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Formulation and Characterization of Luliconazole Loaded Niosomal Gel

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ABSTRACT

Background: Luliconazole is an effective imidazole antifungal; however, its lipophilicity and poor aqueous solubility can limit topical performance and may require frequent application. Vesicular carriers such as niosomes can improve dermal localization and provide controlled release.

Objective: This study aimed to develop luliconazole-loaded niosomes using Span 60 and cholesterol by thin-film hydration, optimize vesicle composition, and incorporate the optimized dispersion into a Carbopol 934 gel for sustained topical delivery

Methods: Luliconazole was characterized by organoleptic examination, melting point and UV–Visible spectroscopy (λmax 296 nm), and preformulation studies included solubility profiling and FTIR-based compatibility. Eight niosomal batches (F1–F8) were prepared using chloroform:methanol (2:1) with rotary evaporation, hydration in PBS (pH 7.4), and probe sonication. Vesicle size, PDI and zeta potential were determined by DLS. Entrapment efficiency was evaluated by centrifugation and UV quantification of free drug. The optimized batch was incorporated into Carbopol 934 gel and evaluated for appearance, pH, viscosity, spreadability, drug content, in vitro drug release (Franz/dialysis) and stability

Results: Niosomes were obtained in the nanosize range (142.8–218.4 nm) with acceptable PDI (0.198–0.321) and negative zeta potential (−19.6 to −26.5 mV). Entrapment efficiency ranged from 58.32% to 82.34%, with batch F4 showing the best overall characteristics (142.8 ± 2.9 nm, PDI 0.198, −26.5 ± 1.3 mV, 82.34 ± 1.25%). The niosomal gel showed skin-compatible pH (6.01 ± 0.03), pseudoplastic rheology, high drug content (98.64 ± 0.51%) and sustained release compared with plain gel (12 h: 76.30% vs 98.76%).

Conclusion: Span 60 niosomal gel provided stable nanosized vesicles, high drug entrapment and sustained release, supporting its potential as an improved topical delivery system for luliconazole**.**

Keywords: *Luliconazole; niosomes; Span 60; Carbopol 934; topical gel; entrapment efficiency; sustained release*

1. INTRODUCTION

Superficial fungal infections such as dermatophytosis and cutaneous candidiasis remain common worldwide and are primarily managed by topical antifungal therapy. Luliconazole is a potent imidazole antifungal widely used for tinea infections; however, its therapeutic effectiveness can be influenced by formulation-related constraints such as low aqueous solubility and limited diffusion across the stratum corneum, which may reduce drug availability at deeper infected sites and necessitate repeated application. Vesicular drug delivery systems have been explored to overcome such barriers by enhancing drug partitioning into skin lipids, improving retention in the epidermis, and modulating drug release. (1-5)

Niosomes are non-ionic surfactant–based vesicles capable of entrapping lipophilic drugs within their bilayer domain and releasing them in a controlled manner. (5-7) Compared with conventional topical gels, niosomal gels can provide a dual-control mechanism: (i) diffusion resistance through the vesicular bilayer and (ii) diffusional limitation through the semisolid gel network. The surfactant–cholesterol ratio is critical because cholesterol stabilizes vesicle membranes by reducing bilayer permeability and increasing packing density, while surfactant concentration affects bilayer fluidity and vesicle size

distribution. Hence, optimizing Span 60 and cholesterol levels is essential for achieving nanosized vesicles with narrow distribution and high entrapment. (8-14)

Carbopol 934 is frequently employed as a topical gelling agent because it forms clear, stable and pseudoplastic gels, supporting ease of application and high residence time at the site of administration. Incorporation of optimized niosomal dispersion into a Carbopol base can improve patient acceptability and stability while sustaining drug release. (15-18) Therefore, this work was designed to formulate luliconazole-loaded Span 60 niosomes using thin-film hydration, optimize vesicle properties across multiple formulations, and develop a Carbopol 934 niosomal gel with sustained release behavior.(19-20)

The present study was designed to develop and optimize a luliconazole-loaded niosomal gel with the objective of overcoming the inherent limitations of conventional topical luliconazole formulations, particularly poor aqueous solubility, limited permeation across the stratum corneum, and suboptimal local drug retention. The research aimed to formulate luliconazole-encapsulated niosomes using appropriate Span 60–cholesterol ratios to achieve nanosized vesicles with high entrapment efficiency and controlled release characteristics. Further, the optimized niosomal dispersion was intended to be incorporated into a Carbopol-based gel system to obtain a stable, cosmetically acceptable, and patient-friendly topical formulation with improved spreadability and rheological properties. The study also sought to systematically evaluate the physicochemical characteristics of the developed niosomal gel, including pH, viscosity, homogeneity, spreadability, and drug content, and to investigate its in-vitro drug release behavior and release kinetics in comparison with a conventional plain gel. Collectively, these objectives were directed toward establishing a sustained-release topical delivery system capable of enhancing dermal retention and antifungal efficacy of luliconazole.,.

2. Materials and methods

2.1. Materials

Luliconazole was used as the active pharmaceutical ingredient (API) for the development of the topical antifungal formulation. Span 60 (sorbitan monostearate) was selected as the non-ionic surfactant for niosome formation, while cholesterol was incorporated as a bilayer stabilizer to enhance vesicle rigidity and encapsulation efficiency. Carbopol 934 served as the gelling polymer for preparation of the topical gel base, with glycerin included as a humectant to improve smoothness and hydration. Triethanolamine (TEA) was used as a neutralizing agent to adjust the pH of the gel formulation. Methyl paraben and propyl paraben were employed as antimicrobial preservatives. Chloroform (AR grade) and methanol (HPLC grade) were used as organic solvents for thin-film formation and analytical procedures, respectively. Phosphate buffer saline (PBS, pH 7.4) was utilized as the hydration medium for niosome preparation and as the receptor medium in *in vitro* release studies. Potassium bromide (KBr) was used for FTIR pellet preparation. Dialysis membrane (12–14 kDa MWCO) and Whatman filter paper No. 1 were employed during *in vitro* release experiments and sample filtration.

2.2 Methods

2.2.1. Drug characterization and preformulation studies

Organoleptic evaluation

Luliconazole was visually examined for color, odor, texture, and appearance under adequate illumination to assess physical purity and exclude visible contamination or degradation.

Melting point

The melting point was determined using a capillary melting point apparatus. Luliconazole was packed in a capillary tube and heated gradually; the onset and completion temperatures of melting were recorded.

UV–Visible spectroscopy and calibration curve

A standard stock solution of luliconazole was prepared in a suitable solvent (e.g., methanol). The spectrum was scanned between 200–400 nm to determine λmax (296 nm). Working standards (e.g., 5–25 µg/mL) were prepared and absorbance was measured at 296 nm to construct a calibration curve for subsequent drug estimation.

Solubility studies

Solubility was assessed using the shake-flask method. Excess luliconazole was added to 10 mL of each medium (distilled water, methanol, ethanol, phosphate buffer pH 6.8, phosphate buffer pH 7.4), shaken at 25 ± 2°C for 24 h, allowed to settle, and filtered (Whatman No. 1). Filtrates were suitably diluted and analyzed at 296 nm.

Drug–excipient compatibility (FTIR)

Physical mixtures (1:1, w/w) of luliconazole with Span 60, cholesterol, and Carbopol 934 were prepared by geometric mixing. FTIR spectra were recorded using the KBr pellet method over 4000–400 cm^{-1} and compared with pure drug spectra to identify peak shifting, disappearance, or new peak formation.

2.2.2. Preparation of luliconazole-loaded niosomes

Thin-film hydration method

Niosomes were prepared by thin-film hydration followed by probe sonication. Luliconazole, Span 60, and cholesterol were dissolved in chloroform:methanol (2:1, v/v) in a round-bottom flask. Solvent was removed using a rotary evaporator at 55–65°C under reduced pressure to form a thin film. The flask was kept under vacuum for 1–2 h to eliminate residual solvent. The dried film was hydrated with pre-warmed PBS (pH 7.4) at 55–60°C for 1 h with gentle rotation to obtain multilamellar vesicles. The dispersion was probe-sonicated (pulsed mode) for 10–15 min using an ice bath to produce nanosized vesicles.

Table 1 Composition of luliconazole-loaded niosomal formulations (F1–F8)

Batch	Luliconazole (mg)	Span 60 (mg)	Cholesterol (mg)	Surfactant:Cholesterol ratio	Organic phase (mL) (Chloroform:Methanol 2:1)	PBS pH 7.4 (mL)
F1	100	100	50	1.81:1	10	20
F2	100	100	100	0.90:1	10	20
F3	100	150	75	1.81:1	10	20
F4	100	150	100	1.35:1	10	20
F5	100	200	50	3.62:1	10	20
F6	100	200	100	1.81:1	10	20
F7	100	250	75	3.02:1	10	20
F8	100	250	125	1.81:1	10	20

2.2.3. Characterization of niosomes

Vesicle size, PDI and zeta potential

Vesicle size distribution and zeta potential were measured by dynamic light scattering at 25°C. Samples were suitably diluted to minimize multiple scattering. Measurements were performed in triplicate and reported as mean ± SD.

Entrapment efficiency

Entrapment efficiency (%EE) was determined by an indirect centrifugation method. Niosomal dispersion was centrifuged at 15,000 rpm for 1 h at 4°C. The supernatant containing free drug was collected, diluted with methanol, and analyzed at 296 nm

Drug content

A measured volume of niosomal dispersion was treated with methanol (or methanol:chloroform) to disrupt vesicles and extract luliconazole. The mixture was vortexed/sonicated, filtered, diluted appropriately, and analyzed at 296 nm. Drug content was expressed as percent of theoretical loading.

In vitro drug release (niosomes)

In vitro release was performed using a dialysis membrane diffusion setup or Franz diffusion cell. Dialysis membrane (pre-soaked) was mounted between donor and receptor compartments. Niosomal dispersion equivalent to a known drug amount was placed in the donor compartment. The receptor compartment contained PBS pH 7.4 (sink maintained; small ethanol fraction may be used if required) and was maintained at 37 ± 0.5°C under continuous stirring. Samples were withdrawn at predetermined intervals and replaced with fresh medium. Drug concentration was determined spectrophotometrically at 296 nm, and cumulative drug release (%) was calculated.

2.2.4. Preparation of luliconazole niosomal gel

Gel base preparation

Carbopol 934 was dispersed in distilled water with continuous stirring and allowed to hydrate for 12–24 h. Glycerin was incorporated as humectant. Preservatives were dissolved separately in a small volume of warm water and added to the hydrated Carbopol dispersion. The gel was neutralized using TEA added dropwise until pH 5.5–6.5, yielding a homogeneous gel base.

Incorporation of niosomes

The optimized niosomal dispersion (F4) containing luliconazole equivalent to 1% w/w was incorporated gradually into the

gel base with gentle stirring to avoid vesicle rupture and air entrapment. The final weight was adjusted with distilled water. The prepared gel was stored in airtight, light-protected containers and equilibrated for 24 h prior to evaluation.

Table 2 Composition of luliconazole-loaded niosomal gel

Component	Function	Quantity (% w/w)
Luliconazole niosomal dispersion (equiv. 1% luliconazole)	Antifungal drug (vesicular form)	1.0
Carbopol 934	Gelling agent	0.8
Glycerin	Humectant	5.0
Methyl paraben	Preservative	0.18
Propyl paraben	Preservative	0.02
TEA	Neutralizer/pH adjuster	q.s. (pH 5.5–6.5)
Distilled water	Vehicle	q.s. to 100

2.2.5 Evaluation of niosomal gel

Appearance and homogeneity

The gel was inspected visually against white and black backgrounds for color, clarity, smoothness, grittiness, air bubbles, and phase separation.

pH

One gram of gel was dispersed in 10 mL distilled water and pH was measured using a calibrated digital pH meter (n = 3).

Viscosity and rheology

Viscosity was measured using a Brookfield viscometer at 25 ± 1°C using an appropriate spindle at different rpm to evaluate shear dependence.

Spreadability

Spreadability was determined using the glass slide method by measuring the time required for the upper slide to move a fixed distance under a standard load; values were expressed as g·cm/s (n = 3).

Drug content

Gel (equivalent to a known luliconazole amount) was extracted with methanol, sonicated, filtered, diluted, and analyzed at 296 nm. Drug content was expressed as percentage of theoretical content.

In vitro release (gel)

In vitro release was performed using a Franz diffusion cell/dialysis membrane. The gel was applied on the membrane in the donor compartment. The receptor compartment contained PBS pH 7.4 maintained at 37 ± 0.5°C with constant stirring. Samples were collected at predetermined intervals and replaced with fresh medium. Drug concentration was quantified at 296 nm and cumulative release (%) was calculated.

2.2.6. Stability studies

The optimized niosomal gel was stored under refrigerated (4–8°C), room temperature (25 ± 2°C), and accelerated conditions (40 ± 2°C/75% RH). At predetermined intervals (up to 1–3 months), samples were evaluated for appearance, pH, viscosity, drug content, and *in vitro*release. All measurements were performed in triplicate and reported as mean ± SD.

3. Results and discussion

The present study aimed to develop and optimize a **luliconazole-loaded niosomal gel** using **Span 60 and cholesterol** to enhance topical delivery, improve drug retention at the infection site, and achieve sustained antifungal release. The results are discussed in a stepwise manner starting from drug characterization and preformulation assessment, followed by optimization of niosomal vesicles (F1–F8), incorporation of the optimized batch into a Carbopol gel base, comparative performance evaluation against a plain gel, and short-term stability assessment. Overall, formulation variables—particularly the **Span 60: cholesterol ratio**—significantly influenced vesicle size distribution, surface charge, drug entrapment, and release behavior, which subsequently governed gel performance and stability.

3.1. Drug characterization

Luliconazole was characterized to establish its baseline physicochemical identity and suitability for vesicular encapsulation. The drug appeared as a white to off-white crystalline powder with no characteristic odor and a fine free-flowing texture, indicating acceptable physical purity and absence of moisture-related degradation. Melting point analysis showed a sharp melting range (151–153 °C), consistent with reported values (152–154 °C), supporting crystalline purity and thermal stability. UV–visible spectrophotometry demonstrated a distinct absorption maximum at **296 nm**, which was subsequently used for quantitative estimation in calibration, drug content, and release studies.

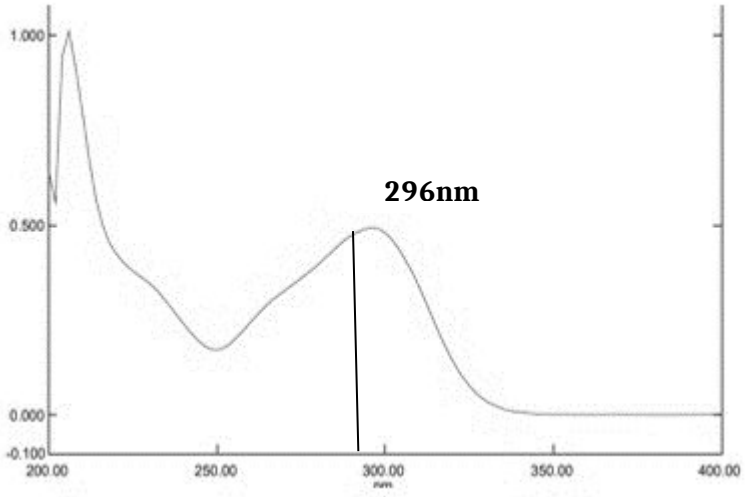


Fig. 7.1. UV–visible absorption spectrum of luliconazole showing λmax at 296 nm.

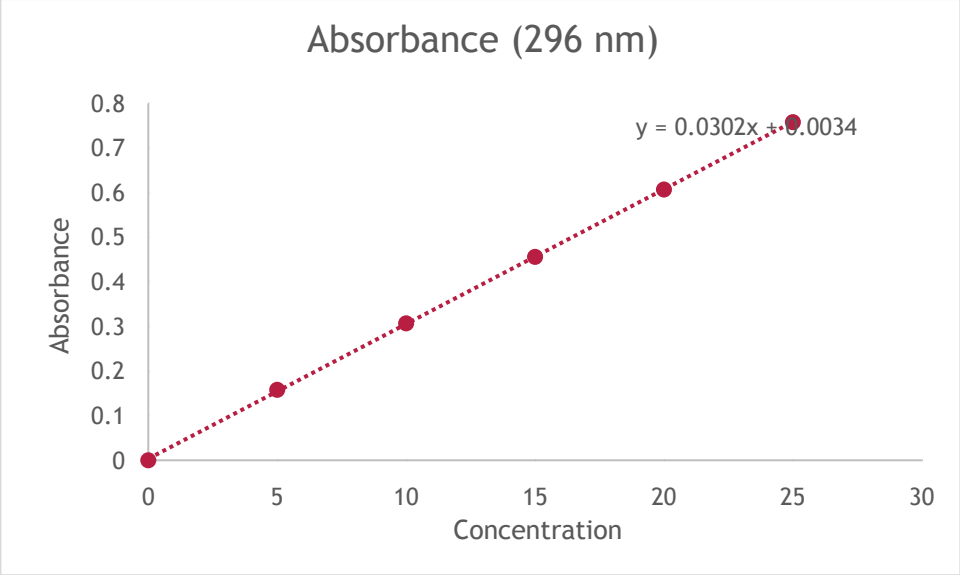
3.2. Calibration curve in phosphate buffer (pH 7.4)

A calibration curve was prepared in phosphate buffer pH 7.4 across 5–25 µg/mL to support quantitative analysis of release samples and drug content. The absorbance increased proportionally with concentration, indicating a linear response over the studied range and confirming the suitability of the selected wavelength for analysis in the release medium.

Table 4 Calibration curve data of luliconazole in phosphate buffer (pH 7.4) at 296 nm.

Concentration (µg/mL)	Absorbance (296 nm)
0	0.000
5	0.158
10	0.307
15	0.456
20	0.607
25	0.758

Fig. 1. Calibration curve of luliconazole in phosphate buffer (pH 7.4) at 296 nm.



3.3. Preformulation studies

Organoleptic properties

The organoleptic profile of luliconazole was consistent with reference descriptions and indicated adequate physical stability for formulation development. The absence of discoloration, odor, and clumping suggested low risk of degradation or moisture uptake during processing.

Table 3 Organoleptic and physical characteristics of luliconazole.

Parameter	Observation	Inference
Color	White to off-white crystalline powder	Pure drug, no discoloration or degradation
Odor	Odorless	Absence of volatile impurities; chemically stable
Texture	Fine crystalline, non-gritty	Suitable for uniform dispersion in formulation
Appearance	Free-flowing, non-hygroscopic	Good stability; no moisture uptake

Solubility profile

Solubility assessment confirmed the lipophilic nature of luliconazole. The drug was practically insoluble in water and showed only slight solubility in phosphate buffers (pH 6.8 and 7.4), while exhibiting high solubility in organic solvents (methanol, ethanol, chloroform). This solubility behavior supports the need for a lipid/surfactant-based vesicular system to improve apparent solubility and control topical delivery.

Table 7.4 Solubility profile of luliconazole in different solvents.

Solvent	Solubility (mg/mL)	Inference
Distilled Water	< 0.01 mg/mL	Highly lipophilic compound with extremely poor aqueous solubility
Phosphate Buffer pH 6.8	0.05 – 0.10 mg/mL	Slight solubility due to limited ionization at near-neutral pH
Phosphate Buffer pH 7.4	0.10 – 0.25 mg/mL	Marginally improved solubility in alkaline pH; still poorly water-soluble
Methanol	> 10 mg/mL (typically 20–50 mg/mL)	Freely soluble; strong affinity for polar organic solvents
Ethanol	> 10 mg/mL (typically 15–40 mg/mL)	Freely soluble; suitable for organic phase preparation

Chloroform	> 20 mg/mL (often > 50 mg/mL)	Excellent solubility in non-polar solvent; ideal for lipid vesicle formation
Propylene Glycol	1 – 5 mg/mL	Moderately soluble; useful as a topical co-solvent and penetration enhancer

Drug–excipient compatibility (FTIR)

FTIR spectra of luliconazole displayed characteristic peaks corresponding to key functional groups (e.g., C=N stretching, aromatic C=C stretching, C–Cl stretching, and ring vibrations). The spectra of physical mixtures of drug with Span 60, cholesterol, and Carbopol 934 retained the principal drug peaks without significant shifting, disappearance, or formation of new peaks. This indicates **no chemical incompatibility**, supporting excipient suitability for niosome formation and gel incorporation.

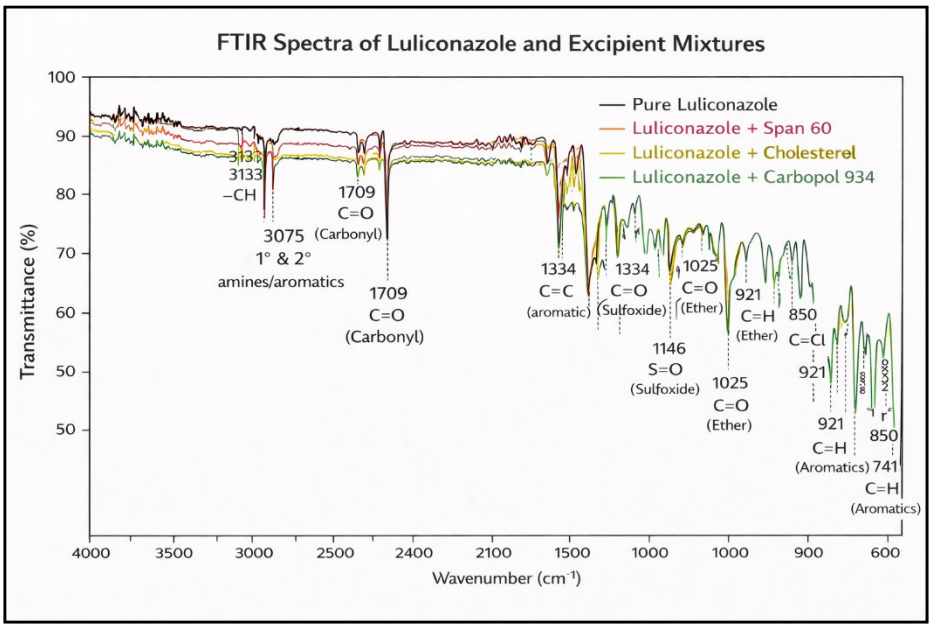


Fig. 7.3. FTIR spectra of luliconazole and physical mixtures with Span 60, cholesterol, and Carbopol 934.

Table 5 FTIR peak assignment of luliconazole and drug–excipient mixtures.

Sample	Characteristic Peaks (cm^{-1})	Assigned Functional Group	Observation	Interpretation
Pure Luliconazole	1580–1600, 1500, 1250, 1020, 780	C=N stretch, Aromatic C=C, C–Cl, C–O, Imidazole ring	Reference spectrum	—
Drug + Span 60	Peaks same as pure drug: 1583, 1502, 1248, 1022	No functional group change	No shift	Compatible; no interaction
Drug + Cholesterol	Peaks at 1584, 1501, 1250, 1021	Drug peaks unchanged	No shift	Compatible; bilayer formation safe
Drug + Carbopol 934	Peaks at 1582, 1503, 1249, 1020	Drug peaks present; Carbopol C=O at ~1710	No shift	No interaction; gel base suitable

3.4. Evaluation and optimization of luliconazole-loaded niosomes (F1–F8)

Niosomal batches (F1–F8) were prepared by thin-film hydration followed by sonication. Variation in **Span 60:cholesterol composition** produced measurable changes in vesicle characteristics. Vesicle size ranged from **142.8 ± 2.9 nm to 218.4 ± 4.2 nm**, confirming nanosized vesicle formation across all batches. The smallest vesicle size and lowest PDI were observed for **F4**, indicating efficient film hydration, bilayer formation, and uniform sonication outcome. The PDI values (0.198–0.321) indicated acceptable distribution, with F4 showing the most homogeneous population (PDI < 0.2). Zeta potential values were

moderately negative (–19.6 to –26.5 mV), suggesting sufficient electrostatic repulsion for dispersion stability, with F4 again showing the most favorable surface charge.

Entrapment efficiency varied markedly (58.32–82.34%). Lower Span 60 content (e.g., F1–F2) likely produced fewer hydrophobic domains for drug partitioning, reducing entrapment. Excess surfactant at high ratios (e.g., F7) may increase bilayer permeability or lamellarity, limiting further improvement. F4 showed the highest entrapment efficiency, which can be attributed to an optimal balance between **bilayer rigidity (cholesterol)** and **bilayer-forming surfactant content (Span 60)**. Drug content remained consistently high (94.85–98.04%), indicating minimal loss during processing and good reproducibility.

Table 6 Physicochemical characterization of luliconazole-loaded niosomal batches (F1–F8).

Batch	Vesicle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)	Drug Content (%)	% CDR at 8 h
F1	218.4 ± 4.2	0.321	–19.6 ± 1.1	58.32 ± 1.24	94.85 ± 0.84	54.62 ± 1.18
F2	195.6 ± 3.8	0.284	–20.8 ± 1.4	64.15 ± 1.62	95.42 ± 0.72	49.81 ± 1.05
F3	168.2 ± 3.1	0.241	–23.4 ± 1.2	72.46 ± 1.38	97.16 ± 0.69	46.72 ± 1.12
F4	142.8 ± 2.9	0.198	–26.5 ± 1.3	82.34 ± 1.25	98.04 ± 0.51	41.92 ± 0.98
F5	176.4 ± 3.4	0.265	–22.1 ± 1.0	68.85 ± 1.54	96.38 ± 0.62	52.14 ± 1.21
F6	161.0 ± 3.0	0.231	–24.3 ± 1.5	75.62 ± 1.42	97.25 ± 0.57	47.83 ± 1.10
F7	188.7 ± 3.6	0.301	–21.4 ± 1.3	70.28 ± 1.33	96.72 ± 0.66	51.60 ± 1.15
F8	173.2 ± 3.2	0.247	–23.1 ± 1.2	77.14 ± 1.29	97.84 ± 0.59	45.30 ± 1.06

Effect of Span 60: cholesterol ratio on vesicle size and PDI

Cholesterol-rich compositions produced larger vesicles due to increased membrane rigidity and reduced bilayer flexibility. In contrast, increasing surfactant proportion reduced vesicle size up to an optimum, beyond which lamellarity and broader distribution may increase. This behavior highlights a formulation "optimum window" where vesicles are small, uniform, and stable.

Table 7 Effect of Surfactant–Cholesterol Ratio on Physicochemical Characteristics of Luliconazole-Loaded Niosomes (F1–F8)

Batch	Surfactant : Cholesterol Ratio	Vesicle Size (nm)	PDI	Zeta Potential (mV)*	Entrapment Efficiency (%EE)	Drug Content (%)	Interpretation
F1	1 : 0.5	218.4 ± 4.2	0.321	–19.6 ± 1.1	58.32 ± 1.24	94.85 ± 0.84	Excess cholesterol increased bilayer rigidity, resulting in larger vesicles, broad size distribution, and low entrapment
F2	1 : 1	195.6 ± 3.8	0.284	–20.8 ± 1.4	64.15 ± 1.62	95.42 ± 0.72	Balanced ratio improved vesicle uniformity and moderately enhanced drug entrapment
F3	2 : 1	168.2 ± 3.1	0.241	–23.4 ± 1.2	72.46 ± 1.38	97.16 ± 0.69	Increased surfactant content reduced vesicle size and significantly improved entrapment
F4	1.5 : 1	142.8 ± 2.9	0.198	–26.5 ± 1.3	82.34 ± 1.25	98.04 ± 0.51	Optimized formulation with

							smallest vesicle size, highest stability, maximum entrapment, and uniform drug loading
F5	4 : 1	176.4 ± 3.4	0.265	–22.1 ± 1.0	68.85 ± 1.54	96.38 ± 0.62	Excess surfactant increased bilayer fluidity, causing moderate polydispersity and reduced EE
F6	2 : 1	161.0 ± 3.0	0.231	–24.3 ± 1.5	75.62 ± 1.42	97.25 ± 0.57	Stable vesicles with good size uniformity and high entrapment efficiency
F7	3.3 : 1	188.7 ± 3.6	0.301	–21.4 ± 1.3	70.28 ± 1.33	96.72 ± 0.66	High surfactant promoted lamellarity, increasing PDI and permeability
F8	2 : 1	173.2 ± 3.2	0.247	–23.1 ± 1.2	77.14 ± 1.29	97.84 ± 0.59	High EE and acceptable size uniformity, but less optimal than F4

In vitro drug release from niosomal suspensions

All batches showed a biphasic release behavior: an early phase attributed to surface-associated drug, followed by sustained diffusion from the bilayer core. Controlled release was enhanced in formulations with appropriate cholesterol content due to reduced bilayer permeability. F4 showed the most sustained release profile among batches while maintaining high entrapment, indicating strong bilayer integrity and controlled diffusional release.

Table 8 *In vitro* cumulative drug release profile of luliconazole-loaded niosomes (F1–F8).

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8
1 h	8.6	12.8	11.4	**14.2**	13.6	12.1	13.9	11.8
2 h	15.3	22.6	20.1	**25.4**	24.8	21.8	23.0	19.9
4 h	29.4	38.4	34.8	**41.7**	40.5	36.2	38.1	33.5
6 h	36.7	49.6	45.2	**52.8**	51.4	47.0	48.3	42.9
8 h	41.9	49.8	46.7	**54.6**	52.1	47.8	51.6	45.3
12 h	52.3	65.4	60.1	**72.8**	68.0	62.7	66.2	58.9

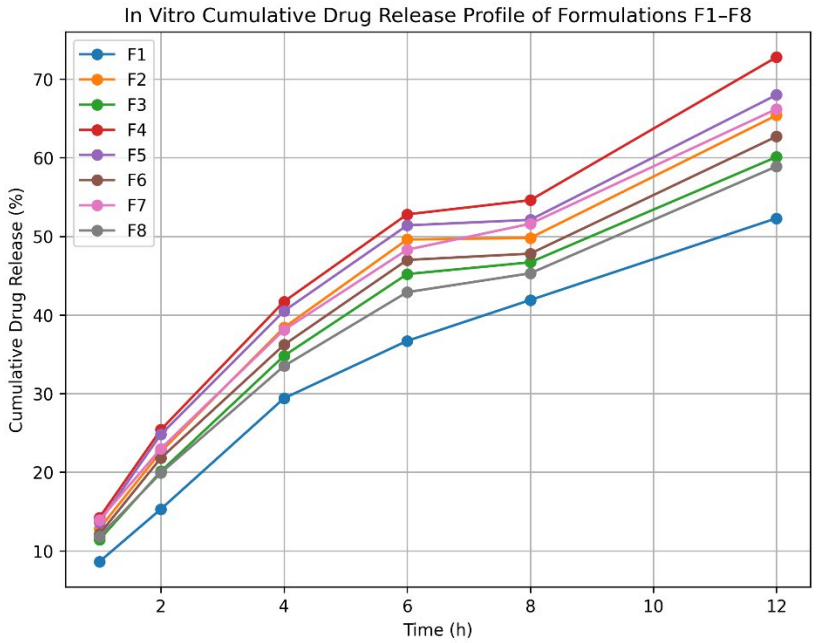


Fig. 4. *In vitro* cumulative drug release profiles of luliconazole-loaded niosomes (F1–F8) over 12 h.

Selection of optimized batch

Based on the collective performance—smallest vesicle size, lowest PDI, most negative zeta potential, highest entrapment efficiency, high drug content, and sustained release—**F4** was selected as the optimized batch for gel incorporation.

Table 9 Key attributes of optimized niosomal batch (F4).

Parameter	**Value (F4)**	**Acceptance / Inference**
Vesicle Size (nm)	142.8 ± 2.9	Ideal nanosize enhances skin penetration
PDI	0.198	Excellent uniformity (<0.3)
Zeta Potential (mV)	–26.5 ± 1.3	Strong electrostatic stability
Entrapment Efficiency (%)	82.34 ± 1.25	High EE; optimal bilayer structure
Drug Content (%)	98.04 ± 0.51	Uniform and efficient drug incorporation
% Release at 2 h	25.4	Minimal burst release
% Release at 4 h	41.7	Controlled initial release
% Release at 8 h	54.6	Most sustained among all batches
% Release at 12 h	72.8	Prolonged release; ideal for topical therapy
Overall Conclusion	—	**Optimized batch with best sustained delivery profile**

3.5. Evaluation of luliconazole niosomal gel

The optimized niosomes (F4) were incorporated into a Carbopol 934 gel base to improve residence time, patient acceptability, and controlled release behavior. The niosomal gel was smooth, translucent, and homogeneous, indicating successful incorporation without visible aggregation or phase separation. The pH (6.01 ± 0.03) remained within the skin-compatible range, supporting topical suitability. Rheological evaluation confirmed pseudoplastic behavior, which is desirable for topical gels because viscosity decreases on shear (easy spreading) while remaining sufficiently high at rest (good retention). Spreadability improved compared to plain gel, suggesting reduced internal resistance and better application comfort. Drug content remained high and uniform, supporting consistent drug distribution within the gel matrix.

Table 10 Physicochemical evaluation of luliconazole niosomal gel (mean ± SD, n = 3).

Parameter	Result (mean ± SD, n = 3)	Remarks
Appearance	Smooth, translucent, homogeneous	No grittiness, no phase separation
pH (25 ± 1°C)	6.01 ± 0.03	Within skin-compatible range (5.5–6.5)
Viscosity at 10 rpm (cps)*	28,500 ± 210	High viscosity at low shear; good retention
Viscosity at 20 rpm (cps)*	22,300 ± 150	Shear-thinning behavior (pseudoplastic)
Viscosity at 50 rpm (cps)*	15,200 ± 130	Marked decrease in viscosity with shear
Spreadability (g·cm/s)	8.40 ± 0.30	Excellent spreadability; easy application
Drug Content (%)	98.64 ± 0.51	Uniform drug distribution in gel matrix
Extrudability (qualitative)	Good, smooth extrusion from collapsible tube	Suitable for patient use and dosage accuracy

3.6. Comparative *in vitro* release: plain gel vs niosomal gel

The plain gel exhibited rapid release and approached near-complete drug diffusion within the study duration, while the niosomal gel showed sustained release with significantly reduced early release. This sustained profile can be explained by the **dual diffusion barrier** created by the vesicular bilayer and the Carbopol gel network, which slows drug partitioning into the receptor medium. The reduced burst release and prolonged delivery support the expected therapeutic advantage for topical antifungal therapy, including improved residence time and potentially reduced dosing frequency.

Table 11 Comparative *in vitro*drug release from plain luliconazole gel and luliconazole niosomal gel.

Time (h)	Plain Luliconazole Gel (% CDR)	Luliconazole Niosomal Gel (% CDR)
0.5	20.15	8.12
1	32.40	12.45
2	38.50	21.40
4	61.72	39.84
6	76.05	51.02
8	88.34	61.92
10	94.10	69.18
12	98.76	76.30

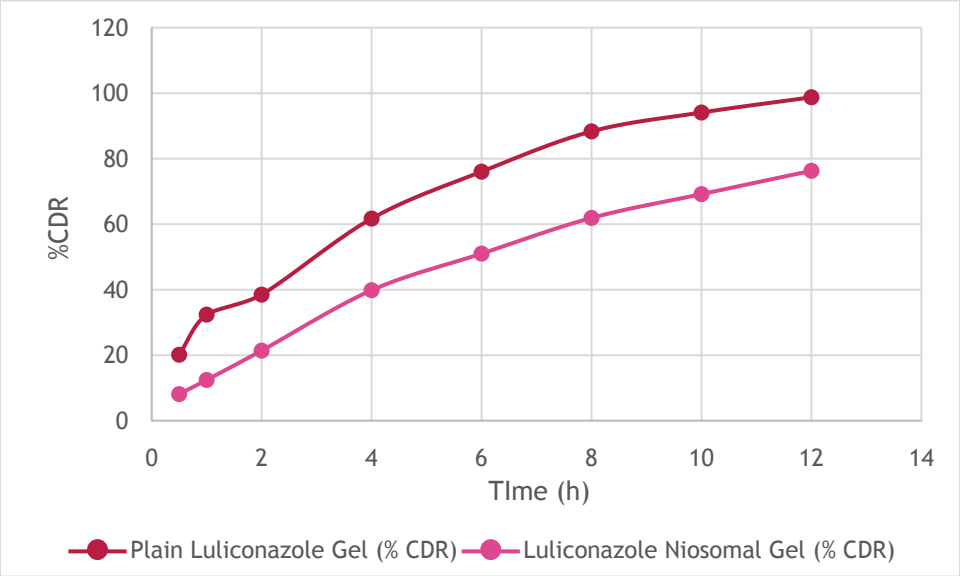


Fig. 5. Comparative *in vitro* release profiles of plain luliconazole gel and luliconazole niosomal gel over 12 h.

Table 12: Comparative evaluation of plain gel and optimized niosomal gel (F4-based).

Parameter	Plain Luliconazole Gel (PG)	Luliconazole Niosomal Gel (Fopt)
Appearance	Smooth, opaque, homogeneous	Smooth, translucent, homogeneous
pH (mean ± SD, n = 3)	6.42 ± 0.05	6.01 ± 0.03
Viscosity (cps) at 25 ± 1°C (20 rpm)	18,500 ± 120	22,300 ± 150
Rheological Behaviour	Pseudoplastic	Pseudoplastic (shear-thinning)
Spreadability (g·cm/s)	6.8 ± 0.25	8.4 ± 0.30
Drug Content (%)	95.72 ± 0.82	98.64 ± 0.51
Physical Stability (Appearance)	Slight opacity increases at 30 days	No change even after 90 days
pH After Stability Study (30 days)	6.48	6.05
Viscosity Change After Stability (%)	–6.4%	–2.2%

3.7. Stability study of optimized niosomal gel

Short-term stability under refrigerated, room, and accelerated conditions showed no major changes in appearance, indicating preserved gel homogeneity and vesicle integrity. The pH remained within a narrow range (6.01–6.05), suggesting minimal hydrolytic changes. Viscosity reduction was small (~2.2%), confirming retention of gel structure and rheological behavior. Drug content decreased only slightly (from 98.64 ± 0.51% to 97.02 ± 0.68%), indicating good chemical stability of luliconazole in the vesicle–gel matrix. Overall, these findings support the robustness of the niosomal gel system and its suitability for topical application with acceptable short-term stability.

Table 13 Stability study data of optimized luliconazole niosomal gel (0–90 days).

Parameter	Initial (Day 0)	30 Days	60 Days	90 Days	Inference
Appearance	Smooth, translucent, no particulate matter	No change	No change	No change	Stable; no phase separation or crystallization
pH	6.01 ± 0.03	6.03 ± 0.04	6.04 ± 0.05	6.05 ± 0.05	Minimal variation; within skin-compatible range
Viscosity (cps, 20 rpm)	22,300 ± 150	21,980 ± 160	21,820 ± 155	21,810 ± 170	~2.2% decrease; retained pseudoplastic nature
Drug Content (%)	98.64 ± 0.51	98.12 ± 0.58	97.58 ± 0.63	97.02 ± 0.68	Excellent retention; no drug degradation
Spreadability (g·cm/s)	8.40 ± 0.30	8.35 ± 0.28	8.28 ± 0.27	8.22 ± 0.25	Negligible change; maintains ease of application
Physical Stability	—	No phase separation	No phase separation	No phase separation	Highly stable gel matrix
Niosome Integrity	Intact vesicles	No aggregation	No aggregation	No aggregation	Vesicular stability confirmed

(Microscopy)					

4. Conclusion

The present investigation successfully demonstrated the potential of a **Span 60–based niosomal gel system** for improving the topical delivery and therapeutic performance of luliconazole. Systematic formulation and optimization of niosomes revealed that the **surfactant-to-cholesterol ratio** played a critical role in governing vesicle size, surface charge, drug entrapment, and release behavior. Among the eight formulations evaluated, batch **F4** exhibited the most desirable characteristics, including nanoscale vesicle size with narrow size distribution, adequate electrostatic stability, high entrapment efficiency, uniform drug content, and a controlled biphasic release profile. These attributes confirm that niosomal encapsulation effectively overcomes the inherent solubility limitations of luliconazole and enables sustained drug delivery at the target site.

Incorporation of the optimized niosomal dispersion into a **Carbopol 934 gel matrix** resulted in a physically stable, skin-compatible, and patient-friendly topical formulation. The niosomal gel demonstrated superior rheological behavior, improved spreadability, and markedly sustained drug release compared to the conventional plain luliconazole gel. The controlled release observed from the niosomal gel can be attributed to the combined diffusion barriers offered by the vesicular bilayer and the semisolid gel network, which together reduced burst release and prolonged drug availability. Stability studies further confirmed that the niosomal gel retained its physicochemical integrity, drug content, and performance characteristics under storage conditions, highlighting its robustness and formulation reliability.

Overall, the findings of this study establish that **luliconazole-loaded niosomal gel** is a promising topical delivery system capable of enhancing local drug retention, sustaining antifungal release, and potentially reducing dosing frequency. The developed formulation offers clear advantages over conventional topical gels and represents a viable strategy for improving the clinical effectiveness of antifungal therapy. Future investigations involving **ex vivo skin permeation, antifungal efficacy studies, and in vivo dermatological evaluations** are warranted to further validate the translational and therapeutic potential of this niosomal delivery platform.

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