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(RESEARCH ARTICLE)

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Development of formulation and evaluation of topical micro emulsion gel loaded with terbinafine HCL micro emulsion

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Abstract

Fungal infections, particularly in immunocompromised patients, present significant health challenges and are often difficult to treat with conventional topical therapies due to bioavailability issues. This study explores the development of a topical gel formulation using solid lipid nanoparticles (SLNs) loaded with Terbinafine, an antifungal agent, to improve drug delivery and efficacy. SLNs were prepared by a solvent diffusion method and optimized with stearic acid and poloxamer 188. The formulation with the highest entrapment efficiency (SLN F6) exhibited 92.13% ± 0.975. The optimized SLN formulation was incorporated into a gel base containing carbopol 934, resulting in SLN gel G3 with 1.5% carbopol showing the highest drug entrapment (91.39% ± 0.187). The gel was evaluated for physicochemical properties, including viscosity (369 cP), pH (6.12 ± 0.255), and spreadability (4.5). In vitro release studies indicated controlled drug release, fitting best with the Higuchi and Korsmeyer-Peppas models. FTIR analysis confirmed no significant interactions between the drug and excipients, supporting the formulation's purity and effectiveness. Scanning electron microscopy (SEM) confirmed the spherical shape and smooth surface of the nanoparticles. This study demonstrates that Terbinafine-loaded SLNs in a topical gel formulation provide a promising approach for sustained drug delivery in treating fungal infections.

Keywords: Terbinafine; Solid Lipid Nanoparticles (SLN); Topical Gel; Drug Delivery; Fourier Transform Infrared Spectroscopy (FTIR); Scanning Electron Microscopy (SEM)

1. Introduction

Fungal infections pose significant health risks, particularly to immune compromised individuals, resulting in high morbidity and mortality rates, especially among patients with hematologic conditions, allogeneic grafts, prolonged leukopenia, and autologous graft disorders. Subcutaneous mycoses, such as sporotrichosis caused by Sporothrix schenckii, present serious challenges as they target the dermis and subcutaneous tissues (1). Despite the availability of topical treatments, bioavailability barriers often hinder effective drug delivery, impacting patient compliance. Controlled drug delivery systems (CDDS), including sustained release, controlled release, and targeted delivery systems, are crucial for enhancing therapeutic outcomes by maintaining drug concentrations within the therapeutic range and minimizing side effects. Among these, transdermal drug delivery systems (TDDS) are particularly promising, as they facilitate the passage of drugs through the skin for systemic or local effects, overcoming the skin's barrier functions like the stratum corneum. Advances in gel formulations support TDDS by providing stable, non-irritating mediums for drug delivery, enhancing the pharmacological effects of antifungal treatments. Terbinafine (2) an allylamine class antifungal, with a molecular formula of C21H25N and a molecular weight of 291.43 g/mol, is well-absorbed orally, binds to proteins

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such as albumin, and accumulates in fat cells, skin, and nails. It is metabolized by the liver into inactive compounds excreted in feces and urine. As a moderate CYP2D6 inhibitor, terbinafine has a terminal half-life of 200-400 hours. Stearic acid, carbopol 934, and poloxamer 188 are key excipients used in gel formulations for TDDS, each with specific properties that enhance drug delivery and efficacy, thus supporting the development of more effective antifungal treatments.

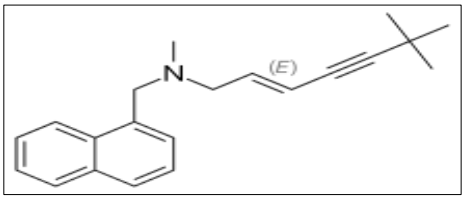

Figure 1 Structure of Terabinafine

2. Material and methods

The reagents and chemicals used in this study include terbinafine, which was a gift sample from SMS Pharmaceuticals in India. Carbopol 934 was purchased from Sigma Aldrich in Italy, while stearic acid was sourced from Fisher Scientific India Pvt. Ltd. in India. Ethanol was obtained from Merck in India, and n-octanol was purchased from SD Fine-Chem. Ltd. in Mumbai, India. Methanol was also acquired from Fisher Scientific India Pvt. Ltd. Poloxamer 188 was purchased from Central Drug House (P) Ltd. in India. Sodium hydroxide, potassium dihydrogen orthophosphate, and disodium hydrogen orthophosphate were all sourced from Thomas Baker in New Delhi, India.

2.1. Preformulation Studies

2.1.1. Determination of the Absorption Maximum of Terbinafine in Ethanol

The absorption maximum of terbinafine was determined using modified standard protocols. A stock solution (1 mg/mL in methanol) was prepared, followed by serial dilutions to 2, 4, 6, 8, and 10 µg/mL. UV spectrophotometric analysis was conducted at 299 nm, with measurements performed in triplicate and statistically analyzed.

2.1.2. Determination of Aqueous Solubility

The aqueous solubility of terbinafine was determined using the saturation shake-flask method. Terbinafine was dissolved in distilled water and acetate buffer (pH 5.5), then vortexed and centrifuged at 50 rpm at 37°C for 48 hours. The solution was filtered and analyzed spectrophotometrically at 283 nm, with measurements in triplicate.

2.1.3. Determination of Lipophilicity

Lipophilicity was assessed using a modified shake-flask method. Terbinafine was added to flasks with stearic acid, prectrol, and dynasan 114, vortexed, and centrifuged at 50 rpm at 37°C for 48 hours. The supernatant was filtered and analyzed at 299 nm. The partition coefficient (log P) was determined using an n-octanol and water system, shaken for 48 hours to equilibrium, then analyzed spectrophotometrically. Measurements were in triplicate.

2.1.4. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectral analysis of terbinafine and stearic acid was conducted using a Win-IR Bio-Rad FTS spectrophotometer, with samples mixed with potassium bromide and observed over 4000 to 400 cm−1.

2.1.5. Preparation of Terbinafine-Loaded Solid Lipid Nanoparticles (SLN)

SLNs were prepared using a modified solvent diffusion method. Terbinafine and stearic acid were dissolved in ethanol and heated to 60±3.0°C, then added to an aqueous poloxamer 188 solution at 4–8°C under stirring at 2000 rpm. SLNs were recovered by centrifugation and further processed via high-pressure homogenization at 1200 bars. The mixture stabilized at room temperature, resulting in clear nanocrystals.

2.1.6. Evaluation of SLN

Estimation of Entrapment Efficiency (EE) of SLN

Entrapment efficiency was estimated by dissolving 5 mg of dried SLNs in ethanol, filtering, and analyzing at 299 nm. Measurements were in triplicate, and the batch with the highest EE was selected.

2.1.7. Calculation of Entrapment Efficiency (EE)

EE % = [(W_{aa}dded drug – W^{f}ree drug) / W_{aa}dded drug] × 100

2.2. Physicochemical Property

SLN dispersions were characterized for color, odor, pH, and solubility in an aqueous medium.

2.2.1. Determination of Average Particle Size and Zeta Potential of SLNs

Average particle size and zeta potential were analyzed at room temperature using a zeta potential/particle size analyzer with phosphate-buffered saline (pH 7.4).

Optical Microscopy

Optimized SLN F6 was analyzed using a digital light optical microscope with a fluorescent lamp at 100x magnification to ensure homogeneity and uniform texture.

FTIR Spectra of SLN F6

FTIR analysis was performed using a Win-IR Bio-Rad FTS spectrophotometer with potassium bromide over 4000 to 400 cm−1.

2.2.2. Development of SLN Gel Formulation

Preparation of Gel Base

Carbopol 934P was dispersed in distilled water with methylparaben sodium and propylparaben sodium, stirred for 30 minutes, and left for 24 hours.

Preparation of SLN Dispersion

SLN formulation F6 was dispersed in propylene glycol and ethanol, then added to the gel base under continuous shaking and stirring. Triethanolamine adjusted the pH to 5.5–6.5.

Formulation Variations

Different formulations (G1 to G4) varied in Carbopol concentration to optimize texture and stability.

Table 1 Preparation of different formulations of solid lipid nanoparticles containing gel

Formulation code	Carbopol 934 % (w/v)
G1	0.5
G2	1
G3	1.5
G4	2

2.2.3. Characterization of Gel

Determination of pH

The pH of the gel was evaluated using a digital pH meter with a glass electrode.

Determination of Viscosity

Viscosity was measured using a Brookfield Viscometer.

Determination of Entrapment Efficiency

Entrapment efficiency was estimated by extracting free drug with ethanol, centrifuging, and analyzing the supernatant at 299 nm.

Spread ability

Spread ability was determined by measuring the spread diameter of 500 mg of gel under a 500 g weight.

2.2.4. In-vitro Drug Release and Kinetics Profiling of Optimized SLN G3 Gel

Preparation of Samples

Gel samples were placed in dialysis membranes and immersed in ethanol and phosphate buffer, stirred at 37°C. Samples were taken at intervals and analyzed at 299 nm.

Kinetic Modeling

Drug release profiles were analyzed using various kinetic models to determine the mechanism of drug release.

Fourier Transform Infrared Spectroscopy

FTIR analysis of SLN G3 was conducted with potassium bromide over 4000 to 400 cm−1.

Scanning Electron Microscopy

Morphological analysis of SLN G3 was conducted using SEM, with samples vacuum dried, gold-palladium coated, and observed at 10 kV

3. Results and discussion

3.1. Preformulation study of drug

3.1.1. Solubility Study

Table 2 Solubility studies

S.No	Solvent	Solubility
1	Water	Poorly soluble
2	Ethanol	Soluble
3	Glycerin	Slightly soluble
4	Phosphate buffer	Slightly soluble

3.2. Determination of λ max

Terbinafine showed absorbance maxima at 288nm.

3.3. Determination of Standard Curve

Terbinafine calibration curves were generated by measuring the absorbance of standard drug solution containing 0 to 10 g/ml with a UV spectrophotometer at 288nm.Calibration curve with R2 value 0.996 using pH 7.4 Phosphate buffer indicates high linearity.

Table 3 Calibration curve data of Terbinafine in buffer pH 7.4

Concentration (µg/ml)	Absorbance
0	0
2	0.187
4	0.362
6	0.552
8	0.742
10	0.952

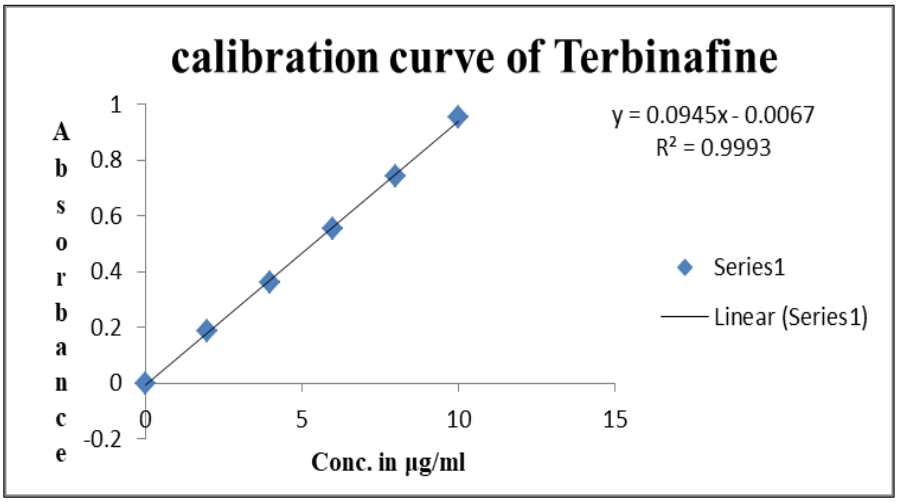

Figure 2 Calibration curve of Terbinafine

Table 4 FTIR interpretation of Terbinafine

Characteristics Peaks	Reported (cm^{-1})	Observed(cm^{-1})
C-H stretch	2850 - 3000	2979.43
C≡N Stretch	2100 - 2400	2198.82
C=C aromatic stretch	1450 - 1650	1554.35
C=C-C Aromatic ring stretch	1510 - 1450	1471.35
para C-H distribution	860 - 800	820.41
C-Cl stretch	600 - 800	759.46

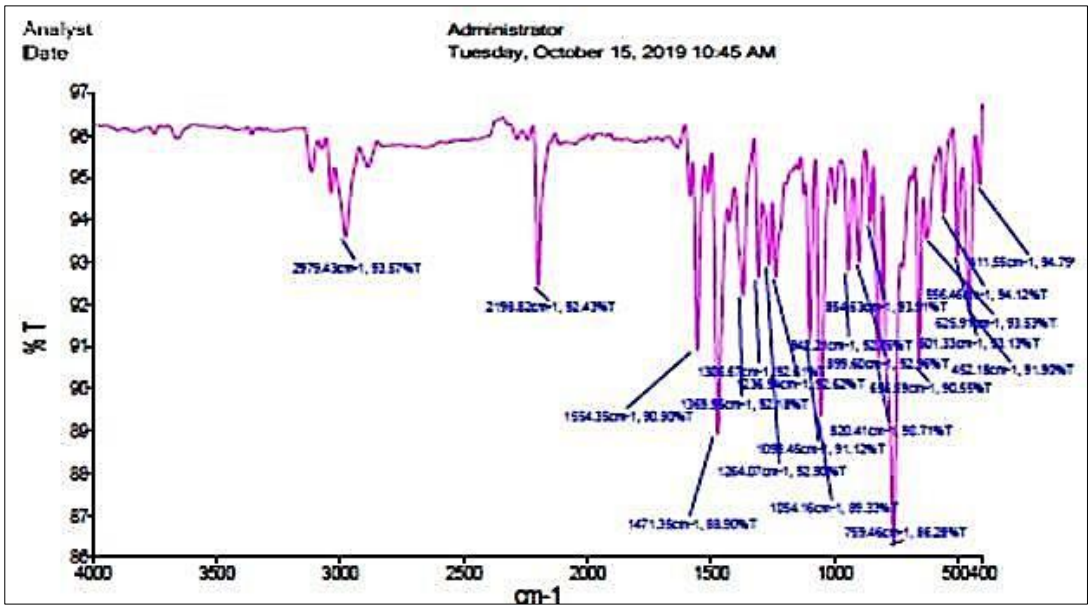

Figure 3 FTIR spectrum of Terbinafine

The FTIR analysis performed of Terbinafine and stearic acid for better compatibility analysis of leading moiety before and after formulation. FTIR spectra of Terbinafine is shown in Figure 4; Table 5. principal IR absorption peaks of Terbinafine at 2979.43 cm-1 (C-H stretch), 2198.82 cm-1 (C≡N stretch), 1554.35 cm-1 (C-H aromatics stretch), 1471.35 cm-1 (C=C-C aromatic ring stretch), 820.41 cm-1 (para C–H distribution) and 759.46cm-1 (C-Cl stretch) were all detected in spectra of Terbinafine. These detected principal peaks confirmed purity and authenticity of Terbinafine as similar to referenced report.

Table 5 FTIR interpretation Stearic acid

Characteristics Peaks	Reported (cm^{-1})	Observed(cm^{-1})
C–H stretch alkanes	2850 - 3000	2915.20
C-H stretch aldehyde	2800 - 2860	2848.02
C=O stretch saturated	1700 – 1730	1700.89
C-C stretch	1400 - 1500	1471.59
C-O stretch, aromatic aster	1250 - 1310	1295.47
O-H bend	910 – 950	936.42
C=C bend	665 - 730	719.89
C-I stretch	500 - 600	547.03

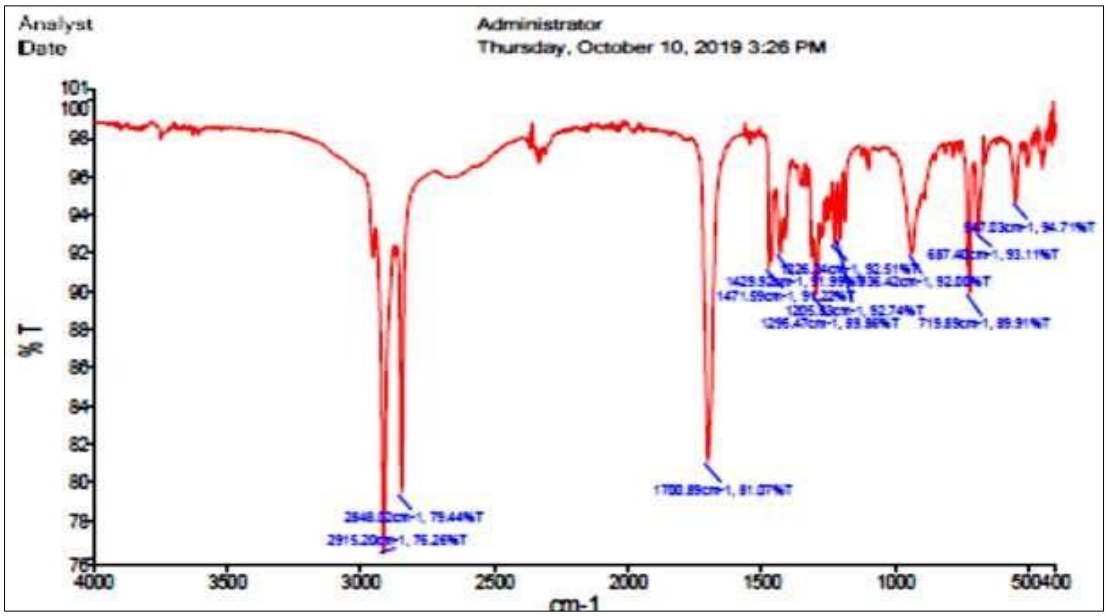

Figure 4 FTIR spectrum of stearic acid

3.4. Development of the method for Terbinafine loaded solid lipid nanoparticles (SLN)

The method employed various modified nano-precipitation techniques to optimize solid lipid nanoparticles (SLN) for Terbinafine entrapment efficiency (EE), utilizing both nano-precipitation and cooling sonication probe methods at temperatures of 4°C and 25°C. Immediate precipitation occurred upon adding the organic phase to the aqueous phase at 4°C, ensuring homogeneity. High-pressure homogenization reduced crystal size and bead milling aggregation, enhancing uniformity. Optimization involved varying stearic acid and poloxamer 188 concentrations (0.5-2% w/v). SLN batches were coded and evaluated spectrophotometrically at 299 nm for Terbinafine entrapment. Data were statistically analyzed to select the SLN with the highest entrapment for further evaluation.

Table 6 Preparation of different Terbinafine solid lipid nanoparticles

SLN code	Terbinafine % (w/v)	Different concentration of leading reagents for the formation of SLN	
		Stearic acid % (w/v)	Poloxomer 188 % (w/v)
F1	1	0.5	1
F2	1	0.7	1
F3	1	1	1
F4	1	2	1
F5	1	1	0.5
F6	1	1	0.7
F7	1	1	1.5
F8	1	1	2

3.5. Evaluation of SLN

3.5.1. Evaluation of entrapment efficiency of SLN

In pre-formulation studies, Terbinafine was characterized physicochemically and spectroscopically. Following the preparation of various nanoparticle batches, entrapment efficiency (EE) was evaluated spectrophotometrically at 299 nm. SLN F6 exhibited the highest EE at 92.13% ± 0.975, while SLN F1 had the lowest at 53.78% ± 1.052. These results align with Ige et al.'s reported EE range of 90–95% w/w. Consequently, SLN F6 was selected for further evaluation,

including physicochemical properties and gel formation. Graphical representation of EE for all SLN groups is shown in Figure 5.

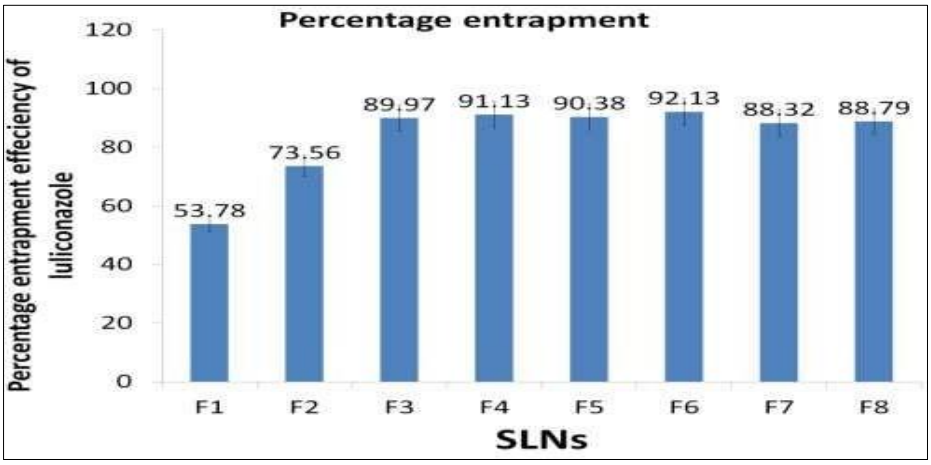

Figure 5 Percentage entrapment efficiency of Terbinafine in SLN

3.5.2. Physicochemical property

The SLN F6 evaluated based on their physicochemical characteristics such as color, odor, pH stability, and aqueous solubility. physicochemical results reveal that SLN has white transparent color with homogeneous and uniform texture, aromatic odor, better stability at 7.4 pH, and water solubility found 0.01819 ± 0.035 mg/ml, i.e. much enough than Terbinafine solubility.

3.5.3. Zeta potential and particle size and size distribution identification

Particle size and zeta potential of Terbinafine SLN were measured using the Nano ZS90 zetasizer. The high zeta potential of ~18.8 mV indicates good stability, as it provides strong repulsive forces between nanoparticles. Particle size analysis revealed a mean diameter of ~344.3 nm, a unimodal size distribution, and a polydispersity index (PDI) of 0.168, suggesting low aggregation. The PDI value under 0.5 supports minimal nanoparticle aggregation.

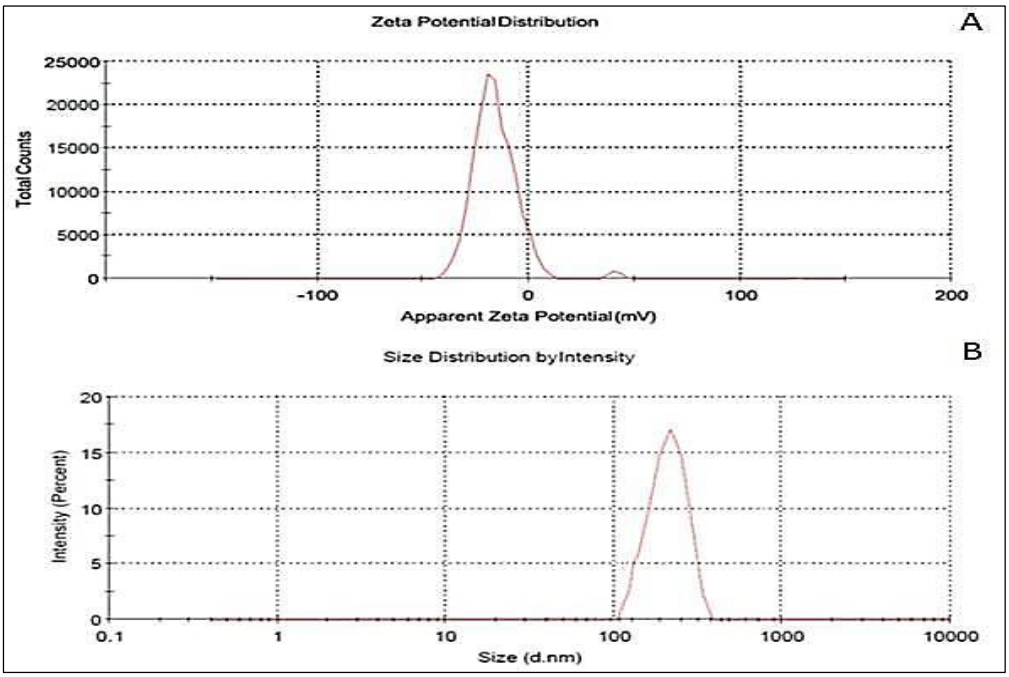

Figure 6 Zeta potential, particle size and size distribution of Terbinafine SLN F6

3.5.4. Optical microscopy

Optical microscopy of the optimized SLN F6, observed at 100x magnification, revealed that Terbinafine SLN has a homogeneous and uniform texture within the dispersion. Only particles with diameters greater than 2.5 µm were visible, and no self-assembled or micellar structures were observed. Images of SLN F6 are shown in Figure 8.

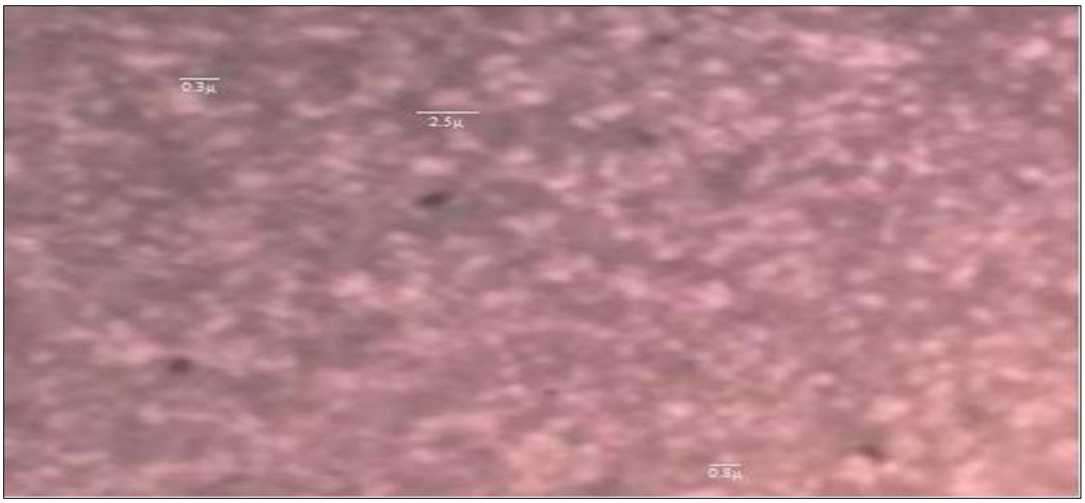

Figure 7 Optical microscopy images of Terbinafine loaded SLN F6

3.5.5. Drug-excipient comparability study by FTIR

FTIR analysis of SLN F6 confirmed interactions between Terbinafine and additives. Key absorption peaks for Terbinafine included 2955.75 cm^{-1} (C-H stretching), 2523 and 2647 cm^{-1} (S-H stretching), 2201.52 cm^{-1} (C≡N stretching), 1556.90 cm^{-1} (C=N stretching), 1471.88 cm^{-1} (C=C aromatic stretching), and 720.33 and 1101.29 cm^{-1} (C-Cl stretching). For stearic acid, peaks were at 2914.97 and 2848.05 cm^{-1} (CH_2 stretching) and 1698.03 cm^{-1} (COOH stretching). The spectral data indicated no significant changes in Terbinafine after SLN formation, aligning with referenced values.

Table 7 FTIR interpretation of SLN F6

Characteristics Peaks	**Reported (cm^{-1})**	**Observed(cm^{-1})**
C-H stretch	2850 - 3000	2955.75
		2914.97
		2848.05
C≡N Stretch	2100 - 2400	2201.52
C=C alkene stretch	1650 - 2000	1698.03
C=C Aromatic stretch	1450 - 1650	1463.82
C-Cl stretch	550 - 850	609.29

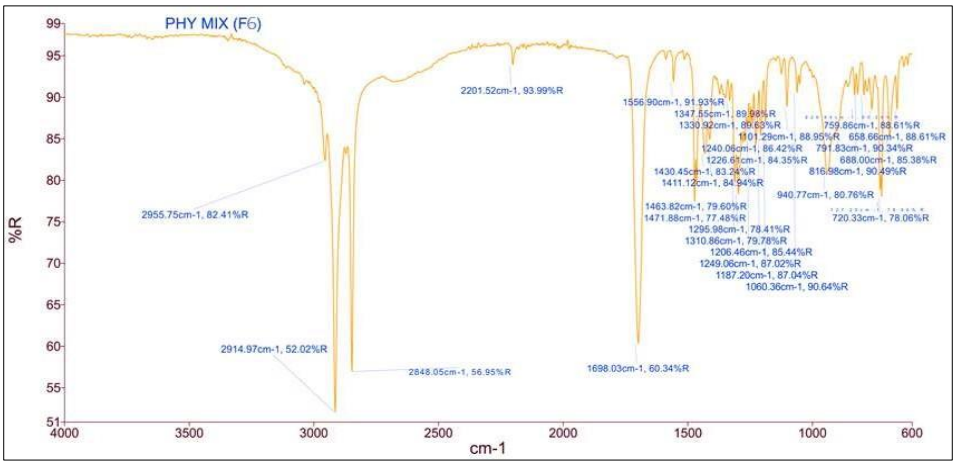

Figure 8 FTIR spectra of SLN F6

3.5.6. Optimization and evaluation of SLN gel

The topical gel containing SLN-loaded Terbinafine was successfully prepared using carbopol 934 as a gelling agent. Among the different formulations, SLN G3 with 1.5% carbopol exhibited the highest drug entrapment at 91.39% ± 0.187. This optimized gel was further evaluated for physicochemical properties, revealing a viscosity of 369 cP, pH of 6.12 ± 0.255, and a spread ability factor of 4.5. These results indicate that SLN G3 has excellent spread ability and conforms to desirable characteristics for an effective topical formulation.

Figure 9 Visual appearance of SLN G3 gel

3.5.7. In vitro drug release and kinetics study

Statistical models were employed to analyze the *In-vitro* release profile of Terbinafine from SLNs using the dialysis bag technique over 24 hours. Release percentages increased with time, indicating controlled drug release. SLNs demonstrated effective drug release due to uniform entrapment, aligning with Ekambaram et al.'s findings that controlled release is achieved with homogeneous drug distribution in the lipid matrix. Poloxamer 407, with a higher HLB value compared to Cremophor RH40, enhanced drug release rates by improving interfacial tension effects and reducing drug particle accumulation. Additionally, the lipid mass in SLNs influenced nanoparticle size and drug desolvation strength, resulting in prolonged drug release.

Table 8 Percentage drug release profile of G3 and control gel

Sl. no.	Time inhours	Percentage drugrelease of G3	Percentage drug releaseof control gel
1	0	0	0
2	0.25	7.375±0.153	1.923± 0.011
3	0.5	14.002±0.185	2.052± 0.155
4	1	22.064±0.102	3.042± 0.158
5	2	32.289±0.173	3.182± 0.162
6	3	40.622±0.165	5.094± 0.122
7	4	47.048±0.151	7.815± 0.205
8	6	55.582±0.163	8.706± 0.215
9	8	62.309±0.134	9.387± 0.118
10	12	69.939±0.115	9.035± 0.205
11	24	79.578±0.213	9.773± 0.158

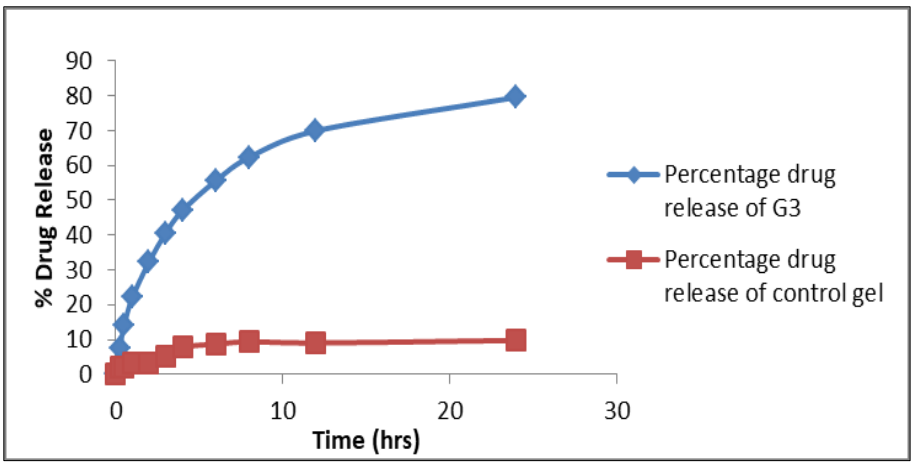

Figure 10 *In-vitro* drug release profile of SLN gel and control gel

The *In-vitro* drug release profile of the optimized SLN formulation was analyzed using various kinetic models (zero-order, first-order, Higuchi, and Korsmeyer-Peppas). Statistical analysis revealed that the release data fit best with the Higuchi and Korsmeyer-Peppas models, indicating controlled drug release from a homogeneous matrix. The zero-order model showed limited suitability. These findings suggest that SLN G3 provides sustained drug delivery, consistent with previous research. The kinetics of SLN G3 gel is illustrated in Figure 12.

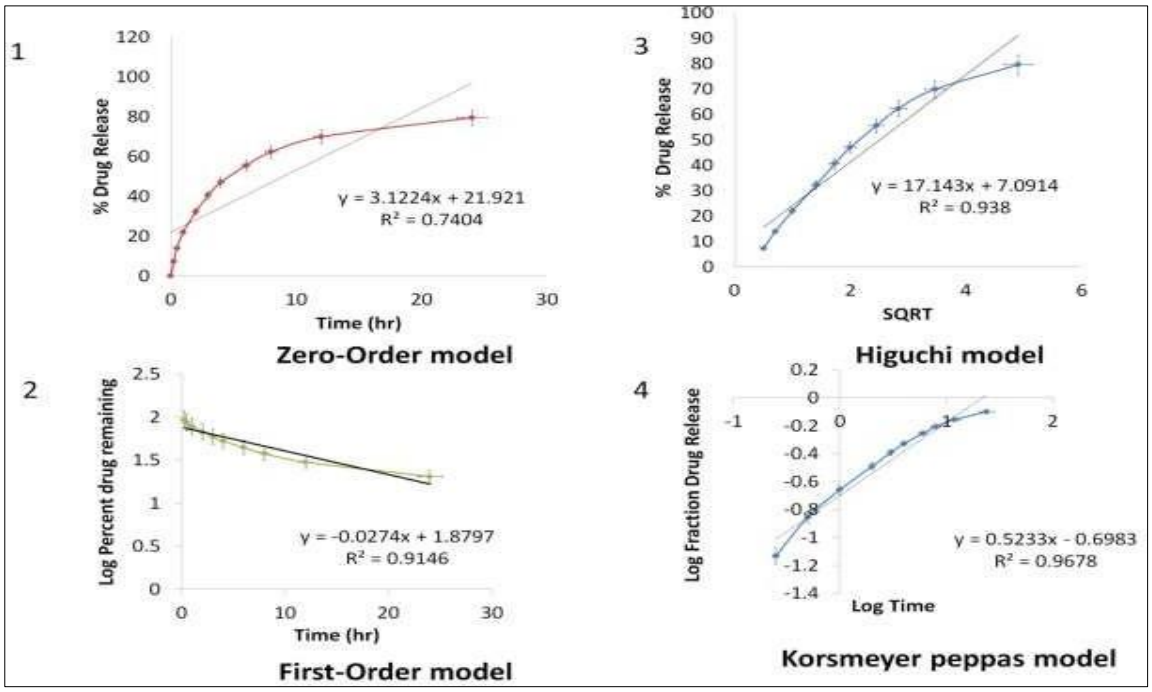

Figure 11 Kinetics order of SLN G3 gel

3.5.8. FTIR spectral analysis of SLN G3 gel

FTIR analysis of SLN gel G3 showed that the spectral data of the optimized formulation matched those of Terbinafine and stearic acid. Key peaks for Terbinafine were at 3331.36 cm^{-1} (N-H stretching), 2961.88 cm^{-1} (C-H stretching), and 2193.49 cm^{-1} (C≡N stretching). For stearic acid, peaks were at 2932.49 cm^{-1} and 2863.16 cm^{-1} (CH_2 stretching), and 1639.31 cm^{-1} (COOH stretching). The results confirm no significant interaction between drug and additives, indicating the purity and authenticity of SLN G3 gel.

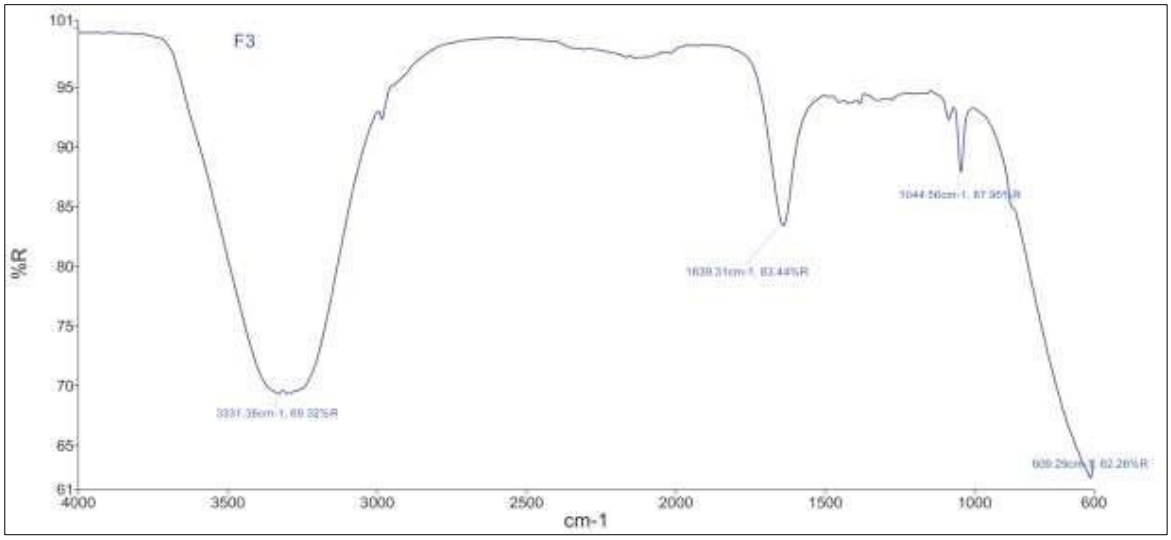

Figure 12 FTIR spectra of SLN gel G3

Table 9 FTIR interpretation of SLN G3 gel

Characteristics Peaks	Reported (cm-1)	Observed(cm-1)
N-H stretch	3300 – 2400	3331.36
C=C stretch	1638 – 1648	1639.31
CO - O – CO stretch	1040 – 1050	1044. 56
C – Cl stretch	550 – 850	609. 26

3.5.9. Scanning Electron Microscopy

The shape of enhanced formulation confirmed through SEM study and is shown in Figure 14. Most of vesicles are well specified, spherical, and discreet having large internal aqueous space. Low density of nanoparticles is shown in SEM analysis which may lead due to factor of dilution of nanosuspension before preparing SEM photographs. SEM studies reveal that Terbinafine loaded SLN in gel had spherical shape with smooth surface.

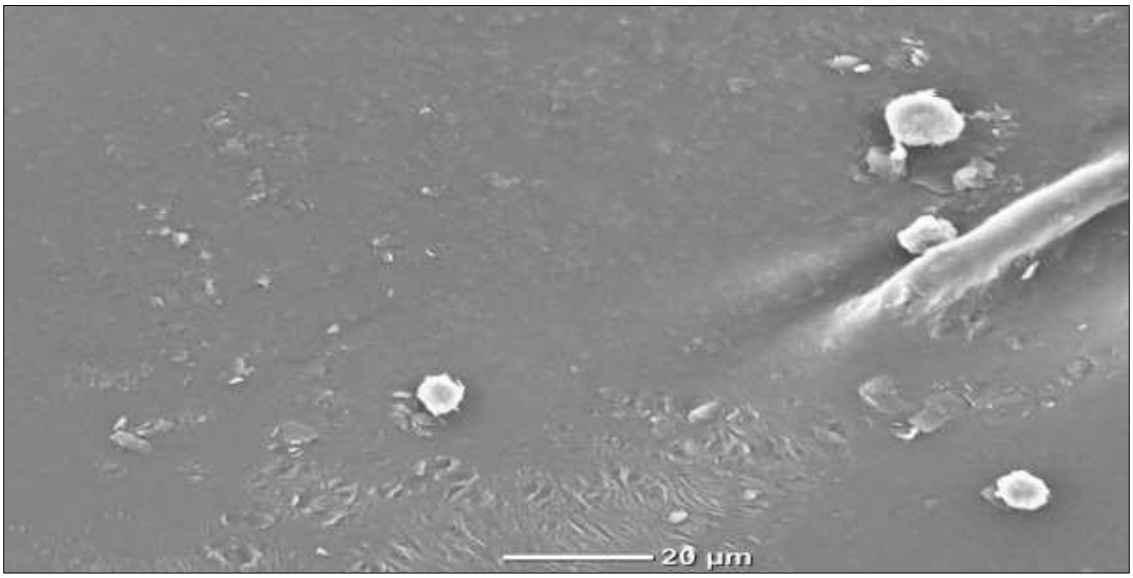

Figure 13 SEM analysis of SLN G3 gel

4. Conclusion

The purpose of topical drug delivery system is to allow therapeutic quantity of drug to correct place in body and to achieve and sustain desired effect of drug for while. In present investigation, we have designed solid lipid nanoparticles (SLN) loaded with Terbinafine to enhance skin permeation and controlled drug release at targeted site and incorporate them in topical gel of carbopol 934 with good skin retention time physicochemical property of prepared gel determined as per standards protocol to overcome compliance after patient use. Even spectroscopical analysis reveals no chemical interactivity between Terbinafine and excipients. Microscopic examination (optical microscopy and scanning electron microscopy) of gel showed uniform distribution of SLN inside gel with good order of kinetics of drug release. Hence, it can be concluded that SLN gel provides controlled release of drug and these systems can be good source as drug carriers for lipophilic drugs, bioavailability enhancer for poorly water-soluble drugs by nanoparticles, drug delivery system.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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