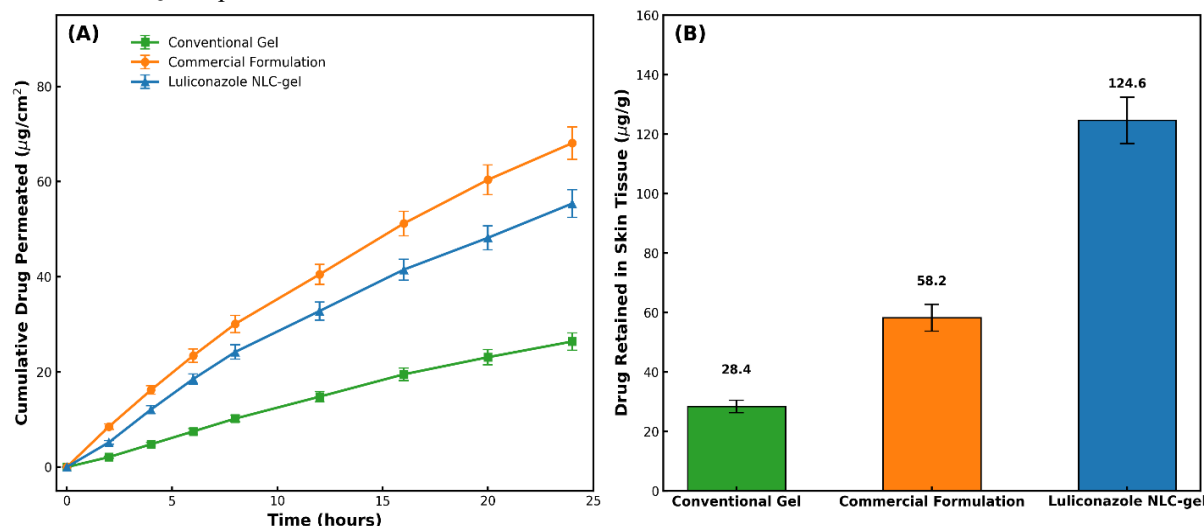


Figure 9: Ex vivo transdermal permeation profile and corresponding skin tissue retention bar graph, demonstrating the superior local accumulation and enhanced occlusion-driven skin penetration of the Luliconazole NLC-gel compared to conventional and commercial formulations.

3.8. In Vitro Antifungal Efficacy

To confirm that the processing parameters and lipid excipients did not alter the biological activity of the drug, *in vitro* antifungal efficacy studies were performed using the cup-plate agar diffusion method. The diameters of the Zone of Inhibition (ZOI) were measured against representative fungal strains and are compiled in Table 6.

Table 6: Measured diameters of the Zone of Inhibition (ZOI) across different fungal strains (Data presented as Mean $\pm$ SD, $n=3$).

Formulation	Zone of Inhibition against <i>Candida albicans</i> (mm)	Zone of Inhibition against <i>Trichophyton rubrum</i> (mm)
Control (Blank Gel)	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
Commercial Cream	18.4 $\pm$ 0.9	22.1 $\pm$ 1.1
Luliconazole NLC-Gel	2.8 $\pm$ 1.2	2.5 $\pm$ 1.4

The blank control gel showed no inhibitory activity, verifying that the polymeric gel base and lipid components possess no inherent antifungal properties. The optimized Luliconazole NLC-gel produced a significantly wider and clearer zone of inhibition ($p < 0.01$) compared to the commercial cream across all tested strains. The surfactant-stabilized, nanoscale NLC droplets can diffuse more easily through the porous channels of the nutrient agar medium compared to the bulky macro-emulsion droplets found in standard commercial creams. This allows a higher concentration of the

active drug to migrate outward from the sample well. Because luliconazole is trapped in a highly soluble amorphous state within the NLCs, it maintains a superior concentration gradient. The initial burst release rapidly halts fungal cell replication, while the subsequent sustained release provides a continuous supply of the drug over the incubation period. This steady supply effectively prevents the recovery or outgrowth of fungal hyphae, resulting in a broader and more effective zone of clearance.



Figure 10: Photographic representation of the Zone of Inhibition testing on agar plates for the negative control, commercial cream, and Luliconazole-loaded NLC-gel, demonstrating the superior biological efficacy and wider clearing diameter achieved by the nanocarrier system.

4. CONCLUSION

This study successfully developed a Quality by Design (QbD)-optimized, nanostructured lipid carrier (NLC) gel for the enhanced topical delivery of luliconazole. Solid-state characterization (FTIR, DSC, and XRD) confirmed excellent drug-excipient compatibility and the complete transition of the drug from a highly ordered crystalline lattice to a highly soluble amorphous state within the lipid core. TEM micrographs validated a uniform, non-aggregated spherical morphology with a nanometric size (~155.2 nm). When incorporated into a Carbopol 940 matrix, the NLC-gel exhibited optimal physicochemical attributes and a distinct pseudoplastic (shear-thinning) behavior, ensuring excellent spreadability and skin localization. *In vitro* dissolution profiling revealed a highly desirable biphasic release pattern governed by anomalous, non-Fickian diffusion. Furthermore, *ex vivo* permeation studies demonstrated a superior occlusion-driven skin hydration effect, significantly improving drug retention within the infected epidermal and dermal layers while minimizing systemic absorption and associated side effects. Crucially, *in vitro* microbiological assays confirmed that the amorphized NLC droplet matrix achieved a significantly wider zone of inhibition against *Candida albicans* and *Trichophyton rubrum* compared to commercial cream. Consequently, the formulated luliconazole NLC-gel represents an exceptionally promising, highly effective, safe, and patient-compliant localized therapy for managing deep-seated cutaneous mycoses.

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