



Formulation and Evaluation of Novel Nanoemulgel for the Topical Drug Delivery of Isavuconazole

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ABSTRACT :

Isavuconazole is a broad-spectrum triazole antifungal agent used in the treatment of invasive fungal infections; however, its topical delivery is limited due to poor aqueous solubility and inadequate skin permeation. The present research work was aimed at the formulation and evaluation of a novel nanoemulgel system for the effective topical delivery of Isavuconazole, with the objective of improving drug solubility, stability, skin penetration, and therapeutic efficacy. A nanoemulsion was developed using Oleic acid as the oil phase, Tween 80 as the surfactant, and Transcutol® as the co-surfactant, selected based on solubility and emulsification efficiency studies. Pseudo-ternary phase diagrams were constructed to identify the nanoemulsion region, and formulation optimization was carried out using Box–Behnken design by evaluating critical parameters such as droplet size, polydispersity index, and zeta potential. The optimized nanoemulsion was incorporated into a Carbopol-based gel to form a nanoemulgel suitable for topical application. The prepared nanoemulgel was evaluated for physicochemical properties including pH, viscosity, spreadability, extrudability, drug content, and in vitro drug release. The optimized formulation exhibited nanosized droplets, uniform distribution, excellent stability, and sustained drug release characteristics. FTIR studies confirmed the absence of drug–excipient incompatibility. Stability studies indicated that the nanoemulgel remained stable under different storage conditions. Overall, the developed Isavuconazole-loaded nanoemulgel demonstrated improved physicochemical and release characteristics, suggesting that it is a promising and effective topical drug delivery system for antifungal therapy.

Keywords: Isavuconazole, Nanoemulgel, Topical drug delivery, Nanoemulsion, Antifungal formulation

INTRODUCTION

Fungal infections represent a growing global health concern, particularly affecting immunocompromised individuals and patients with chronic conditions. Superficial and cutaneous fungal infections remain among the most common dermatological disorders worldwide, often requiring prolonged therapy and repeated treatment due to poor drug penetration, recurrence, and resistance development [1]. Conventional topical antifungal formulations such as creams, ointments, and lotions frequently exhibit limited therapeutic efficacy owing to inadequate drug solubility, poor skin permeation, and low retention at the site of infection [2].

Isavuconazole is a second-generation triazole antifungal agent with a broad spectrum of activity against yeasts, molds, and dimorphic fungi. It acts by inhibiting lanosterol 14- α -demethylase, thereby disrupting fungal cell membrane synthesis [3]. Despite its potent antifungal activity, the topical application of Isavuconazole is challenging due to its poor aqueous solubility and limited permeability across the stratum corneum, which restricts its clinical utility in localized fungal infections [4]. These limitations necessitate the development of advanced drug delivery systems capable of enhancing solubility, stability, and dermal penetration.

Nanotechnology-based drug delivery systems have emerged as a promising approach for overcoming the drawbacks associated with conventional topical formulations. Among these systems, nanoemulsions have gained significant attention due to their small droplet size, high surface area, thermodynamic stability, and enhanced drug solubilization capacity [5]. Nanoemulsions facilitate improved skin penetration by altering the barrier properties of the stratum corneum and promoting sustained drug release at the target site [6]. However, their low viscosity can limit topical retention, leading to reduced residence time on the skin.

Nanoemulgels, a hybrid system combining nanoemulsions with gel matrices, have been developed to overcome these limitations. By incorporating nanoemulsions into a suitable gel base, nanoemulgels provide enhanced viscosity, improved spreadability, better patient compliance, and prolonged contact time with the skin [7]. The presence of gelling agents such as Carbopol further improves formulation stability and allows controlled drug release [8]. Additionally, the use of penetration enhancers and surfactant systems in nanoemulgels contributes to increased drug permeation across the skin layers.

The selection of appropriate formulation components, including oil phase, surfactant, co-surfactant, and gelling agent, plays a critical role in the performance of nanoemulgels. Oleic acid has been widely reported as an effective oil phase and penetration enhancer due to its ability to disrupt skin lipid bilayers [9]. Surfactants like Tween 80 and co-surfactants such as Transcutol® enhance emulsification efficiency and drug solubility while maintaining skin compatibility. Optimization of formulation variables using statistical tools such as Box–Behnken design ensures reproducibility and robust formulation development [10].

Thus, nanoemulgel-based topical delivery represents a scientifically advanced and clinically relevant strategy for improving the therapeutic performance of Isavuconazole in the management of fungal infections.

MATERIALS AND METHODS

The present study involved the formulation and evaluation of a novel nanoemulgel for topical delivery of Isavuconazole using pharmaceutically acceptable excipients. The materials were selected to ensure optimal solubility, stability, skin compatibility, and enhanced permeation. The methodology included nanoemulsion preparation, gel incorporation, optimization by Box–Behnken Design, and physicochemical evaluation.

1. Materials

Isavuconazole ($\geq 99\%$ purity) was used as the active pharmaceutical ingredient at 1% w/w. Oils such as Caprylic/Capric Triglyceride, Oleic Acid, and Labrafac™ Lipophile WL 1349 were selected to enhance drug solubility. Tween 80, Span 20, and Labrasol® served as surfactants, while Transcutol® P and PEG 400 were used as co-surfactants. Carbopol 940 and HPMC K100M acted as gelling agents. Propylene glycol and DMSO were included as penetration enhancers, parabens as preservatives, and deionized water as the aqueous phase.

The formulation composition is summarized in Table 1.

Table 1: Formulation composition of Novel Nanoemulgel

Component	Function	Concentration (% w/w)
Isavuconazole	Active pharmaceutical ingredient (API)	1%
Caprylic/Capric Triglyceride	Oil phase (solubilization & permeation)	5-10%
Oleic Acid	Oil phase (permeation enhancement)	2-5%
Labrafac™ Lipophile WL 1349	Oil phase (solubilization)	3-7%
Tween 80	Surfactant (nanoemulsion stabilization)	10-20%
Span 20	Surfactant (nanoemulsion stabilization)	5-10%
Labrasol®	Surfactant (nanoemulsion stabilization)	8-12%
Transcutol® P	Co-surfactant (solubilization & stability)	5-10%
PEG 400	Co-surfactant (solubilization & stability)	4-8%
Carbopol 940	Gelling agent (viscosity & consistency)	0.5-2%
HPMC K100M	Gelling agent (viscosity & consistency)	0.5-2%
Triethanolamine (TEA)	pH Adjuster	q.s. (pH 5.5-6.5)
Citric Acid	pH Adjuster	0.1-0.5%
Propylene Glycol	Penetration enhancer	5-10%
Dimethyl Sulfoxide (DMSO)	Penetration enhancer	2-5%
Methylparaben	Preservative	0.1%
Propylparaben	Preservative	0.05%
Deionized Water	Aqueous phase component	q.s. to 100%

2. Methods

Nanoemulgel formulation was carried out through nanoemulsion preparation followed by incorporation into a gel base. The spontaneous emulsification method was employed to obtain stable nanosized droplets.

2.1 Preparation of Nanoemulsion

Nanoemulsion was developed as the primary delivery system using selected oil, surfactant, co-surfactant, and aqueous phase.

2.1.1 Selection of Oil Phase

Solubility of Isavuconazole in different oils was determined using the shake-flask method. The drug was mixed with oils, equilibrated for 48 h, centrifuged, filtered, and analyzed spectrophotometrically at 255 nm. The oil showing maximum solubility was selected.

2.1.2 Selection of Surfactant and Co-Surfactant

Surfactants were screened using dilution tests based on clarity and stability. Co-surfactants were evaluated by mixing with selected surfactants and observing emulsification efficiency. The most effective combinations were selected.

2.2 Construction of Pseudo-Ternary Phase Diagram

A pseudo-ternary phase diagram was constructed using the water titration method to identify the nanoemulsion region.

2.1.3.1 Preparation of Surfactant-Mixture (Smix)

Different surfactant:co-surfactant ratios were prepared and evaluated for clarity and stability. Observations are presented in Table 2.

Table 2: Preparation of Surfactant-Mixture (Smix) with Different Ratios

Smix Ratio (Surfactant:Co-Surfactant)	Visual Appearance	Phase Stability	Inference
1:1	Clear solution	Stable	Suitable
2:1	Slightly turbid	Stable	Suitable
3:1	Opaque	Unstable	Unsuitable
1:2	Clear solution	Stable	Suitable
1:3	Phase separation	Unstable	Unsuitable

Titration with water was performed for various oil-to-Smix ratios to determine nanoemulsion formation. Results are shown in Table 3.

Table 3: Oil-to-Smix Ratios and Corresponding Nanoemulsion Formation

Oil:Smix Ratio	Visual Appearance	Nanoemulsion Formation	Phase Stability (24h)	Inference
1:9	Transparent	Yes	Stable	Suitable
2:8	Transparent	Yes	Stable	Suitable
3:7	Slightly turbid	Partial	Phase separation	Unsuitable
4:6	Turbid	No	Phase separation	Unsuitable
5:5	Opaque	No	Phase separation	Unsuitable

2.3 Nanoemulsion Formulation

Optimized oil and Smix were homogenized, followed by gradual water addition and ultrasonication to obtain a stable nanoemulsion. The formulation steps are summarized in Table 4.

Table 4: Summary of Nanoemulsion Preparation Steps

Step	Process	Conditions/Parameters
Oil Selection	Solubility test of Isavuconazole in different oils	10 mg drug in 5 mL oil, equilibrated for 48 h at 25°C
Surfactant & Co-Surfactant Selection	Emulsification efficiency using dilution method	Surfactant (10%) + Oil, titrated with water
Phase Diagram Construction	Determination of nanoemulsion region	Oil:Smix ratio optimization, water titration
Homogenization	High-speed homogenization	15,000 rpm, 10 min
Nanoemulsion Formation	Dropwise addition of water to Smix-oil blend	Stirring at 500 rpm
Ultrasonication	Reduction of droplet size	5 min, 40 kHz, 60% amplitude
Storage & Stability	Testing for droplet size, zeta potential, phase separation	Room temperature (25°C), 1 month

2.3.1 Preparation of Nanoemulgel

The optimized nanoemulsion was incorporated into a gel base to obtain a nanoemulgel suitable for topical application.

2.3.2 Gel Preparation

Gel base was prepared using Carbopol 940 and HPMC K100M. TEA was used for pH adjustment to skin-compatible range.

2.3.3 Selection of Gelling Agents

Carbopol 940 provided viscosity and clarity, while HPMC K100M enhanced stability and bioadhesion. Both were used in optimized concentrations.

2.3.4 Preparation of Carbopol Gel Base

Carbopol was dispersed in water, allowed to hydrate, and neutralized with TEA to obtain a uniform gel with pH 5.5–6.5.

2.3.5 Preparation of HPMC-Based Gel

HPMC was hydrated in water with mild heating, allowed to swell, and incorporated into the Carbopol gel under controlled stirring.

2.3.6 Incorporation of Nanoemulsion into the Gel Base

The optimized nanoemulsion was slowly added to the gel base under continuous stirring to ensure uniform distribution. The final nanoemulgel was stored at 4°C for complete gelation.

2.4 Optimization of Formulation by Box-Behnken Design

Box-Behnken Design (BBD) was used to optimize formulation variables and evaluate their effects on nanoemulsion characteristics.

2.4.1 Selection of Independent and Dependent Variables

Independent variables included oil concentration, Smix ratio, and water content. Dependent variables were droplet size, PDI, and zeta potential.

2.4.2 Experimental Design Using Box-Behnken Model

A 3-factor, 3-level BBD with 17 experimental runs was generated using Design-Expert software. The coded levels are shown in *Table 5*.

Table 5: Coded and Actual Levels of Independent Variables in BBD

Variable	Low (-1)	Medium (0)	High (+1)
Oil (%) (X_1)	5%	10%	15%
Smix Ratio (X_2)	1:1	2:1	3:1
Water (%) (X_3)	20%	30%	40%

2.4.3 Experimental Procedure for Formulation Preparation

Nanoemulsions were prepared as per design runs using homogenization and sonication, followed by characterization for droplet size, PDI, and zeta potential.

2.4.4 Statistical and Mathematical Modeling

Experimental data were analyzed using RSM and second-order polynomial equations. Model adequacy was evaluated using ANOVA, R^2 , and lack-of-fit tests.

2.4.5 Optimization and Validation

Numerical optimization was performed using desirability function, and the optimized formulation was experimentally validated.

Evaluation of Nanoemulgel Preparation Process

The formulation was assessed for appearance, pH, viscosity, centrifugation stability, and drug content uniformity to ensure homogeneity and stability.

Final Composition of Nanoemulgel

The optimized nanoemulgel composition is shown in *Table 6*.

Table 6: Final Composition of Nanoemulgel

Component	Concentration (% w/w)
Isavuconazole (API)	1%
Nanoemulsion (Oil + Surfactant + Co-Surfactant)	20-30%
Carbopol 940	1-2%
HPMC K100M	1-2%
Triethanolamine (TEA)	q.s. (pH 5.5-6.5)
Deionized Water	q.s. to 100%

2.5 Drug Excipient Interaction Study by FTIR

FTIR analysis was performed to assess compatibility between Isavuconazole and excipients.

2.5.1 Sample Preparation

Pure drug, excipients, and physical mixtures (1:1) were prepared and stored prior to analysis.

2.5.2 FTIR Spectral Analysis

Spectra were recorded in the range of 4000–400 cm^{-1} using ATR or KBr pellet method.

2.5.3 Data Interpretation

Characteristic peaks were compared to identify any interaction or incompatibility.

2.6 Evaluation of Nanoemulsion

Nanoemulsion was evaluated for droplet size, PDI, zeta potential, pH, drug content, and viscosity using standard analytical techniques.

2.7 Evaluation of Nanoemulgel

Nanoemulgel was evaluated for spreadability, extrudability, in vitro drug release, and stability under different storage conditions to confirm its suitability for topical delivery.

RESULTS AND DISCUSSION

The results obtained from the formulation and evaluation of the Isavuconazole-loaded nanoemulgel are presented and discussed in this section. The outcomes include oil selection, surfactant and co-surfactant screening, phase behavior analysis, optimization by Box–Behnken design, physicochemical characterization of nanoemulsion, evaluation of nanoemulgel performance, stability studies, and drug–excipient compatibility analysis. Data are presented in tabular and graphical form to support interpretation.

1. Selection of Oil Phase

Selection of a suitable oil phase is essential for achieving high drug solubility, stability, and effective nanoemulsion formation. Since Isavuconazole is lipophilic, its solubility was evaluated in Caprylic/Capric Triglyceride (MCT oil), Oleic Acid, and Labrafac™ Lipophile WL 1349. The results are shown in *Table 7*.

Table 7: Solubility of Isavuconazole in Different Oils

Oil Type	Solubility (mg/mL) $\pm$ SD	Rank
Caprylic/Capric Triglyceride (MCT)	4.92 ± 0.21	2
Oleic Acid	6.85 ± 0.30	1
Labrafac™ Lipophile WL 1349	3.76 ± 0.18	3

Oleic Acid exhibited the highest solubility (6.85 ± 0.30 mg/mL), followed by MCT oil and Labrafac™ Lipophile WL 1349.

2. Selection of Surfactant and Co-Surfactant

Surfactants and co-surfactants are critical in stabilizing nanoemulsions by reducing interfacial tension and improving droplet uniformity. Tween 80, Span 20, and Labrasol® were evaluated for emulsification efficiency and clarity, as shown in Table 8.

Table 8: Emulsification Efficiency of Different Surfactants

Surfactant	Emulsification Efficiency (%) $\pm$ SD	Clarity (Turbidity Index)
Tween 80	92.5 ± 1.8	0.25 ± 0.03
Span 20	78.6 ± 2.1	0.40 ± 0.05
Labrasol®	85.2 ± 1.5	0.30 ± 0.04

Tween 80 exhibited the highest emulsification efficiency (92.5%) and lowest turbidity index, indicating superior emulsification performance and formation of smaller droplets. Its non-ionic nature, high HLB value (15), excellent miscibility with Oleic Acid, and proven safety profile make it ideal for topical nanoemulsion systems.

Labrasol® showed moderate emulsification efficiency, while Span 20 demonstrated poor emulsification ability due to its low HLB value, making it unsuitable for oil-in-water nanoemulsions.

Selection of Co-Surfactant

Transcutol® was selected as the co-surfactant due to its excellent solubilizing ability, compatibility with Tween 80 and Oleic Acid, skin permeability enhancement, and biocompatibility. The Tween 80–Transcutol® combination provided an optimal surfactant system for nanoemulsion formulation.

3. Pseudo-Ternary Phase Diagram Analysis

Pseudo-ternary phase diagrams were constructed to identify nanoemulsion regions and optimize oil-to-Smix ratios. Smix ratios of 1:1, 2:1, and 1:2 formed clear and stable systems, whereas 3:1 and 1:3 ratios were unsuitable due to opacity or phase separation.

Transparent and stable nanoemulsions were observed at oil-to-Smix ratios of 1:9 and 2:8. The nanoemulsion region was mapped and is represented in Figure 1, while compositional data are summarized in Table 9.

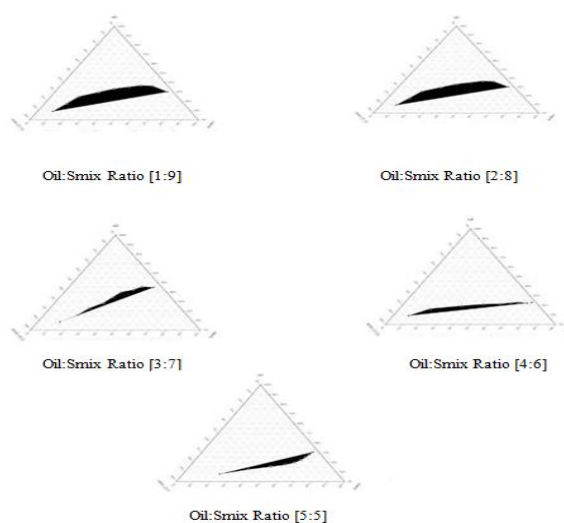
**Figure 1: Pseudo-Ternary Phase Diagram Analysis**

Table 9: Nanoemulsion Region in Pseudo-Ternary Phase Diagram

Oil (%)	Smix (%)	Water (%)	Nanoemulsion Formation	Stability
10	60	30	Yes	Stable
15	55	30	Yes	Stable
20	50	30	Yes	Stable
25	45	30	Partial	Unstable
30	40	30	No	Unstable

Nanoemulsions formed successfully when oil concentration ranged between 10–20%, Smix between 50–60%, and water around 30%. At higher oil concentrations, instability and phase separation were observed. The pseudo-ternary phase diagram thus served as a critical tool in identifying stable nanoemulsion compositions.

4. Optimization of Nanoemulsion Formulation by Box-Behnken Design

Box–Behnken Design (BBD) was employed to evaluate the effects of oil concentration (X_1), surfactant concentration (X_2), and co-surfactant concentration (X_3) on droplet size (Y_1), PDI (Y_2), and zeta potential (Y_3). Seventeen experimental runs were conducted.

4.1 Box-Behnken Design Matrix and Experimental Results

The experimental design and observed responses are presented in Table 10.

Table 10: Box-Behnken Design Matrix and Observed Responses

Run	Oil Concentration (%) (X_1)	Surfactant (%) (X_2)	Co-Surfactant (%) (X_3)	Droplet Size (nm) (Y_1) $\pm$ SD	PDI (Y_2) $\pm$ SD	Zeta Potential (mV) (Y_3) $\pm$ SD
1	5	1	1.5	115.4 $\pm$ 3.5	0.21 $\pm$ 0.02	-38.2 $\pm$ 1.2
2	10	1	1.5	150.2 $\pm$ 4.2	0.28 $\pm$ 0.03	-34.6 $\pm$ 1.5
3	5	3	1.5	102.8 $\pm$ 2.9	0.18 $\pm$ 0.02	-42.1 $\pm$ 1.1
4	10	3	1.5	135.7 $\pm$ 4.0	0.25 $\pm$ 0.03	-36.8 $\pm$ 1.3
5	5	1	3.0	140.6 $\pm$ 4.1	0.27 $\pm$ 0.03	-33.4 $\pm$ 1.6
6	10	1	3.0	170.3 $\pm$ 4.8	0.34 $\pm$ 0.04	-30.2 $\pm$ 1.5
7	5	3	3.0	120.9 $\pm$ 3.2	0.23 $\pm$ 0.02	-40.6 $\pm$ 1.2
8	10	3	3.0	145.1 $\pm$ 4.3	0.29 $\pm$ 0.03	-35.9 $\pm$ 1.4
9	2.5	2	2.25	98.4 $\pm$ 2.8	0.17 $\pm$ 0.02	-44.3 $\pm$ 1.2
10	12.5	2	2.25	160.7 $\pm$ 4.5	0.30 $\pm$ 0.03	-32.1 $\pm$ 1.5
11	7.5	0.5	2.25	140.2 $\pm$ 3.9	0.26 $\pm$ 0.03	-33.8 $\pm$ 1.4
12	7.5	3.5	2.25	110.3 $\pm$ 3.2	0.22 $\pm$ 0.02	-41.2 $\pm$ 1.3
13	7.5	2	0.5	128.5 $\pm$ 3.7	0.24 $\pm$ 0.02	-37.9 $\pm$ 1.3
14	7.5	2	4.0	145.8 $\pm$ 4.3	0.28 $\pm$ 0.03	-35.3 $\pm$ 1.4
15	7.5	2	2.25	105.6 $\pm$ 3.1	0.19 $\pm$ 0.02	-42.5 $\pm$ 1.1
16	7.5	2	2.25	106.2 $\pm$ 3.2	0.18 $\pm$ 0.02	-43.1 $\pm$ 1.1
17	7.5	2	2.25	107.0 $\pm$ 3.3	0.19 $\pm$ 0.02	-42.8 $\pm$ 1.2

Observed droplet size for all 17 Box-Behnken experimental runs.



Y_1 = droplet size (nm); values shown are mean observations.

Figure . Droplet Size Across Box-Behnken Experimental Runs

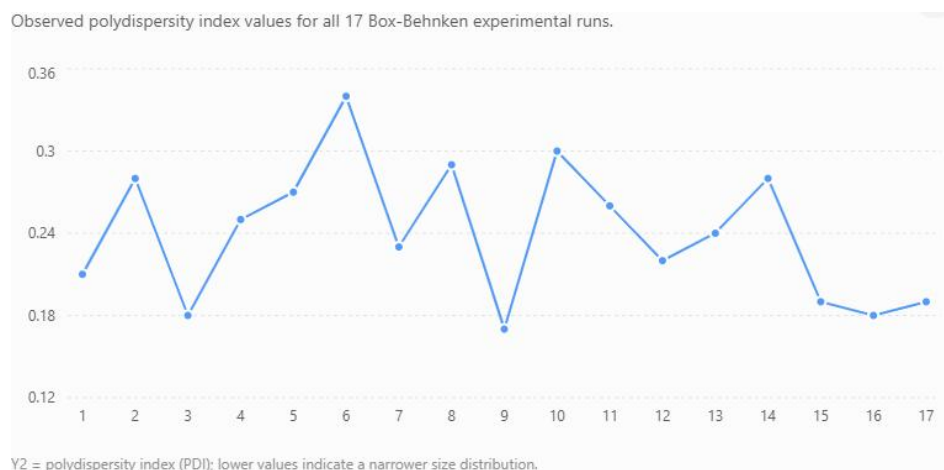


Figure . PDI Across Box-Behnken Experimental Runs

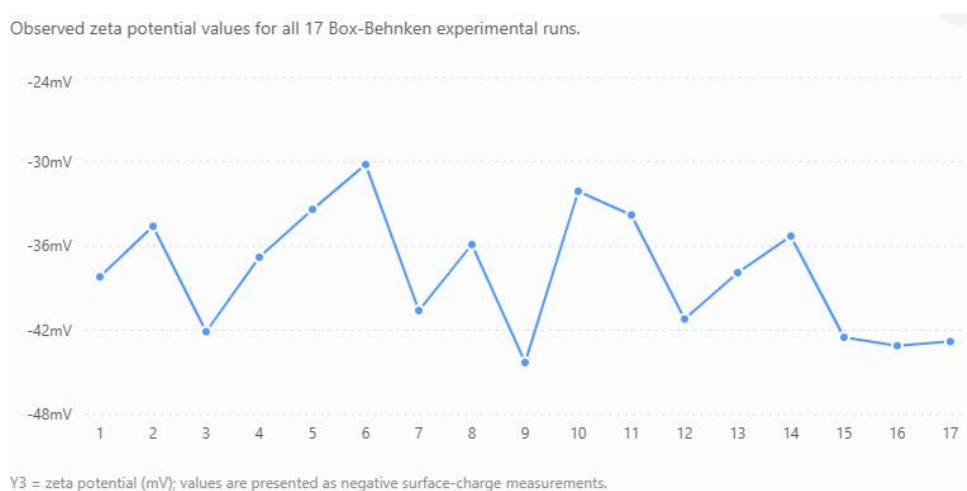


Figure . Zeta Potential Across Box-Behnken Experimental Runs

4.2 Response Surface Analysis and Model Fitting

Quadratic models showed significant correlation ($p < 0.05$) for all responses. Oil concentration significantly influenced droplet size and zeta potential, whereas surfactant concentration primarily affected PDI.

5. Optimization of the Nanoemulsion Formulation

Numerical optimization identified an optimal formulation containing 5.5% oil, 2.8% surfactant, and 2.2% co-surfactant. Predicted and experimental values showed close agreement.

5.1 Validation of Optimized Formulation

The optimized formulation demonstrated a droplet size of ~ 104 nm, PDI ~ 0.19 , and zeta potential ~ -43 mV, confirming the reliability of the optimization model.

6. Evaluation of Nanoemulsion

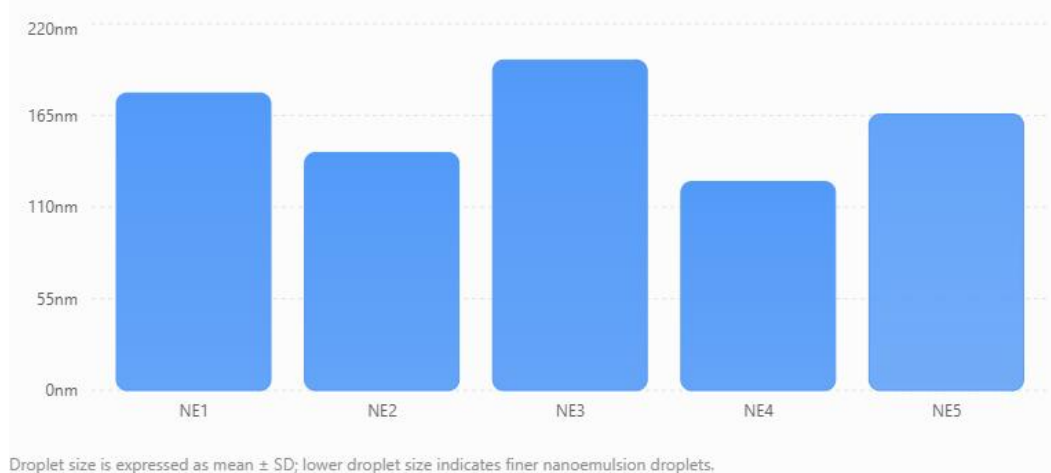
6.1 Droplet Size and Polydispersity Index (PDI)

Droplet size and PDI data are presented in Table 11.

Table 11: Droplet Size and Polydispersity Index (PDI) of Nanoemulsion

Formulation Code	Droplet Size (nm) $\pm$ SD	PDI $\pm$ SD
NE1	178.4 $\pm$ 5.2	0.295 $\pm$ 0.014
NE2	142.7 $\pm$ 4.8	0.221 $\pm$ 0.012
NE3	198.2 $\pm$ 6.3	0.312 $\pm$ 0.015
NE4	125.3 $\pm$ 4.1	0.198 $\pm$ 0.010
NE5	165.8 $\pm$ 5.5	0.278 $\pm$ 0.013

Comparison of mean droplet size values for NE1–NE5 formulations.

**Figure . Droplet Size and PDI of Nanoemulsion Formulations**

NE4 exhibited the smallest droplet size (125.3 nm) and lowest PDI (0.198), indicating a uniform and stable nanoemulsion.

6.2 Zeta Potential

Zeta potential values are shown in Table 12.

Table 12: Zeta Potential of Nanoemulsion

Formulation Code	Zeta Potential (mV) $\pm$ SD
NE1	-28.6 $\pm$ 1.2
NE2	-33.4 $\pm$ 1.4
NE3	-25.2 $\pm$ 1.1
NE4	-41.7 $\pm$ 1.5
NE5	-30.1 $\pm$ 1.3

Comparison of zeta potential values for NE1–NE5 formulations.

**Figure . Zeta Potential of Nanoemulsion Formulations**

NE4 showed the highest zeta potential (-41.7 mV), suggesting excellent electrostatic stability.

6.3 pH Measurement

pH values remained within the skin-compatible range (5.4–6.2), as shown in *Table 13*.

Table 13: pH Values of Nanoemulsion

Formulation Code	pH $\pm$ SD
NE1	5.8 ± 0.1
NE2	5.6 ± 0.1
NE3	5.4 ± 0.2
NE4	6.2 ± 0.1
NE5	5.7 ± 0.2

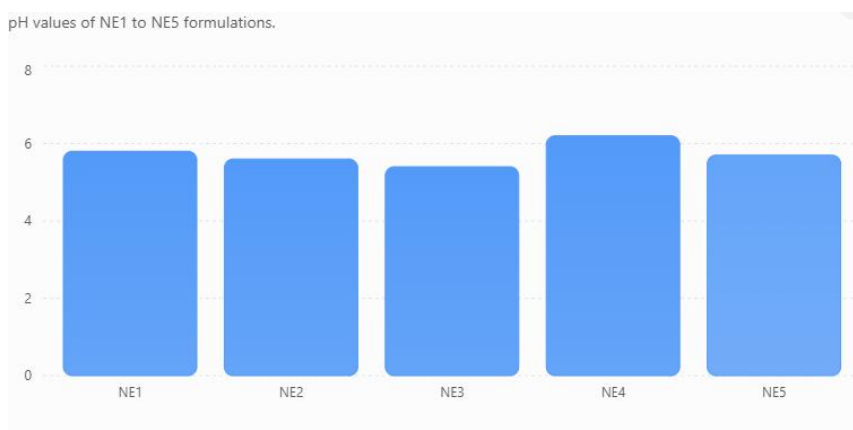


Figure . pH Values of Nanoemulsion Formulations

6.5 Drug Content

Drug content results are summarized in *Table 14*.

Table 14: Drug Content in Nanoemulsion

Formulation Code	Drug Content (%) $\pm$ SD
NE1	94.2 ± 2.1
NE2	96.8 ± 2.0
NE3	92.7 ± 1.9
NE4	98.4 ± 2.2
NE5	95.1 ± 2.1

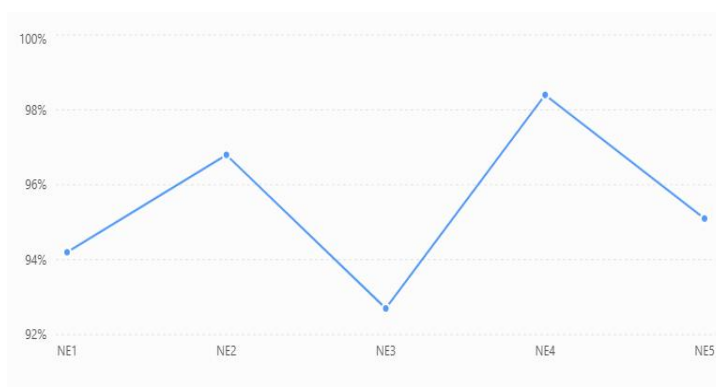


Figure . Drug Content of Nanoemulsion Formulations

NE4 exhibited the highest drug content (98.4%), confirming efficient solubilization.

6.6 Viscosity Measurement

Viscosity values are shown in *Table 15*.

Table 15: Viscosity of Nanoemulsion

Formulation Code	Viscosity (cP) $\pm$ SD
NE1	42.6 $\pm$ 2.1
NE2	48.2 $\pm$ 2.3
NE3	38.9 $\pm$ 2.0
NE4	51.3 $\pm$ 2.5
NE5	44.7 $\pm$ 2.2

NE4 showed optimal viscosity, balancing stability and ease of application.

Based on overall physicochemical evaluation, NE4 was identified as the optimized nanoemulsion formulation.

7. Evaluation of Nanoemulgel

7.1 Spreadability

Spreadability results are shown in *Table 16*.

Table 16: Spreadability of Nanoemulgel Formulations

Formulation Code	Spreadability (cm) $\pm$ SD	Inference
NG1	5.2 $\pm$ 0.3	Moderate
NG2	6.1 $\pm$ 0.2	Good
NG3	4.9 $\pm$ 0.4	Low
NG4	6.8 $\pm$ 0.3	Excellent
NG5	5.5 $\pm$ 0.3	Satisfactory

NG4 exhibited the highest spreadability, indicating superior ease of application.

7.2 Extrudability

Extrudability data are presented in *Table 17*.

Table 17: Extrudability of Nanoemulgel Formulations

Formulation Code	Extrudability (g) $\pm$ SD	Inference
NG1	18.2 $\pm$ 1.1	Moderate
NG2	21.4 $\pm$ 1.3	Good
NG3	16.8 $\pm$ 1.0	Low
NG4	23.7 $\pm$ 1.4	Excellent
NG5	19.5 $\pm$ 1.2	Satisfactory

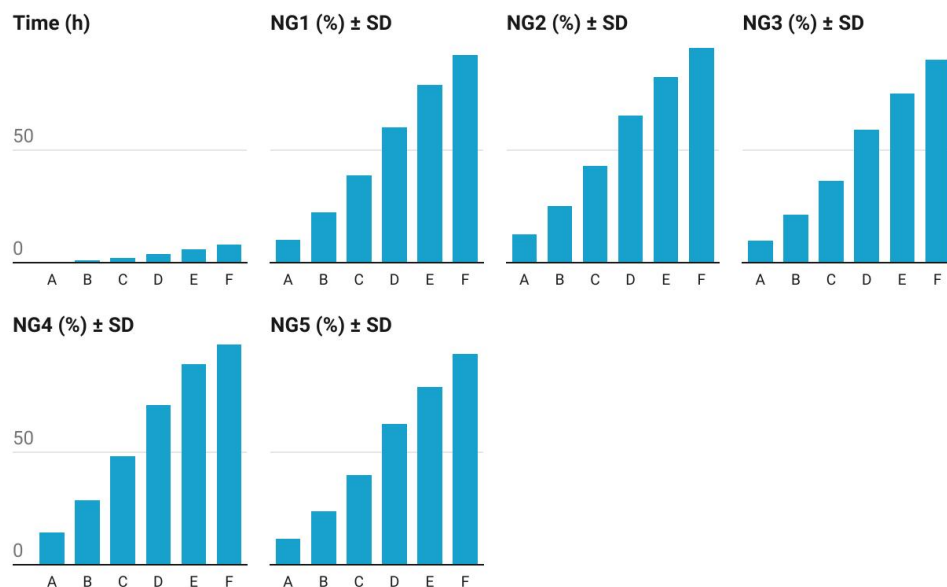
NG4 demonstrated excellent extrudability, enhancing patient compliance.

7.3 In Vitro Drug Release Study

Drug release profiles are shown in *Table 18* and *Figure 2*.

Table 18: Cumulative Drug Release from Nanoemulgel Formulations

Time (h)	NG1 (%) $\pm$ SD	NG2 (%) $\pm$ SD	NG3 (%) $\pm$ SD	NG4 (%) $\pm$ SD	NG5 (%) $\pm$ SD
0.5	10.2 $\pm$ 1.1	12.5 $\pm$ 1.3	9.8 $\pm$ 1.2	14.2 $\pm$ 1.4	11.5 $\pm$ 1.2
1.0	22.4 $\pm$ 1.5	25.2 $\pm$ 1.5	21.3 $\pm$ 1.3	28.6 $\pm$ 1.6	23.8 $\pm$ 1.4
2.0	38.7 $\pm$ 1.8	42.8 $\pm$ 1.8	36.5 $\pm$ 1.6	48.3 $\pm$ 2.0	39.7 $\pm$ 1.7
4.0	60.1 $\pm$ 2.0	65.4 $\pm$ 2.1	58.9 $\pm$ 2.1	70.8 $\pm$ 2.4	62.5 $\pm$ 2.2
6.0	78.9 $\pm$ 2.3	82.6 $\pm$ 2.3	75.2 $\pm$ 2.3	88.9 $\pm$ 2.6	79.1 $\pm$ 2.5
8.0	92.3 $\pm$ 2.5	95.3 $\pm$ 2.5	90.1 $\pm$ 2.6	97.8 $\pm$ 2.7	93.5 $\pm$ 2.6

**Figure 2: Cumulative Drug Release from Nanoemulgel Formulations**

NG4 showed the highest cumulative drug release (97.8% at 8 h).

7.4 Stability Study

Stability results are summarized in Table 19.

Table 19: Stability Study of Nanoemulgel at Different Storage Conditions

Storage Condition	Time (Months)	pH $\pm$ SD	Viscosity (cP) $\pm$ SD	Drug Content (%) $\pm$ SD
25°C $\pm$ 2°C / 60% RH	0	5.8 $\pm$ 0.2	3900 $\pm$ 120	99.2 $\pm$ 1.5
	1	5.7 $\pm$ 0.3	3850 $\pm$ 110	98.5 $\pm$ 1.4
	2	5.6 $\pm$ 0.2	3825 $\pm$ 115	97.9 $\pm$ 1.3
	3	5.5 $\pm$ 0.2	3800 $\pm$ 110	97.4 $\pm$ 1.2
40°C $\pm$ 2°C / 75% RH	0	5.8 $\pm$ 0.2	3900 $\pm$ 120	99.2 $\pm$ 1.5
	1	5.6 $\pm$ 0.3	3750 $\pm$ 115	97.2 $\pm$ 1.3
	2	5.4 $\pm$ 0.2	3650 $\pm$ 110	96.1 $\pm$ 1.2
	3	5.2 $\pm$ 0.2	3550 $\pm$ 105	94.7 $\pm$ 1.2

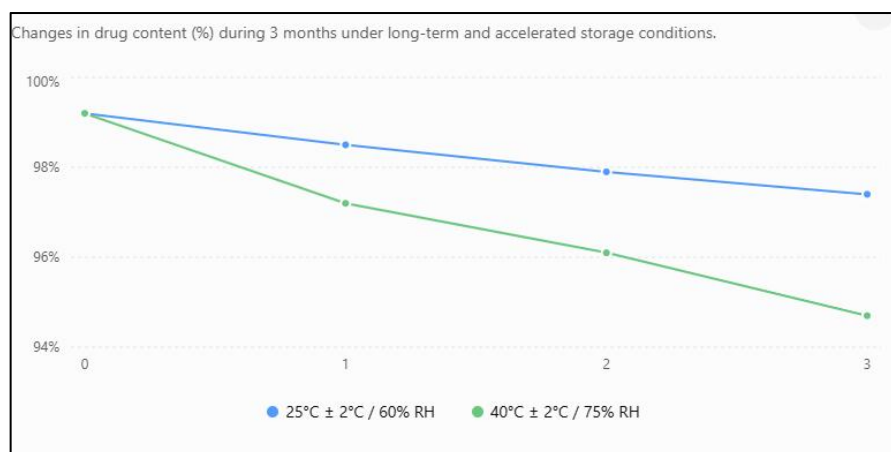


Figure : Stability Study of Nanoemulgel

NG4 remained stable over three months under both storage conditions.

7.5 Drug-Excipient Interaction Study by FTIR

FTIR spectra are presented in Figure 3.

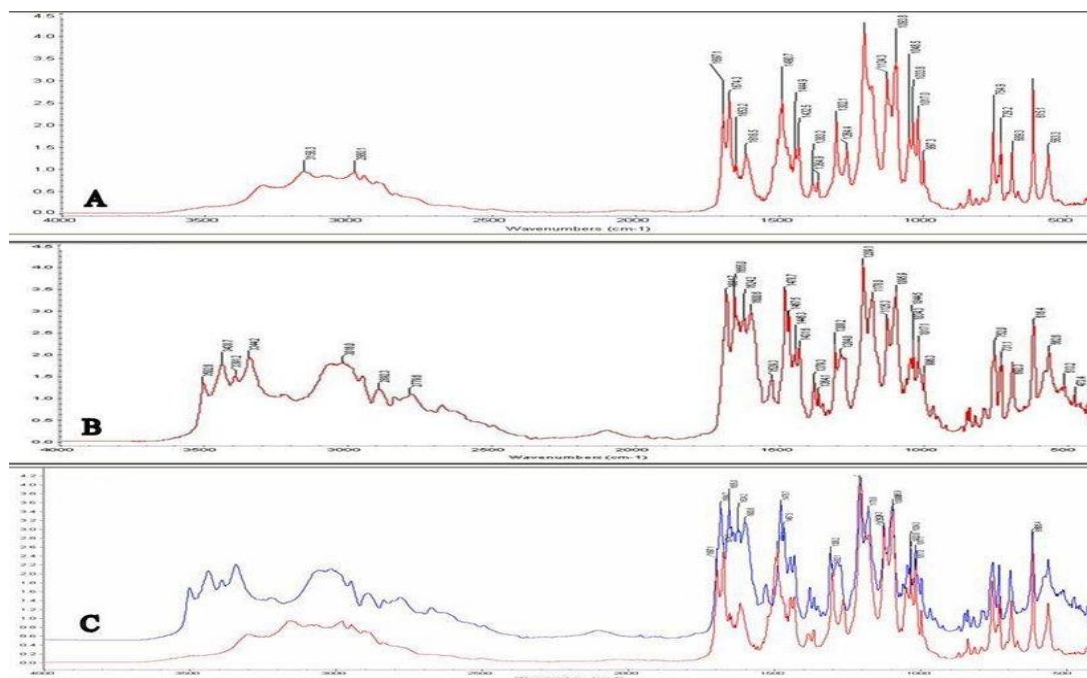


Figure 3: FTIR spectra of Pure drug and excipients

7.5.1 FTIR Spectral Analysis of Pure Isavuconazole

The FTIR spectrum of pure Isavuconazole exhibited characteristic absorption bands corresponding to its functional groups. The major peaks observed were:

- *N-H Stretching (Amide Group):* ~3340 cm⁻¹
- *C=O Stretching (Carbonyl Group):* ~1702 cm⁻¹
- *C-N Stretching (Aromatic Amine):* ~1250 cm⁻¹
- *C-H Stretching (Aromatic Ring):* ~3000-3100 cm⁻¹

These peaks serve as reference signals for identifying any potential interactions with excipients in the formulation.

7.5.2 FTIR Spectra of Individual Excipients

The selected excipients, including oleic acid (oil phase), Tween 80 (surfactant), and Carbopol 940 (gelling agent), were analyzed separately to determine their characteristic absorption bands:

- Oleic Acid: A strong C=O stretching peak around 1710 cm^{-1} and a broad O-H stretching band between 3200-3600 cm^{-1} .
- Tween 80: Displayed a broad O-H stretching peak near 3440 cm^{-1} and characteristic C-O stretching at 1100-1200 cm^{-1} .
- Carbopol 940: Exhibited a broad O-H stretching peak at 3200-3500 cm^{-1} , and a strong C=O peak around 1720 cm^{-1} , typical of carboxyl functional groups.

Each excipient showed distinct peaks without interference from other components. These findings helped establish a baseline for comparison with drug-excipient mixtures.

7.5.3 FTIR Spectra of Physical Mixtures

To evaluate potential interactions, the FTIR spectra of *physical mixtures of Isavuconazole with each excipient (1:1 ratio)* were recorded. The main findings included:

1. *Isavuconazole + Oleic Acid:*
 - The characteristic peaks of Isavuconazole remained largely unchanged in the mixture.
 - A slight shift in the C=O stretching band (1702 cm^{-1} to 1705 cm^{-1}) was observed, indicating weak hydrogen bonding but no significant chemical interaction.
 - No disappearance of major peaks confirmed compatibility.
2. *Isavuconazole + Tween 80:*
 - The broad O-H stretching of Tween 80 (~3440 cm^{-1}) overlapped with the N-H peak of Isavuconazole, but the integrity of the drug's functional groups was maintained.
 - Minor peak shifts in the C-O region (~1100-1200 cm^{-1}) suggested possible weak Van der Waals interactions.
 - No new peaks were observed, indicating no significant chemical modification.
3. *Isavuconazole + Carbopol 940:*
 - The characteristic peaks of Isavuconazole remained visible without substantial changes.
 - A slight shift in the O-H stretching region (3200-3500 cm^{-1}) was noted, likely due to hydrogen bonding.
 - No additional peaks or disappearance of critical functional groups indicated the absence of major drug-excipient interactions.

Minor peak shifts suggested weak intermolecular interactions without chemical incompatibility. The FTIR results confirmed stability and suitability of the selected excipients.

CONCLUSION

The present study successfully developed and evaluated an Isavuconazole-loaded nanoemulgel for topical antifungal therapy. The optimized formulation demonstrated nanosized droplets, uniform drug distribution, satisfactory physicochemical properties, and enhanced in vitro drug release, indicating improved solubility. The incorporation of nanoemulsion into a gel matrix provided suitable viscosity, spreadability, and prolonged skin residence time, thereby improving patient compliance. Compatibility studies confirmed the stability of the formulation, while stability testing indicated no significant changes under different storage conditions. Overall, the developed nanoemulgel represents a promising topical delivery system for effective management of fungal infections.

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