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Microemulsion-Based Gel of Terbinafine Hydrochloride for Enhanced Topical Delivery

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A B S T R A C T

Terbinafine hydrochloride (Terbinafine HCl) was formulated as a microemulsion-based gel to improve its suitability for topical administration. Preformulation studies included melting-point determination, UV-visible analysis, solubility screening, and FTIR compatibility assessment. Pseudo-ternary phase diagrams of isopropyl myristate (IPM), Tween 80/PEG 400 (Smix), and water were constructed to identify the microemulsion region. A Tween 80:PEG 400 ratio of 2:1 produced the largest clear and isotropic region and was selected for formulation. Six Terbinafine HCl-loaded microemulsions (F1-F6) were prepared by spontaneous emulsification. F4 was selected as the optimized microemulsion because it remained clear and stable during heating-cooling and freeze-thaw testing, showed transmittance above 98%, and had a drug content of 99.1 ± 1.2%. F4 was incorporated at 80% w/w into Carbopol 934P gels containing 0.5%, 1.0%, or 1.5% polymer (TG1-TG3). TG2, containing 1.0% Carbopol 934P, showed the most favorable balance of pH, viscosity, spreadability, extrudability, drug content, and controlled in vitro release and was selected as the optimized gel. Three-month storage under long-term and accelerated conditions produced only minor changes in the measured physicochemical and release parameters. The study supports the feasibility of a Terbinafine HCl microemulsion-based gel as a stable topical formulation platform, while ex vivo skin permeation and in vivo/clinical efficacy remain to be established.

I. Introduction

Terbinafine hydrochloride is an allylamine antifungal drug used for dermatophytic and other superficial fungal infections. Although topical therapy can provide high local drug concentrations with limited systemic exposure, effective delivery is constrained by the stratum corneum and by the physicochemical properties of the drug. The thesis therefore investigated a formulation strategy designed to maintain Terbinafine HCl in a solubilized state and improve retention of the dosage form at the application site [1-3].

Microemulsions are clear or translucent, thermodynamically stable dispersions of oil and water stabilized by surfactant and co-surfactant. Their high solubilization capacity and low interfacial tension make them useful carriers for poorly soluble drugs. However, their low viscosity can limit topical residence time. Incorporation of a microemulsion into a polymeric gel provides a semisolid system that combines the solubilization characteristics of the microemulsion with the viscosity, spreadability, and retention of a gel [1,3,5-8].

Accordingly, the present experimental work focused on selection of suitable oil, surfactant, and co-surfactant; optimization of the microemulsion region; preparation of Terbinafine HCl-loaded microemulsions; incorporation of

the optimized microemulsion into Carbopol 934P gels; and evaluation of physicochemical properties, in vitro drug release, and short-term stability. The study did not include ex vivo skin permeation, antifungal efficacy, skin-irritation testing, or clinical evaluation.

2. Materials and Methods

2.1 Materials and formulation components

Terbinafine HCl (IP grade) was used as the antifungal drug. The formulation screening included IPM, oleic acid, castor oil, and Labrafac as oily vehicles; Tween 80, Tween 20, and Cremophor RH 40 as surfactants; and PEG 400, propylene glycol, Transcutol P, and ethanol as co-surfactants. Carbopol 934P was used as the gelling polymer and triethanolamine as the neutralizing agent. Phosphate-buffer salts, methanol, sodium chloride, distilled water, and a suitable semi-permeable/dialysis membrane were used for analytical and in vitro release studies [8,10].

2.2 Preformulation studies

The melting point of Terbinafine HCl was determined by capillary method in triplicate. UV-visible scanning was performed in phosphate buffer pH 7.4 containing 10% v/v methanol over 200-400 nm. A calibration curve was prepared from standard solutions and used for subsequent drug-content and release analyses. Equilibrium solubility screening was performed by the shake-flask method at 25 ± 2 °C for 24-48 h in the candidate oils, surfactants, and co-surfactants. Drug-excipient compatibility was assessed by FTIR spectroscopy over 4000-400 cm^{-1} using the pure drug and approximately 1:1 physical mixtures with IPM, Tween 80, PEG 400, and Carbopol 934P [10].

2.3 Construction of pseudo-ternary phase diagrams and Smix selection

Pseudo-ternary phase diagrams of IPM/Smix/water were constructed by water titration. Smix contained Tween 80 and PEG 400 at ratios of 1:1, 2:1, 3:1, and 1:2. Oil-Smix blends were titrated gradually with water under gentle stirring, and clear, isotropic compositions were recorded as the microemulsion region. The Smix ratio giving the largest continuous microemulsion region was selected for drug loading [1,4].

2.4 Preparation and evaluation of Terbinafine HCl microemulsions

Terbinafine HCl-loaded microemulsions were prepared by spontaneous emulsification. The drug (0.3% w/w) was dissolved in IPM, followed by addition of pre-mixed Tween 80:PEG 400 (2:1) and gradual addition of distilled water under continuous stirring until a clear isotropic system formed. Six formulations were prepared by varying the IPM and Tween 80 proportions while maintaining PEG 400, water, and drug at the thesis-reported levels [1,3,6,7].

Table 1. Composition of Terbinafine HCl microemulsions (F1-F6), per 100 g formulation.

Formulation	IPM (g)	Tween 80 (g)	PEG 400 (g)	Water (mL)	Terbinafine HCl (g)
F1	4.0	36.0	15.0	44.7	0.3
F2	7.0	32.0	15.0	44.7	0.3
F3	9.0	31.0	15.0	44.7	0.3
F4	11.0	29.0	15.0	44.7	0.3
F5	12.0	28.0	15.0	44.7	0.3
F6	15.0	25.0	15.0	44.7	0.3

Microemulsions were examined for clarity, transparency, homogeneity, turbidity, creaming, cracking, and phase separation. Percent transmittance was measured after suitable dilution. The optimized formulation was subjected to heating-cooling cycles (4 ± 2 °C and 40 ± 2 °C) and freeze-thaw cycling (-20 °C to room temperature), followed by visual assessment and drug-content determination by UV spectrophotometry.

2.5 Preparation of microemulsion-based gels

Carbopol 934P was dispersed in distilled water, allowed to hydrate for approximately 24 h, and neutralized to form a homogeneous gel base. The optimized microemulsion F4 was incorporated at 80% w/w into gel bases containing 0.5%, 1.0%, or 1.5% w/w Carbopol 934P to produce TG1, TG2, and TG3. The final mass was adjusted with water to 100% w/w. Because F4 contained 0.3% w/w Terbinafine HCl and constituted 80% of each final gel, the calculated drug concentration was 0.24% w/w [5,8].

Table 2. Composition of microemulsion-based gels.

Formulation	F4 microemulsion (% w/w)	Carbopol 934P (% w/w)	Water q.s. (% w/w)	Final drug (% w/w)
TG1	80.0	0.5	19.5	0.24
TG2	80.0	1.0	19.0	0.24
TG3	80.0	1.5	18.5	0.24

2.6 Evaluation of microemulsion gels

The gels were examined for physical appearance and homogeneity. pH was measured after dispersing 1 g of gel in 10 mL distilled water. Viscosity was determined using a Brookfield viscometer at 25 ± 1 °C with a suitable spindle and selected speed. Spreadability was assessed by the slip-and-drag method. Extrudability from collapsible tubes was graded qualitatively as good, excellent, or moderate. Drug content was determined after extraction with phosphate buffer pH 7.4 containing 10% methanol and UV analysis at 291 nm; the thesis states that measurements were performed in triplicate.

2.7 In vitro drug release study

In vitro release from TG1-TG3 was evaluated using a Franz-type diffusion assembly fitted with a suitable semi-permeable membrane. The receptor compartment contained phosphate buffer pH 7.4 with a suitable co-solvent and was maintained at 37 ± 0.5 °C under continuous stirring. Samples were withdrawn at predetermined intervals, replaced with fresh receptor medium, and analyzed spectrophotometrically at 291 nm. Cumulative percentage release was calculated over 8 h [2,3,7].

2.8 Stability study

The optimized gel TG2 was stored for three months at 25 ± 2 °C/60 ± 5% RH and 40 ± 2 °C/75 ± 5% RH. At 3 months, appearance, pH, viscosity, drug content, and 8-h in vitro release were compared with baseline [9].

3. Results and Discussion

3.1 Preformulation and analytical observations

Terbinafine HCl exhibited a sharp melting range of 202-206 °C without visible discoloration or decomposition. The thesis reports a distinct UV absorption maximum of 283 nm in the spectral-scan result, whereas the calibration, drug-content, and release analyses were performed at 291 nm. This internal wavelength discrepancy should be checked against the original spectrum before journal submission. The calibration table contains absorbance values of 0.225, 0.346, 0.459, 0.583, and 0.690 at 4, 8, 12, 16, and 20 µg/mL, respectively, with a reported regression equation $y = 0.03312x + 0.05262$ and $R^2 = 0.9812$. The method section, however, describes a 2-12 µg/mL calibration range; therefore, the final analytical range also requires reconciliation.

Solubility screening showed the general formulation trend that Terbinafine HCl was more readily accommodated by the surfactant/co-surfactant systems than by nonpolar oily vehicles. IPM was selected as the oil phase, Tween 80 as surfactant, and PEG 400 as co-surfactant. The thesis contains conflicting numerical values for water solubility, so the present rewrite retains the component-selection conclusion but does not use the conflicting water-solubility number as a definitive result.

FTIR spectra of the pure drug and physical mixtures were reported to retain the principal bands without major shifts, disappearance, or appearance of new bands, which was interpreted as absence of gross drug-excipient incompatibility. The thesis itself notes that the detailed functional-group assignments should be cross-checked against the chemical structure of Terbinafine HCl; consequently, this paper does not restate the questionable assignments.

3.2 Microemulsion optimization

Among the investigated Smix ratios (1:1, 2:1, 3:1, and 1:2), Tween 80:PEG 400 at 2:1 produced the largest clear and isotropic microemulsion region and was selected for formulation. Increasing surfactant availability was associated with expansion of the clear region, consistent with improved interfacial stabilization in the reported phase-behavior study.

All F1-F6 formulations were described as clear, transparent, and isotropic, with no visible phase separation, creaming, or turbidity. Percent transmittance exceeded 98% for all formulations. F4 was selected as the optimized microemulsion and remained clear and isotropic after heating-cooling and freeze-thaw stress. Its drug content was 99.1 ± 1.2% of the theoretical value. Although droplet size, polydispersity index, and zeta potential were included in the thesis plan of work, numerical results for these parameters were not reported in the results section and are therefore not presented here.

3.3 Physicochemical evaluation of microemulsion gels

All three gels were reported as smooth, homogeneous, and free from grittiness, syneresis, visible phase separation, or lump formation. The quantitative evaluation is summarized in Table 3.

Table 3. Physicochemical evaluation of TG1-TG3.

Parameter	TG1 (0.5% Carbopol)	TG2 (1.0% Carbopol)	TG3 (1.5% Carbopol)
pH	5.6	5.7	5.8
Viscosity (cP)	9,700	17,500	24,400
Spreadability (g·cm/s)	16.2	19.9	13.1
Extrudability	Good	Excellent	Moderate
Drug content (%)	98.2	99.0	98.5

A clear polymer-concentration effect was evident. Increasing Carbopol concentration increased viscosity, while the highest polymer level reduced spreadability and ease of extrusion. TG1 was least viscous and therefore provided low structural resistance, whereas TG3 was the most viscous and least easily extruded. TG2 combined intermediate viscosity with the highest reported spreadability, excellent extrudability, and drug content close to 100%. Selection of TG2 therefore represented a balance between retention-related rheology and practical application properties rather than a simple maximization of viscosity or release.

3.4 In vitro release and selection of the optimized gel

Table 4. Cumulative percentage Terbinafine HCl release over 8 h.

Time (h)	TG1 (% release)	TG2 (% release)	TG3 (% release)
0.5	13.4	15.8	9.6
1	25.7	26.6	19.2
2	41.2	46.9	32.5
3	56.6	62.8	45.3
4	67.3	74.5	56.7
6	84.9	89.4	69.1
8	94.7	92.2	78.5

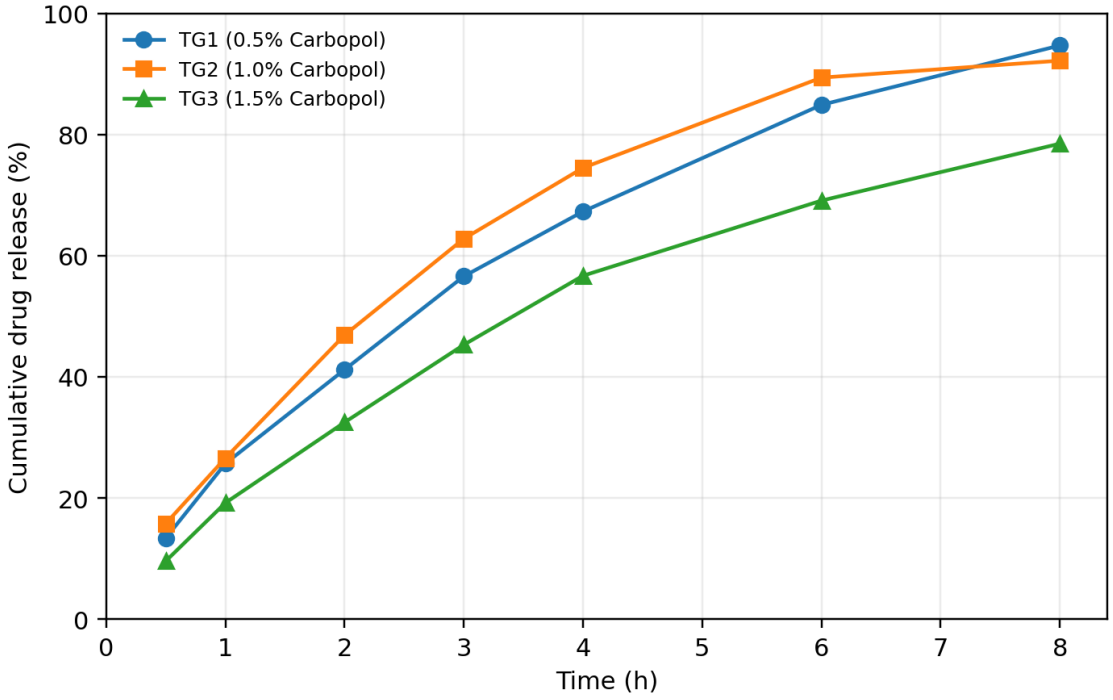

Figure 1. Cumulative in vitro release profiles of TG1, TG2, and TG3 as reported in the thesis.

TG1 ultimately showed the highest 8-h release (94.7%), which is consistent with its lower viscosity and less dense

gel network. TG3 showed the slowest release (78.5%), consistent with the higher Carbopol concentration and greater diffusional resistance. TG2 reached 92.2% at 8 h while retaining favorable viscosity, spreadability, and extrudability; on this combined basis, the thesis selected TG2 as the optimized formulation. Thus, the optimization criterion was a balanced dosage-form performance profile rather than the fastest possible drug liberation.

The reported release study used a semi-permeable membrane and therefore demonstrates drug release from the formulation into a receptor medium. It does not by itself establish transport through intact stratum corneum. Consequently, the experimental data support improved formulation characteristics and controlled in vitro release, but not a direct claim of enhanced dermal permeation.

3.5 Stability of optimized formulation TG2

Table 5. Three-month stability data for TG2.

Parameter	Initial	3 months: 25 °C/60% RH	3 months: 40 °C/75% RH
Appearance	Clear, smooth	No change	No change
pH	5.7	5.8	5.7
Viscosity (cP)	16,500	16,300	16,100
Drug content (%)	99.0	98.4 ± 1.2	97.9
Release at 8 h (%)	90.7	89.8	89.1

TG2 remained clear, smooth, and homogeneous under both storage conditions, with no reported phase separation, grittiness, discoloration, or syneresis. pH remained essentially unchanged. Viscosity showed only a small decrease, and drug content remained close to the initial value. The 8-h release value also decreased only modestly in the stability table. These observations support short-term physical and chemical stability of the formulation under the reported conditions.

The stability table uses an initial TG2 viscosity of 16,500 cP and an initial 8-h release of 90.7%, whereas the primary characterization/release tables report 17,500 cP and 92.2%, respectively. The thesis itself flags the release inconsistency. These differences should be reconciled with raw laboratory records before calculation of percentage change, statistical testing, or journal submission. The thesis also mentions non-significant changes ($p > 0.05$) without providing the statistical test; no inferential claim is therefore made in this focused rewrite.

3.6 Overall experimental interpretation

The experimental sequence demonstrates a rational formulation workflow: preformulation screening was used to select IPM, Tween 80, and PEG 400; phase-diagram studies identified a 2:1 Tween 80:PEG 400 Smix; F4 provided acceptable optical and thermodynamic characteristics; and incorporation into Carbopol 934P yielded semisolid formulations with polymer-dependent rheology and release. TG2 (1.0% Carbopol 934P) provided the best overall compromise between viscosity, spreadability, extrudability, drug content, and release behavior. The formulation approach is also consistent with the thesis-cited literature on topical terbinafine emulsion-gel systems [11,12].

However, the reported experimental program does not include ex vivo skin permeation, skin retention/deposition, antifungal activity against dermatophytes, skin irritation, or in vivo efficacy. Accordingly, “enhanced topical delivery” remains a formulation objective rather than a directly demonstrated biological outcome in this dataset. These experiments would be required to establish enhanced dermal delivery and therapeutic superiority over a conventional comparator.

4. Conclusion

The thesis demonstrates that Terbinafine HCl can be incorporated into a clear and thermodynamically stable IPM/Tween 80/PEG 400 microemulsion and subsequently converted into a Carbopol 934P gel with acceptable physicochemical characteristics. Tween 80:PEG 400 at 2:1 generated the largest microemulsion region, F4 was selected as the optimized microemulsion, and TG2 containing 1.0% Carbopol 934P provided the best overall balance of handling properties and controlled in vitro drug release. The three-month stability study showed only minor changes under both long-term and accelerated conditions. These findings support formulation feasibility, but they do not establish enhanced skin permeation or superior antifungal efficacy because those experiments were not included.

4.1 Key Findings

- The Tween 80:PEG 400 Smix ratio of 2:1 produced the largest clear and isotropic microemulsion region.
- F4 was selected as the optimized microemulsion; all formulations showed transmittance above 98%, and F4 had a reported drug content of 99.1 ± 1.2%.
- The optimized microemulsion was incorporated at

80% w/w into Carbopol 934P gels, giving a final Terbinafine HCl concentration of 0.24% w/w.

- TG2 (1.0% Carbopol 934P) showed the most balanced topical properties: pH 5.7, viscosity 17,500 cP, spreadability 19.9 g·cm/s, excellent extrudability, and drug content of 99.0% in the primary evaluation table.
- At 8 h, the primary release table reported 94.7% release for TG1, 92.2% for TG2, and 78.5% for TG3. TG2 was selected because its release behavior was balanced with its viscosity and application properties rather than because it gave the highest total release.
- TG2 remained clear and smooth over three months at 25 °C/60% RH and 40 °C/75% RH, with only minor changes in pH, viscosity, drug content, and release.

4.2 Future Perspectives

Further work should include ex vivo skin-permeation and skin-deposition studies, in vivo evaluation, skin-irritation and tolerability testing, and direct antifungal efficacy studies against relevant dermatophytes. The thesis also identifies clinical efficacy assessment and scale-up feasibility as important next steps. Longer stability studies, formulation reproducibility across batches, and evaluation of the platform with additional antifungal agents would further establish the robustness and broader applicability of the microemulsion-gel approach.

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