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Research Paper

Formulation and Evaluation of Ciclopirox Olamine Loaded Liposomal Gel for Enhanced Topical Delivery in Onychomycosis

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ABSTRACT

Background: Onychomycosis is a persistent fungal infection of the nail unit in which the nail plate represents a major barrier to topical drug delivery. Ciclopirox olamine is a topical antifungal agent, but conventional topical formulations may provide limited drug penetration and relatively rapid drug release. Objective: The present study aimed to formulate and evaluate a ciclopirox olamine-loaded liposomal gel intended to provide sustained topical delivery and improve drug deposition at the nail site. Methods: Ciclopirox olamine liposomes were prepared by the rotary evaporation/thin-film hydration approach using soya lecithin and cholesterol. A central composite design was used to study the effects of cholesterol and soya lecithin concentrations on entrapment efficiency and drug release. The optimized liposomes were incorporated into a Carbopol 934 gel containing propylene glycol, methyl paraben and triethanolamine. The formulation was evaluated for vesicle characteristics, entrapment efficiency, morphology, gel pH, viscosity, spreadability, drug content, in-vitro diffusion, antifungal activity and stability. Results: Batch F6, containing 150 mg cholesterol and 300 mg soya lecithin with 100 mg ciclopirox olamine, was selected as the optimized batch. The experimental entrapment efficiency was 82.10 ± 1.25%, particle size was 743.7 nm with a polydispersity index of 0.152, and zeta potential was −59.1 mV. The optimized liposomal gel was white, homogeneous and smooth, with viscosity of 5417 ± 0.92 cps, pH 6.68 ± 1.8, spreadability of 12 ± 0.56 g·cm/s and drug content of 96.23%. After 8 h, cumulative drug diffusion from the liposomal gel was 47.23 ± 1.20%, compared with 66.72 ± 2.35% from the marketed/conventional gel. The liposomal gel showed higher antifungal activity than the conventional gel in the reported screening study. Conclusion: The developed ciclopirox olamine liposomal gel demonstrated high drug entrapment, good physicochemical characteristics, sustained drug diffusion and promising antifungal activity. The formulation therefore represents a potential topical delivery approach for onychomycosis; however, further validated transungual permeation, safety

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and clinical studies are required before therapeutic claims or commercialization.

INTRODUCTION

Onychomycosis is a fungal infection of the nail unit caused by dermatophytes, non-dermatophyte molds and yeasts. It commonly affects toenails and is characterized by nail discoloration, thickening, subungual hyperkeratosis and onycholysis. The nail plate is a dense keratinized barrier that can restrict penetration of topically applied antifungal drugs. The supplied project document identifies poor nail penetration as an important limitation of conventional topical ciclopirox therapy and proposes a vesicular delivery system to improve local drug delivery.

Liposomes are phospholipid vesicles capable of incorporating active pharmaceutical ingredients within an aqueous compartment and/or lipid bilayer. Their composition, size, surface charge and lamellarity can be adjusted to modify drug retention and release. Soya lecithin provides the phospholipid component while cholesterol can improve membrane organization and stability. Incorporation of an optimized liposomal dispersion into a Carbopol-based gel may further improve residence time and handling at the application site.

Previous formulation work summarized in the supplied dissertation reports that lipid- and nano-sized systems can improve topical or nail delivery of ciclopirox and that optimized topical systems may provide sustained release. The present work therefore focused on preparation of ciclopirox olamine-loaded liposomes, optimization of lipid composition using a central composite design, incorporation of the optimized dispersion into gel and evaluation of its physicochemical and in-vitro performance.

2. MATERIALS AND METHODS

2.1 Materials

Material	Supplier reported in dissertation	Function
Ciclopirox olamine	SM Pharmaceuticals	Antifungal drug
Soya lecithin	Research-Lab Fine Chem Industries, Mumbai	Phospholipid/vesicle former
Cholesterol	Research-Lab Fine Chem Industries, Mumbai	Membrane stabilizer
Chloroform	Research-Lab Fine Chem Industries, Mumbai	Organic solvent
Carbopol 934	Research-Lab Fine Chem Industries, Mumbai	Gelling agent
Propylene glycol	Research-Lab Fine Chem Industries, Mumbai	Penetration enhancer/humectant
Methyl paraben	Research-Lab Fine Chem Industries, Mumbai	Preservative
Triethanolamine	Research-Lab Fine Chem Industries, Mumbai	Neutralizing/pH-adjusting agent

2.2 Preformulation and drug characterization

Organoleptic properties and melting point were assessed. UV spectrophotometric analysis was performed in phosphate buffer pH 7.4. The calibration range reported in the dissertation was 1–5 µg/mL, with analysis at approximately 310.5 nm. Drug–excipient compatibility was evaluated by FTIR spectroscopy, DSC and X-ray diffraction.

2.3 Experimental design and optimization

A central composite design was applied using Design-Expert software. Cholesterol (X1) and soya lecithin (X2) were selected as independent variables, each at low, middle and high levels. Entrapment efficiency (Y1) and in-vitro drug release (Y2) were selected as responses.

Variable	Low (−1)	Middle (0)	High (+1)
Cholesterol (mg)	50	100	150
Soya lecithin (mg)	100	200	300

2.4 Preparation of ciclopirox olamine-loaded liposomes

Ciclopirox olamine, cholesterol and soya lecithin were combined and dissolved in approximately 10 mL chloroform in a rotary evaporator flask. The organic phase was evaporated under reduced pressure at approximately 50–55 °C to obtain a dry thin lipid film. The film was hydrated with 10 mL phosphate buffer pH 7.4 at 50–55 °C for 1 h with rotation at approximately 250 rpm. The resulting liposomal dispersion was sonicated in a bath sonicator for 2 min and stored at 2–4 °C overnight before characterization.

Batch	Ciclopirox olamine (mg)	Cholesterol (mg)	Soya lecithin (mg)	Chloroform (mL)	PBS pH 7.4 (mL)
F1	100	150	200	10	10
F2	100	50	200	10	10
F3	100	100	200	10	10
F4	100	100	100	10	10
F5	100	50	100	10	10
F6	100	150	300	10	10
F7	100	50	300	10	10
F8	100	100	300	10	10
F9	100	150	100	10	10

2.5 Evaluation of liposomes

Vesicle appearance was examined microscopically. Particle size and polydispersity were measured using a particle-size analyzer after dilution. Zeta potential was determined after dilution with distilled water. Entrapment efficiency was evaluated following ultracentrifugation at 10,000 rpm for 30 min at 4 °C and spectrophotometric analysis at approximately 310 nm. In-vitro drug release was assessed by dialysis-bag diffusion using 100 mL phosphate-buffered saline pH 7.4 with sampling over the study period. Surface morphology was examined by scanning electron microscopy.

2.6 Preparation of liposomal gel

Carbopol 934 (1% w/w) was slowly dispersed in distilled water with continuous stirring and allowed to hydrate for approximately 2–3 h. Methyl paraben (0.02% w/w) was dissolved in propylene glycol (5% w/w) and incorporated into the hydrated polymer. Triethanolamine was added dropwise to adjust the pH to approximately 5–6 and produce a clear gel. The optimized liposomal dispersion was then incorporated slowly with gentle stirring to obtain a homogeneous liposomal gel

Ingredient	Role	Concentration
Carbopol 934	Gelling agent	1% w/w
Propylene glycol	Penetration enhancer	5% w/w
Triethanolamine	pH adjustment	q.s. to pH 5–6
Methyl paraben	Preservative	0.02% w/w
Distilled water	Vehicle	q.s. to 100%

2.7 Evaluation of liposomal gel

The optimized gel was evaluated for appearance, homogeneity, texture, viscosity, pH, spreadability, drug content and in-vitro diffusion. Antifungal screening was performed by a modified agar-well diffusion method using Candida albicans as reported in the supplied dissertation. Stability was assessed at 40 ± 2 °C/75 ± 5% RH and at 25 ± 2 °C/60 ± 5% RH for up to three months.

3. RESULTS AND DISCUSSION

3.1 Preformulation and compatibility studies

The drug was described as a white, odourless, crystalline solid. The reported melting point was 143–144 °C. The UV study identified an analytical wavelength of approximately 310–310.5 nm. FTIR spectra retained the characteristic functional-group bands of ciclopirox olamine in the presence of formulation excipients, and the dissertation interpreted these findings as indicating no significant chemical interaction. The reported DSC thermogram of ciclopirox olamine showed a sharp endothermic peak at approximately 153.1 °C. The drug–excipient mixture retained the characteristic drug peak without evidence of a well-defined interaction. XRD showed distinct diffraction peaks, consistent with a crystalline drug state.

Sample	Reported characteristic FTIR peaks (cm^{-1})	Interpretation
Ciclopirox olamine	3448.1; 3245.61; 2921.63; 1633.41; 1556.27; 1444.42	O–H, N–H, C–H, C=O, C=C and C–C vibrations
Soya lecithin	3386.39; 2915.84; 2850.27; 1735.62	O–H, C–H and C=O bands
Cholesterol	3413.39; 2927.41; 1673.91; 1369.21	O–H, aliphatic C–H, C=C and C–C bands
CPO + soya lecithin + cholesterol	3459.67; 3274.54; 2923.56; 1735.62; 1635.34; 1373.07; 1238.08	Characteristic drug/excipient bands retained

3.2 Optimization of liposomes

The nine experimental batches showed entrapment efficiencies from 65.50% to 82.10% and 24-h drug release values from 83.20% to 93.80%. Increasing cholesterol and soya lecithin concentrations was associated with increased entrapment efficiency and a reduction in the release rate in the reported design study. Batch F6, containing 150 mg cholesterol and 300 mg soya lecithin, showed the highest experimental entrapment efficiency (82.10 ± 1.25%) and 24-h drug release of 83.20%. Numerical/graphical optimization identified the F6 composition as the selected optimized formulation.

Batch	Cholesterol (mg)	Soya lecithin (mg)	Entrapment efficiency (%)	24-h drug release (%)
F1	150	200	78.32	88.32
F2	50	200	79.10	86.68
F3	100	200	80.07	85.39
F4	100	100	65.50	93.80
F5	50	100	66.86	92.01
F6	150	300	82.10	83.20
F7	50	300	80.40	83.45
F8	100	300	74.68	89.24
F9	150	100	70.30	91.49

The numerical optimization section of the supplied dissertation reports an estimated optimum of 150 mg cholesterol and 300 mg soya lecithin, with predicted entrapment efficiency of 81.73% and predicted drug release of 84.75%; the reported desirability was 0.914. The experimental F6 batch was subsequently selected as the optimized formulation.

3.3 Characterization of optimized liposomes

Parameter	Optimized F6 result
Vesicle appearance	Uniform/spherical vesicles reported
Particle size	743.7 nm
Polydispersity index	0.152
Zeta potential	−59.1 mV
Entrapment efficiency	82.10 ± 1.25%
SEM morphology	Spherical vesicles with smooth surface; approximately 1 µm reported in SEM

The optimized dispersion showed a particle size of 743.7 nm and a low reported polydispersity index of 0.152. The zeta potential of −59.1 mV was interpreted in the dissertation as indicating good physical stability. SEM demonstrated predominantly spherical vesicles with a smooth surface. The combination of high entrapment efficiency and relatively slower drug release at higher lipid concentrations supported selection of F6.

3.4 Evaluation of optimized liposomal gel

Evaluation parameter	Marketed/conventional gel	Optimized liposomal gel
Appearance	—	White, homogeneous, smooth
Viscosity	5467 ± 0.88 cps	5417 ± 0.92 cps
pH	6.7 ± 1.3	6.68 ± 1.8
Spreadability	11.53 ± 0.23 g·cm/s	12.00 ± 0.56 g·cm/s
Drug content	—	96.23%

The optimized liposomal gel exhibited a white colour, uniform homogeneity and smooth texture. Its viscosity was close to that of the marketed/conventional gel, while the spreadability was slightly higher. The pH of 6.68 was reported as suitable for topical application. Drug content was 96.23%, indicating satisfactory drug incorporation into the final gel system.

3.5 In-vitro diffusion study

Time (h)	Liposomal gel (% drug release)	Marketed gel (% drug release)
0	0	0
1	6.50 ± 1.23	9.51 ± 2.32
2	10.38 ± 2.41	13.15 ± 1.84
3	12.14 ± 1.95	25.97 ± 1.75
4	22.34 ± 2.20	38.93 ± 0.96
5	24.96 ± 1.74	47.43 ± 1.02
6	29.50 ± 2.65	55.11 ± 2.84
7	38.46 ± 1.54	59.30 ± 1.67
8	47.23 ± 1.20	66.72 ± 2.35

The liposomal gel exhibited slower drug diffusion than the marketed/conventional gel. At 8 h, cumulative drug release was 47.23 ± 1.20% from the liposomal gel compared with 66.72 ± 2.35% from the conventional gel. The slower release profile is consistent with retention of drug within the lipid vesicles and subsequent diffusion through the gel matrix.

3.6 Antifungal activity

Sample	Test organism	Concentration	Reported activity
Pure ciclopirox olamine	Candida albicans	100 µg/mL	++ (moderately active)
Marketed gel	Candida albicans	100 µg/mL	++ (moderately active)
Liposomal gel	Candida albicans	100 µg/mL	+++ (highly active)

The supplied dissertation reports that the liposomal gel produced a greater inhibition response than pure drug and marketed gel after 24 h. The activity was reported using a qualitative symbol system rather than exact inhibition-zone measurements: ++ represented moderate activity (5–8 mm) and +++ represented high activity (>9 mm). These findings support the potential of the formulation but should be confirmed using a validated antifungal assay with exact zone measurements and appropriate controls before publication.

3.7 Stability studies

Under accelerated conditions (40 ± 2 °C/75 ± 5% RH), no visible change in colour was reported over three months. Viscosity changed from 5417 ± 0.44 to 5402 ± 0.74 cps, pH from 6.68 ± 0.56 to 6.65 ± 0.85, spreadability from 12.0 ± 1.41 to 10.0 ± 1.34 g·cm/s, and 8-h drug release from 47.23 ± 2.12 to 46.65 ± 1.65%. Under long-term conditions (25 ± 2 °C/60 ± 5% RH), only small changes were reported through three months.

Parameter	0 month	1 month	2 months	3 months
Accelerated viscosity (cps)	5417 ± 0.44	5414 ± 0.65	5413 ± 0.98	5402 ± 0.74
Accelerated pH	6.68 ± 0.56	6.67 ± 0.63	6.67 ± 0.74	6.65 ± 0.85
Accelerated spreadability (g·cm/s)	12.0 ± 1.41	11.6 ± 1.85	11.2 ± 1.67	10.0 ± 1.34
Accelerated 8-h release (%)	47.23 ± 2.12	47.20 ± 2.98	47.20 ± 2.73	46.65 ± 1.65

DISCUSSION

The formulation strategy combined the vesicular properties of liposomes with the residence and application advantages of a Carbopol gel.

Optimization showed that lipid composition influenced drug entrapment and release. The highest entrapment was obtained at the high levels of cholesterol and soya lecithin used in F6. Cholesterol can contribute to membrane rigidity and organization, while the phospholipid concentration determines the available lipid bilayer for drug incorporation. The observed increase in entrapment and slower release at higher lipid concentrations is therefore consistent with the formulation rationale.

The optimized liposomes displayed a zeta potential of −59.1 mV and a PDI of 0.152. These values, together with the reported spherical morphology, indicate a relatively uniform vesicular system with good electrostatic stabilization under the tested conditions. Following incorporation into Carbopol gel, the formulation maintained suitable pH, viscosity, spreadability and high drug content.

The comparative diffusion study demonstrated a clear reduction in the rate of ciclopirox olamine release from the liposomal gel relative to the conventional/marketed gel. This sustained-release behaviour may improve local drug residence, although the present study does not by itself establish enhanced transungual permeation. Importantly, the dissertation's stated objective included transungual delivery, but the reported results available in the supplied document primarily demonstrate in-vitro diffusion and antifungal screening. A dedicated nail permeation/deposition experiment with validated methodology should therefore be included in a future publication if available.

The antifungal screening result was favourable for the liposomal gel, but the reported result is qualitative. Exact inhibition-zone values, replicate statistics and validated controls would strengthen the evidence. Similarly, stability was demonstrated for three months under the reported conditions, but longer-term studies and additional critical quality attributes would be needed for a development-stage formulation.

CONCLUSION

Ciclopirox olamine-loaded liposomal gel was successfully formulated using soya lecithin and cholesterol and optimized using a central composite design. Batch F6, containing 150 mg cholesterol and 300 mg soya lecithin, was selected as the optimized liposomal formulation and demonstrated 82.10 ± 1.25% entrapment efficiency, 743.7 nm particle size, PDI 0.152 and −59.1 mV zeta potential. The corresponding Carbopol 934 liposomal gel showed acceptable physical properties, pH 6.68 ± 1.8, viscosity 5417 ± 0.92 cps, spreadability 12.00 ± 0.56 g·cm/s and 96.23% drug content. The formulation produced sustained drug diffusion compared with the conventional gel and showed promising antifungal activity in the reported screening study. These results support further development of the formulation as a potential topical system for onychomycosis. However, dedicated transungual permeation/deposition, safety, reproducibility and clinical studies are necessary before making definitive therapeutic or commercialization claims.

6. Limitations and Future Work

The supplied experimental record does not provide complete quantitative transungual permeation/deposition data, complete statistical outputs for all responses, or exact inhibition-zone measurements. These should be added if available before submission. Future work should include validated nail permeation and retention studies, formulation robustness testing, extended stability studies, irritation/safety assessment and appropriately designed clinical evaluation.

7. Declarations

Ethics approval: Not applicable to the reported in-vitro formulation studies; confirm according to the final experimental protocol.
Consent to participate: Not applicable.
Consent for publication: Not applicable.
Competing interests: The authors should declare any financial or non-financial competing interests.
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Data availability: The underlying experimental data should be made available by the authors on reasonable request, subject to institutional policy.
Author contributions: [Insert author contribution statement according to the journal requirements.]

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