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Original Article

Nanoemulsion-Based Delivery System for Naftifine Hydrochloride: A Promising Approach for Solubility Enhancement

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ABSTRACT

Aim/Background: Naftifine hydrochloride, a BCS Class IV antifungal agent, suffers from poor aqueous solubility, limiting its therapeutic efficacy. This study aims to enhance its solubility using a nanoemulsion-based drug delivery system. **Materials and Methods:** A systematic formulation approach identified oleic acid, Kolliphor® RH40, and Transcutol-P® as optimal components. Pseudo ternary phase diagrams have been utilized to identify and select the optimal emulsification zone and a 3^2 factorial design optimized the formulation. **Results:** The nanoemulsion demonstrated improved solubility, thermodynamic stability, and uniform globule size. **Conclusion:** These results indicate that nanoemulsion technology holds great potential for improving both the solubility and bioavailability of Naftifine hydrochloride for effective topical antifungal therapy.

Keywords: Naftifine hydrochloride, Nanoemulsion, 3^2 factorial design, Solubility enhancement.

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INTRODUCTION

Naftifine hydrochloride, a synthetic allylamine antifungal agent, is widely utilized in managing superficial fungal infections, including those caused by *Candida* species and *Trichophyton rubrum*.[1] Despite its potent antifungal activity, its therapeutic efficacy is significantly limited due to poor aqueous solubility and low permeability, classifying it as a Biopharmaceutical Classification System (BCS) Class IV drug.[2] Effective topical therapy requires the drug to permeate the stratum corneum and reach deeper skin layers, where fungal pathogens typically reside. However, the highly lipophilic nature of Naftifine hydrochloride (log P: 5.4) often results in its accumulation in the outermost layer of the skin, which restricts drug transport to the infection site and reduces clinical effectiveness.[3,4]

The increasing incidence of dermatophytic and yeast infections, often aggravated by immunosuppression, antibiotic misuse, or climate changes, calls for more effective and targeted antifungal therapies. Current topical formulations, such as creams and gels, often suffer from poor drug retention, instability, and insufficient permeation through the skin barrier. Thus, there is a growing interest in advanced delivery systems that can overcome these challenges and enhance the localized delivery of antifungal agents.[5]

Nanoemulsions have emerged as a promising class of drug delivery systems to address solubility and penetration barriers associated with hydrophobic drugs. These thermodynamically or kinetically stable dispersions consist of nanoscale droplets typically in the range of 20-200 nm, formed using oil, water, surfactants, and co-surfactants.[3] Their small droplet size and large surface area enhance drug solubilization, improve contact with the skin surface, and facilitate penetration through the stratum corneum. Moreover, nanoemulsions have shown potential in enhancing drug retention in skin layers while minimizing systemic absorption, thereby improving local bioavailability and reducing adverse effects.[6,7]

Nanoemulsions, owing to their nanoscale droplet size (typically 20-200 nm), provide several critical benefits over conventional formulations. Their small droplet size results in a large surface area, which significantly enhances drug solubilization and bioavailability. Unlike microemulsions, nanoemulsions are

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kinetically stable but thermodynamically unstable, which allows easier preparation without requiring high-energy input or toxic solvents. This stability facilitates long shelf life and maintains drug integrity during storage. Additionally, nanoemulsions possess high optical clarity and low viscosity, which improve patient compliance when applied topically.

The flexibility in composition, including the choice of oils, surfactants, and co-surfactants, allows for tailoring physicochemical properties such as droplet size, charge, and release profile, thus optimizing drug delivery to target tissues. Furthermore, nanoemulsions can bypass the skin's natural barrier by enhancing penetration through the stratum corneum via multiple mechanisms, including lipid disruption and improved hydration of skin layers. This results in enhanced localized drug concentrations with reduced systemic exposure, minimizing side effects.[5,6]

Moreover, nanoemulsions have been reported to exhibit inherent antimicrobial and anti-inflammatory properties when formulated with bioactive oils, which may synergistically enhance the therapeutic effect of antifungal drugs. Their ease of scale-up and cost-effectiveness also make nanoemulsions an attractive platform for commercial topical formulations. Collectively, these attributes position nanoemulsions as promising carriers to overcome the limitations of poorly soluble and permeable drugs like Naftifine hydrochloride.[8,9]

Recent research has demonstrated the versatility of nanoemulsion systems for delivering antifungal agents such as clotrimazole, miconazole, and terbinafine. However, limited studies have been reported for Naftifine hydrochloride in nanoemulsion systems, especially those focusing on biocompatible and skin-friendly components. Furthermore, earlier formulations have relied heavily on synthetic surfactants, which may cause irritation or toxicity upon prolonged use.[5]

This study aims to formulate and characterize a novel nanoemulsion-based delivery system for Naftifine hydrochloride using oils and surfactants, such as oleic acid (as oil phase) and Kolliphor® RH40 (as surfactant), which are known for their antimicrobial, anti-inflammatory, and skin-penetrating properties. The formulation was optimized using Pseudo ternary phase diagrams to determine the most stable region, followed by comprehensive evaluation of physicochemical properties, *in vitro* drug release, skin permeation, and antifungal efficacy.[9]

To the best of our knowledge, this is the study to develop a nanoemulsion-based delivery system incorporating Naftifine hydrochloride with oleic acid, Kolliphor® RH40, and Transcutol P®. This specific combination not only represents a novel approach for enhancing the solubility and delivery of Naftifine hydrochloride but also offers a sustainable and biocompatible alternative to conventional synthetic excipients. The synergistic action of the selected components is expected to significantly enhance antifungal efficacy. The formulated nanoemulsion aims to address the limitations of existing topical treatments by promoting deeper skin penetration, prolonging drug release, and ultimately improving therapeutic outcomes in the management of superficial fungal infections.

Alghaith *et al*, developed and optimised the nanoemulsion loaded with clove oil-naftifine antifungal for the management of tinea. Clove oil possesses good anti-inflammatory and antifungal properties that can support naftifine action. Box-Behnken designs were used to prepare plain and naftifine loaded SNEDDS. The designed nanoemulsions containing a combination of clove oil and naftifine could be considered promising delivery systems for the treatment of tinea.[10] Erdal *et al* studied *In vitro* skin permeation and antifungal activity of naftifine microemulsions[11] also, Gusliakova *et al* explained the Transdermal platform for the delivery of the antifungal drug Naftifine hydrochloride based on porous vaterite particles.[12] Stefan *et al*, detected the relevance of Naftifine hydrochloride in the stratum corneum up to four weeks following the last application of naftifine cream and 2% gel.[13]

MATERIALS AND METHODS

Materials

Naftifine hydrochloride was generously provided by Baoji Guokang Bio-Technology Co., Ltd. (China). Transcutol P® (Diethylene glycol monoethyl ether) was generously provided by Gattefossé (Cedex, France), while Kolliphor® RH40 was a generous contribution from BASF (Limburgerhof, Germany). Oleic acid was purchased from Sigma (St. Louis, MO, USA) and all other reagents and chemicals used were of high-purity analytical grade.

Components Screening for NE

For optimization of the nanoemulsion, solubility of Naftifine hydrochloride was evaluated in range of oils (oleic acid, clove oil and castor oil), surfactants (Tween 20, Tween 80, Span 20, Span 80 and Kolliphor® RH40) and co-surfactants (propylene glycol, PEG 400 and Transcutol-P®).

An excessive amount of Naftifine hydrochloride was incorporated to 10 mL of every component in separate vials and gently agitated over 24 hr, subsequently equilibrated at room temperature over 72 hr under continuous stirring. After centrifugation (10,000 rpm, 10 min) to remove undissolved drug, the supernatant was filtered and examined by a UV spectrophotometer at 222.5 nm. This systematic approach provided critical insights into selecting an optimal oil phase and surfactant system to enhance Naftifine hydrochloride's solubility and bioavailability for improved topical delivery.[14-17]

Development of pseudo ternary phase diagram

The nanoemulsion region was determined through pseudo ternary phase diagrams to enhance formulation components. Solubility

studies led to the selection of oleic acid as the oil phase, while Kolliphor® RH40 and Transcutol-P® were selected as the surfactant and co-surfactant. For the construction of the phase diagram, different Surfactant to co-surfactant (Smix) weight ratios (1:1, 2:1, 3:1, 1:2 and 4:1) were prepared and incorporated with the oil phase in varying weight ratios (oil:Smix) of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. Each blend was vortex-mixed to ensure homogeneity before proceeding with water titration. The aqueous phase was incrementally added dropwise until turbidity appeared, marking the transition point. The nanoemulsion region was identified based on the generation of clear, free-flowing oil in water (o/w) nanoemulsions formed within the phase diagram. This approach provided a comprehensive understanding of the formulation boundaries, guiding the development of an optimized nanoemulsion system.[18-20]

Formulation of Naftifine hydrochloride NE

Naftifine hydrochloride-loaded Oil-in-Water (o/w) nanoemulsions were developed using the spontaneous emulsification technique. Oleic acid was chosen as the oil phase, Transcutol-P® as the co-surfactant and Kolliphor® RH40 as the surfactant. The surfactant-to-co-surfactant (Smix) weight ratio was fixed at 2:1 to ensure optimal emulsification. To prepare the nanoemulsion, Naftifine hydrochloride was first solubilized in the oil phase, ensuring uniform drug distribution. The surfactant mixture (Smix) was subsequently incorporated into the oil phase and gently titrated with distilled water under continuous stirring at room temperature. This process led to the spontaneous formation of a clear, monophasic nanoemulsion with a drug loading concentration of 2% (w/w).[21]

Nanoemulsions were formulated by adjusting the concentrations of oil and surfactant. The generated formulations (NFH1-NFH9) subjected to a 24-hr equilibration period before undergoing comprehensive characterization to evaluate their physicochemical properties.

Design Expert® software (Version 13.0, Stat-Ease Inc., USA) was utilized to implement a 3^2 factorial design for optimizing the formulation. The impact of two independent variables X_1 (oil concentration %) and X_2 (Concentration of Smix %) was systematically assessed concerning key parameters, including drug content (Y_1), globule size (Y_2), and formulation Polydispersity Index (PDI) (Y_3). The relationship between independent variables and response parameters was analyzed using ANOVA (F-value) to assess statistical significance. Table 1 presents the coded levels of the independent variables used in the design.[17,22,23]

Characterization of nanoemulsion

Drug content

The Naftifine hydrochloride nanoemulsions drug content was measured and analyzed using a UV spectrophotometric method. After precisely measuring 1 mL of the nanoemulsion, 10 mL of methanol was added to dilute it. The resulting solution was introduced in a shaking incubator (LSI-2005 RL, Lab Tech Co., Korea) at 50 rpm and 37±0.5°C for 30 min to facilitate uniform drug dispersion. Following incubation, the supernatant was carefully collected and analyzed using a UV spectrophotometer (UV-1700 Pharma Spec, Shimadzu, Japan) at 222.5 nm, with methanol serving as the blank reference.[24,25]

Determination of Solubility

Naftifine hydrochloride solubility in distilled water and nanoemulsion was assessed using a previously established HPLC method at 265 nm. To ensure equilibrium, an excess quantity of the pure drug or its formulation was introduced into distilled water in conical flasks, with each experiment conducted in triplicate. The samples were then incubated in a mechanical water shaker bath (Nirmal International, New Delhi, India) at a controlled temperature of 25±1°C for 72 hr. After the incubation period, samples were filtered, suitably diluted with distilled water and evaluated for drug concentration using HPLC at 265 nm.[26,27]

pH Determination

As a topical formulation, ensuring physiological compatibility is crucial to prevent skin irritation. pH of the Naftifine hydrochloride nanoemulsion was measured in ambient conditions by a digital pH meter (Rolex, India) to confirm its suitability for dermal application.[28]

Globule size, PDI and Zeta potential

All the prepared nanoemulsions was evaluated for globule size, zeta potential and PDI using a Horiba particle size analyser to ensure stability and uniformity.[29]

Morphology

The globule size of the optimized batch was examined through TEM, providing a direct visualization of the globules. This analysis confirmed the globule size obtained from the Zetasizer, ensuring the accuracy of the measurement.[30]

Dilution study

The dilution study was used to evaluate the nanoemulsion's phase inversion behaviour. In this procedure, water (10 mL) and optimized nanoemulsion (1 mL) were mixed in a test tube, and any signs of phase inversion were monitored.[24]

Thermodynamic stability study of nanoemulsion

Heating and cooling cycles

The stability of the formulations was assessed through a series of heating and cooling cycles. These cycles involved alternating storage between refrigeration temperature 4°C and 45°C, with each temperature maintained for a minimum of 48 hr. A total of six cycles were conducted. Centrifugation was then applied to formulations that held up well in these circumstances.[30,31]

Centrifugation

For the centrifugation test, samples were spun at 3500 rpm for 30 min. Only those formulations that exhibited no signs of creaming, phase separation or cracking proceeded to the next stage of evaluation, the Freeze-Thaw Tolerance Test.[31]

Freeze-Thaw cycles

The freeze-thaw test involved three cycles, where formulations were exposed to temperatures ranging from -21°C to +25°C, with each condition maintained for 48 hr. Formulations that maintained stability, showing no evidence of creaming, phase separation, phase inversion, or coalescence, were selected for further kinetic destabilization studies.[31]

RESULTS

Components Screening for NE

Figure 1 illustrates the solubility of drug in various oils, Surfactants and co-surfactants. These results led to the selection of oleic acid as the oil phase, for the creation of nanoemulsions, Kolliphor® RH40 serves as the surfactant and Transcutol-P® as the co-surfactant.

Development of pseudo ternary phase diagram

The pseudo ternary phase diagram illustrates the formation of monophasic and biphasic dispersion systems based on different combinations of ternary components, including Smix, water and an oil mix. The phase diagram delineates regions corresponding to transparent nanoemulsions and turbid coarse dispersions. Various surfactant-to-co-surfactant (Smix) ratios (1:1, 1:2, 2:1, 3:1 and 4:1) were evaluated, revealing the extent of the nanoemulsion region.[32]Among these, the 2:1 Smix ratio demonstrated the largest emulsification region and was selected as the optimized composition (Figure 2).

Formulation of Naftifine hydrochloride NE

A 3^2 full factorial design was utilized to optimize the formulation of Naftifine hydrochloride nanoemulsions, assessing the impact of the oil phase concentration (A) and the surfactant-co-surfactant mixture (Smix) concentration (B) on critical formulation parameters, including drug content (Y1), globule size (Y2) and polydispersity index (PDI) (Y3) (Table 2). Response Surface Methodology (RSM) was utilized and contour plots were constructed to illustrate the influence of independent variables on the selected responses. The ANOVA outcomes obtained validate the statistical relevance of the model for all responses ($p<0.05$), validating its suitability for optimizing nanoemulsion characteristics.

The mathematical equations derived from regression analysis are as follows:

- **Drug Content (Y1):** Y1=74.96+12.62A+4.20B+0.0250 AB+11.02A2-20.
- **Globule Size (Y2):** Y2=139.82-22.48A-22.88B+26.8 5AB
- **Polydispersity Index (PDI)(Y3):** Y3=0.3549+0.1040A+ 0.0380B

Here, A represents the oil conc. and B corresponds to the Smix concentration of (Kolliphor® RH40: Transcutol® P).

The ANOVA results for the dependent variables validated the statistical significance of the model ($p<0.05$). R^2 (the coefficient of determination) values for Y1, Y2, and Y3 were 0.9579, 0.8171, and 0.9188, respectively (Tables 3 and 4), indicating a good fit of the model. The adequate precision values were greater than 4, suggesting a strong signal-to-noise ratio.

- **Drug Content (Y1):** Drug content was notably influenced by the conc. of oil and Smix. The quadratic terms indicated that higher oil concentration enhanced drug content, whereas an excessive amount of Smix resulted in a decrease ($p<0.05$).
- **Globule Size (Y2):** A higher oil concentration led to larger globule size, while higher Smix levels led to a decrease in globule size due to improved emulsification efficiency. The interaction term AB was found to be significant ($p<0.05$), indicating a synergistic effect between oil and Smix.
- **Polydispersity Index (PDI) (Y3):** The PDI values remained below 0.5 for all formulations, suggesting a uniform particle size distribution. Both oil and Smix concentration had a direct impact on PDI, with increased oil levels leading to higher PDI values.

According to the statistical analysis, the 2:1 Smix ratio exhibited the most optimal nanoemulsion characteristics, with the smallest globule size, uniform PDI, and maximum drug content. The 3D response surface plots further illustrated the impact of formulation variables, confirming that reducing oil concentration

Table 1: Coded levels in design.

Independent variables	Levels used		
	-1	0	+1
X1: Oil Concentration	1.25	1.50	1.75
X2: Smix Concentration	1.25	1.50	1.75

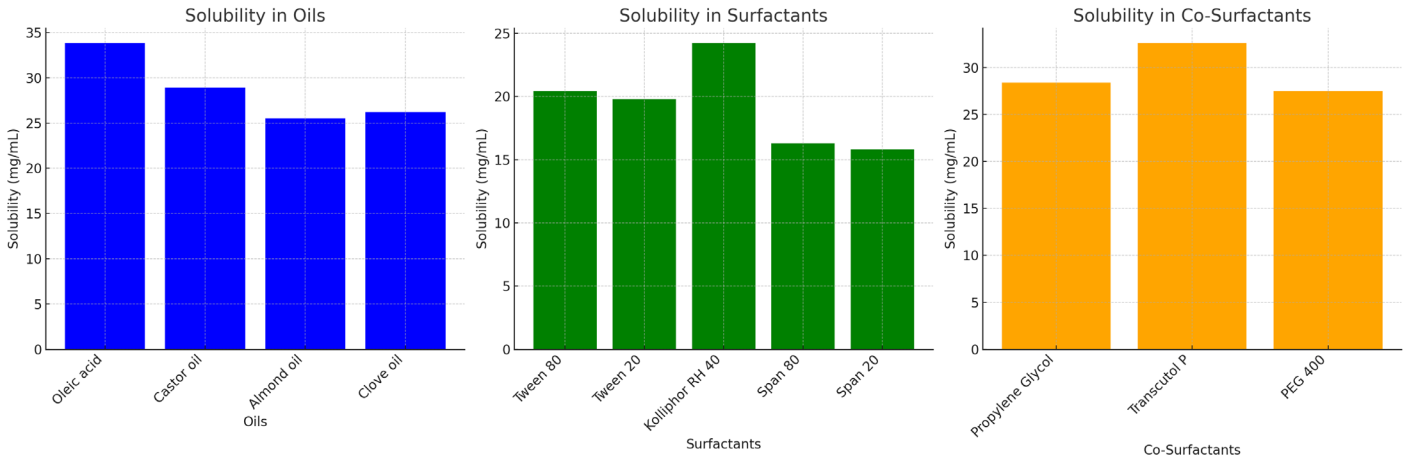


Figure 1: Solubility of the drug in oils, surfactants and co-surfactants.

while optimizing Smix significantly improved nanoemulsion stability (Figures 3A-F).

Model Adequacy and Fit

The ANOVA (Analysis of Variance) confirmed the significance of the model ($p<0.05$) for all selected responses, indicating that the model could reliably predict the outcome within the studied range. The coefficient of determination (R^2) values were found to be >0.95 for all responses, suggesting a strong correlation between predicted and observed values. The adjusted R^2 and predicted R^2 values were in close agreement, indicating the model was not overfitted and had good predictive capability.

Residual Analysis

Normal probability plots of residuals demonstrated a near-linear pattern, indicating that the residuals were normally distributed. Plot of residuals vs predicted values revealed no significant patterns or curvature, confirming homoscedasticity (constant variance). These diagnostic plots validated the assumption that residuals were random and independent.

Lack-of-Fit Test

The lack-of-fit *p*-values were all greater than 0.05, indicating that the model fits the data adequately and that the variation due to lack-of-fit was not significant compared to pure error. This supports that the model is statistically robust and suitable for optimization of the nanoemulsion formulation.

Characterization of nanoemulsion

All nanoemulsion formulations were successfully developed, characterized, and optimized. The optimized nanoemulsion exhibited a globule size of 90.5 nm, PDI of 0.4, a drug content of 92.8%, and a viscosity of 26.20±1.5 cps and zeta potential -29.4mV, pH 5.96±0.10.

The PDI value of approximately 0.4 indicates a moderately polydisperse system, which may be influenced by the nature and ratio of the excipients used. While a lower PDI is desirable, values up to 0.4 are considered acceptable for nanoemulsions, especially when spontaneous emulsification methods are employed. Importantly, no visual instability (such as creaming or phase separation) was observed over the storage period, supporting the physical integrity of the formulation.[32]

The zeta potential of the optimized nanoemulsion formulation was found to be -29.4 mV, indicating a moderately high negative surface charge. Zeta potential is a key parameter influencing the physical stability of nanoemulsions, as values above ±30 mV typically provide strong electrostatic repulsion between droplets, preventing coalescence. Although slightly below this threshold, the -29.4 mV value suggests sufficient repulsive forces to maintain colloidal stability. This indicates that the formulation is likely to remain stable over time without significant aggregation or phase separation, ensuring extended shelf-life and consistent performance.[32,33]

The solubility of Naftifine hydrochloride (NFH) in the nanoemulsion was evaluated and compared with its aqueous solubility. NFH exhibited a solubility of 0.923±1.2 mg/mL in distilled water, whereas its solubility significantly increased to 198.5±2.52 mg/mL in the nanoemulsion system. This enhancement in solubility can be ascribed to the presence of Kolliphor® RH40 as the surfactant and Transcutol® P as the co-surfactant, which facilitate improved drug solubilization and dispersion

Morphology

In TEM pictures, oil droplets with an even surface and a spherical form were seen. The drug particles showed no crystal structure.[17,21] Figure 4 shows a TEM image of the NE.

Dilution study

The dilution test was conducted on the optimized oil-in-water (o/w) nanoemulsion to assess phase inversion stability. The formulation remained stable, exhibiting no signs of phase inversion or precipitation upon dilution. These findings confirm

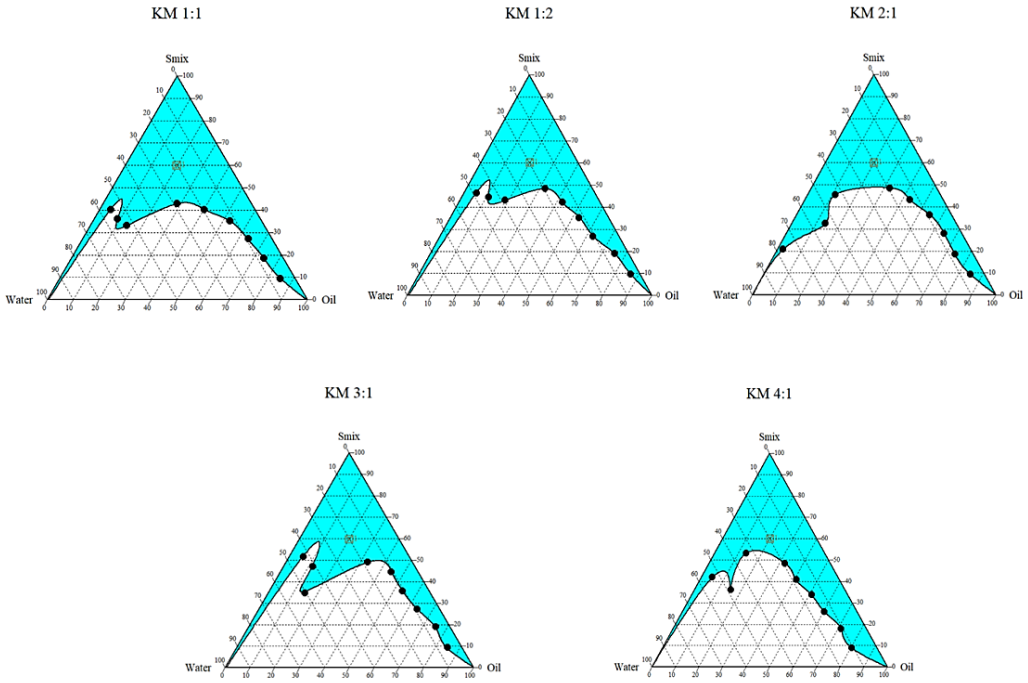


Figure 2: Pseudo ternary phase diagrams Km - 1:1, 1:2, 2:1, 3:1, 4:1

Table 2: 3^2 Factorial design optimization.

Batches	Factor 1 A: Amount of Oil (mL)	Factor 2 B: Amount of Smix (mL)	Response 1 Drug Content (%)	Response 2 Globule size (nm)	Response 3 PDI
NF1	1.25	5.4	48.7	222.4	0.2
NF2	1.25	5.7	73.8	158.8	0.23
NF3	1.25	6.0	56.5	110.2	0.3
NF4	1.50	5.4	47	140.4	0.32
NF5	1.50	5.7	80.3	150	0.38
NF6	1.50	6.0	56.5	120.1	0.41
NF7	1.75	5.4	77	135.4	0.458
NF8	1.75	5.7	92.8	90.5	0.4
NF9	1.75	6.0	84.9	130.6	0.496

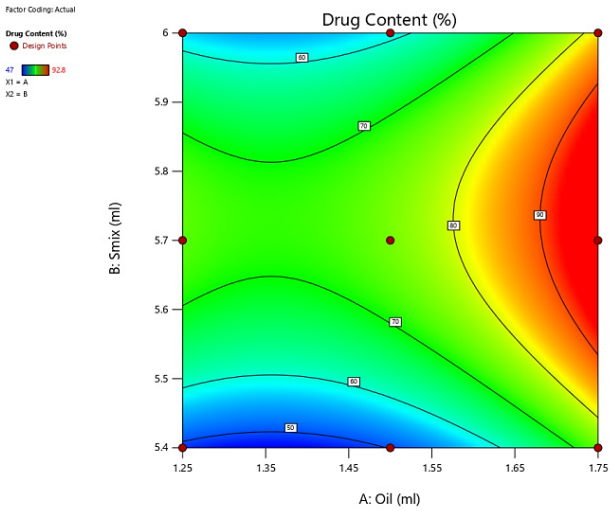
the robustness and stability of the optimized formulation. Dilution stability is a critical parameter for topical nanoemulsions as it simulates the interaction of the formulation with skin moisture or other external fluids during application. Maintaining physical stability upon dilution ensures that the nanoemulsion does not undergo phase separation or drug precipitation, thereby preserving its drug delivery performance and therapeutic efficacy.

Thermodynamic stability study of nanoemulsion

The formulated nanoemulsions were visually assessed for physical stability. The optimized formulation (Batch NF8) appeared transparent, with no evidences of phase separation, turbidity, creaming, or cracking, confirming its stability. The absence of these instability markers indicates the thermodynamic stability of the nanoemulsion, which contributes to an extended shelf life compared to conventional emulsions that exhibit only kinetic stability.

DISCUSSION

This study successfully developed and optimized a nanoemulsion-based delivery system to enhance the solubility and bioavailability of Naftifine hydrochloride (NFH), a BCS Class IV antifungal drug with poor aqueous solubility and permeability. Conventional formulations of Naftifine hydrochloride, such as creams and gels, often suffer from poor penetration into deeper skin layers due to the drug's strong lipophilicity (log P: 5.4), which results in its accumulation in the stratum corneum and reduced therapeutic efficacy. Several studies have reported that



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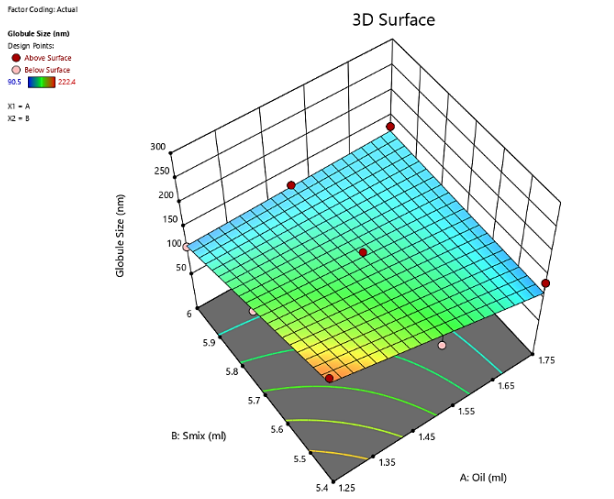

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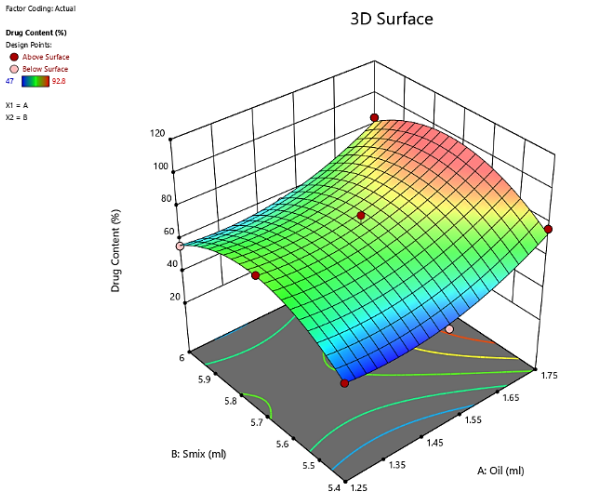

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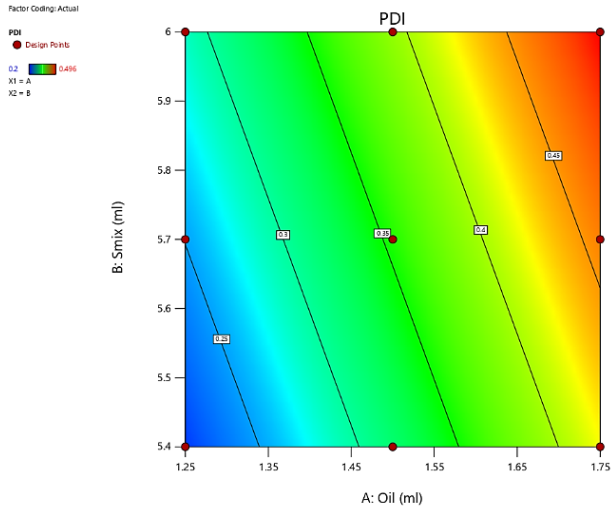

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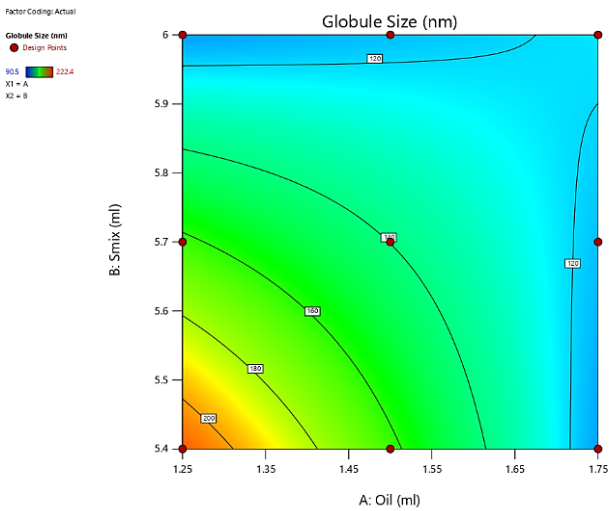

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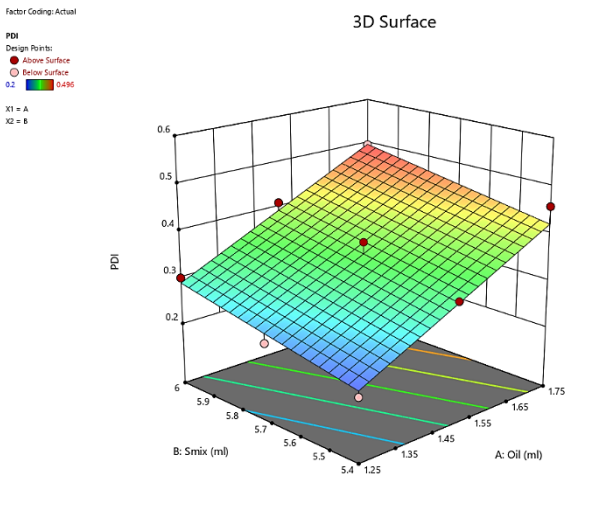

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Figure 3 (A-F): 3D response surface plots A-B-Drug content, C-D-Globule size, E-PDI.

Table 3: Statistic's summary for drug content, globule size and PDI.

Source	SD	R^2	Adjusted R^2	Predicted R^2	PRESS	Remark
Drug content						
Linear	14.03	0.4734	0.2978	0.0162	2204.87	
2FI	15.36	0.4734	0.1574	-0.0621	2380.44	
Quadratic	5.61	0.9579	0.8878	0.6232	844.40	Suggested
Cubic	8.02	0.9713	0.7706	-4.2260	11712.65	Aliased
Globule size						
Linear	30.28	0.3424	0.1231	-1.0122	16830.55	
2FI	14.95	0.8663	0.7861	0.3529	5412.30	Suggested
Quadratic	14.44	0.9253	0.8007	0.3138	5739.80	
Cubic	19.90	0.9527	0.6212	-7.6288	72172.82	Aliased
PDI						
Linear	0.0329	0.9188	0.8917	0.8218	0.0143	Suggested
2FI	0.0333	0.9308	0.8892	0.7948	0.0164	
Quadratic	0.0317	0.9623	0.8993	0.6462	0.0283	
Cubic	0.0423	0.9776	0.8209	-3.0793	0.3266	Aliased

Table 4: Fit statistics.

Parameters	Drug content	Globule size (nm)	PDI
Standard deviation	5.61	20.14	0.0329
Mean	68.61	139.82	0.3549
R^2	0.9579	0.8171	0.9188
Adjusted R^2	0.8878	0.7073	0.8917
Predicted R^2	0.6232	0.1124	0.8218
Adeq precision	10.9088	7.4077	14.9395

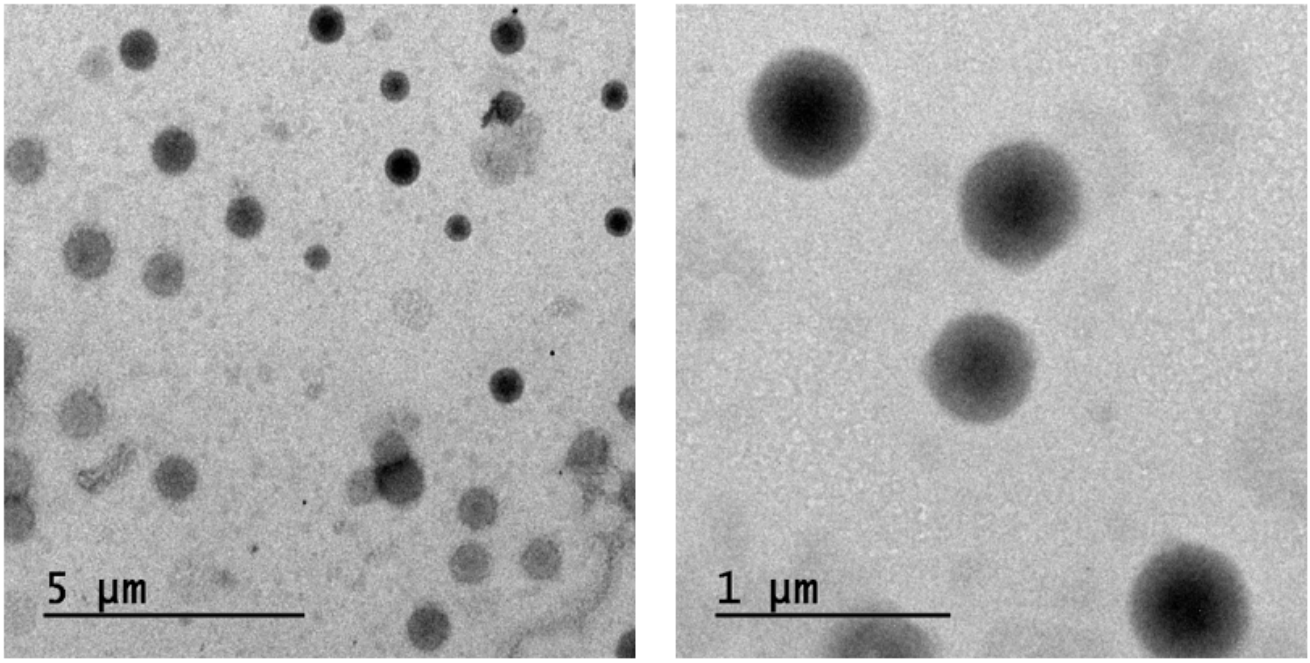

Figure 4: TEM images of NFH8 batch.

such formulations fail to maintain adequate drug levels at the site of infection, particularly in the dermis, limiting their clinical effectiveness.[10-12] This underlines the need for advanced delivery systems such as nanoemulsions, which are capable of enhancing skin penetration and providing sustained drug release.

Using oleic acid as the oil phase, Kolliphor® RH40 as the surfactant, and Transcutol-P® as the co-surfactant, the formulation was optimized via a 3^2 factorial design. The resulting nanoemulsion exhibited a globule size of 90.5 nm, a PDI of 0.4, and a high drug content (92.8%), ensuring stability and uniformity.

Although surface tension was not directly measured, the choice of surfactant (Kolliphor RH40) and co-surfactant (Transcutol-P) plays a pivotal role in reducing interfacial tension between the oil and aqueous phases. The significant reduction in interfacial tension facilitates the spontaneous formation of nano-sized droplets and contributes to the thermodynamic stability of the nanoemulsion. Such surface activity is essential not only for droplet stabilization but also for enhancing the drug's ability to penetrate the stratum corneum, as it improves wetting and spreading on the skin surface.

Nanoemulsions enhance drug permeation through the skin via several mechanisms. The nano-sized droplets provide a large surface area, which facilitates better contact and interaction with the stratum corneum. Components of the nanoemulsion, such as oleic acid, act as permeation enhancers by disrupting the lipid bilayers of the stratum corneum, increasing skin fluidity and reducing barrier resistance. The surfactants (e.g., Kolliphor RH40) and co-surfactants (e.g., Transcutol-P) further aid penetration by fluidizing skin lipids and increasing drug solubility within skin layers. Additionally, the small droplet size and thermodynamic stability of nanoemulsions ensure sustained drug release and improved drug partitioning into deeper skin layers, resulting in enhanced bioavailability at the site of infection.

The system significantly improved NFH solubility due to reduced interfacial tension and enhanced dispersion. Stability studies confirmed its robustness under stress conditions, with no phase separation or degradation. These findings suggest that nanoemulsion-based delivery can enhance NFH penetration through the skin, improving antifungal efficacy. Further *in vivo* and clinical studies are needed to validate its therapeutic potential.

CONCLUSION

The successful formulation of a nanoemulsion-based delivery system for Naftifine hydrochloride offers a strategic advancement in overcoming its inherent biopharmaceutical limitations. The optimized system not only enhanced solubility and permeation but also maintained desirable physicochemical stability. These improvements suggest strong potential for improved therapeutic outcomes in the management of superficial fungal infections. While the *in vitro* and *ex vivo* findings are promising, further *in vivo* evaluations and clinical validation will be essential to confirm translational benefits. The approach demonstrated in this work may also serve as a platform for delivering other poorly water-soluble topical antifungal agents.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest in publication of this research.

ABBREVIATIONS

NE: Nanoemulsion; **NFH:** Naftifine hydrochloride; **BCS:** Biopharmaceutical Classification System; **UV Spectroscopy:** Ultra Violet spectroscopy; **PDI:** Polydispersity Index; **Smix:** Surfactant to Co-surfactant ratio; **TEM:** Transmission Electron Microscopy; **ANOVA:** Analysis of Variance.

SUMMARY

Naftifine hydrochloride (NFH), a BCS Class IV antifungal agent, exhibits poor aqueous solubility, limiting its therapeutic efficacy. This study aimed to enhance its solubility and bioavailability through a nanoemulsion-based drug delivery system. A systematic screening approach identified oleic acid as the optimal oil phase, Kolliphor® RH40 as the surfactant, and Transcutol-P® as the co-surfactant. Pseudo ternary phase diagrams were constructed to determine the emulsification region, and a 3^2 factorial design was employed for optimization.

The optimized nanoemulsion formulation exhibited a mean globule size of 90.5 nm, Polydispersity Index (PDI) of 0.4, and drug content of 92.8%. A significant solubility enhancement was observed, with NFH solubility increasing from 0.923 mg/mL in distilled water to 198.5 mg/mL in the nanoemulsion system. Morphological analysis via Transmission Electron Microscopy (TEM) confirmed the formation of uniform, spherical droplets. Stability studies, including thermodynamic evaluations (freeze-thaw cycles, centrifugation, and heating-cooling cycles), demonstrated the formulation's robustness without phase separation, creaming, or cracking. The findings indicate that the developed nanoemulsion system significantly improves the solubility and stability of NFH, providing a promising approach for enhancing its bioavailability in topical antifungal therapy.

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