STM JOURNALS

International Journal of
Fungi

Volume 2, Issue 2, 2025
July–December
DOI (Journal): 10.37591/IJF

https://journals.stmjournals.com/ijf

Review IJF

Innovative Antifungal Strategies: Terbinafine Hydrochloride in Niosomal Carriers

Shraddha P. Bandgar[1,*], Raju Rathod[2], Vivekanand Teli[3], Pankaj Jadhav[4]

Abstract

Onychomycosis, an infection caused by fungi that affects fingernails or toenails, causes the nails to grow, separate from the nail bed, and become discolored. While anyone can get it, those with weakened immune systems, children, and the elderly are especially susceptible. The present study aimed to formulate an effective nail lacquer that would treat onychomycosis by utilizing Terbinafine hydrochloride. In this study, niosomes of a medication called terbinafine hydrochloride, an antifungal drug, were mixed in nitrocellulose or Eudragit RL 100, a well-known polymer. Nail lacquer is created by a simple mixing procedure. The frequency of application was reduced to twice per week by utilizing polymers, like nitrocellulose, to maintain the release of the drug for a whole day. Infection is characterized by discomfort as well as swelling surrounding the nail, as well as an unpleasant smell. Therefore, ethyl acetate will help to disguise the disagreeable smell and have an anti-inflammatory effect to improve patient acceptability and compliance. Oleic acid serves as a penetration enhancer, boosting the medicament's capacity to enter the nail bed. When improving the formulation, factors including water resistance testing, drying time, and nonvolatile content were considered. For the optimized formulation, the optimal drying time was 2 minutes. Consequently, niosomal nail lacquer containing terbinafine hydrochloride was successfully produced.

Keywords: Terbinafine hydrochloride, nitrocellulose, niosomal nails lacquer, onychomycosis, hyperkeratosis

***Author for Correspondence**
Shraddha P. Bandgar
E-mail: bandgarshraddha@gmail.com

[1]Lecturer, Department of Pharmaceutics, Dr. Shivajirao Kadam College of Pharmacy (Affiliated to Shivaji University, Kolhapur), Kasabe Digraj, Sangli, Maharashtra, India.
[2]Assistant Professor, Department of Pharmaceutics, Shree Ambabai Talim Sanstha's Diploma in Pharmacy College (Affiliated to DBATU University, Lonere), Miraj, Maharashtra, India.
[3]Assistant Professor, Department of Pharmaceutical Chemistry, Riyajbhai Shamanji College of Pharmacy (Affiliated to DBATU University, Lonere), Gadhinglaj. Maharashtra, India.
[4]Associate Professor, Department of Pharmaceutics (PG), Dr. Shivajirao Kadam College of Pharmacy (Affiliated to Shivaji University, Kolhapur), Kasabe Digraj, Sangli, Maharashtra, India.

Received Date: March 14, 2025
Accepted Date: July 13, 2025
Published Date:

Citation: Shraddha P. Bandgar, Raju Rathod, Vivekanand Teli, Pankaj Jadhav. Innovative Antifungal Strategies: Terbinafine Hydrochloride in Niosomal Carriers. International Journal of Fungi. 2025; 2(2): 1–16p.

INTRODUCTION

On the tips of fingers as well as toes, nails are hard coverings. Infections of the nails, including sub-ungual hyperkeratosis, green nail syndrome, onychatrophia, leukonychia, and onychomycosis, are common in them [1]. Particularly vulnerable to these nail diseases are the elderly and those with weakened immune systems. Topical therapy is a very desirable option because of its noninvasiveness, ability to target the medication at the site of action, decreased systemic therapy adverse effects, improved the patient's adherence, and compliance also lowers treatment costs [2].

The primary cause of the topical therapy's lack of effectiveness was the nail plates' low permeability to the medications applied topically. Successful treatment across nail plate requires improving ungual medication penetration [3]. However, because they are easily eliminated by washing as well as rubbing so cream, gel, and

liquid preparations are insufficient for the trans-ungual administration. Their inefficacy at the application location is explained by this occurrence. Drug delivery lasting a few days is thought to be a crucial prerequisite for pharmaceutical formulations administered topically to the nail.

Clinical practice uses film-forming devices for trans-ungual drug delivery; however, the effectiveness of treating onychomycosis depends on these systems' capacity to deliver therapeutic amounts of active ingredients. Niosomal nail lacquers are a possible substitute for topical onychomycosis treatment due to their mechanical properties and water resistance. After applying lacquer, solvents evaporate and a lacquer layer form. Effective medication distribution requires that films created by nail lacquers develop adhesion on the nail surface [4].

By adding rate-controlling polymers to the cosmetic nail lacquers, prescription nail lacquers are created that maintain the release of drugs to the nail bed. When lacquer is put in, it leaves a coating over the nail plate that contains polymers that serve as a drug depot and release the medicine gradually into the ungual region. Current nail lacquers that have been documented in the literature include ciclopirox, ketoconazole, and luliconazole. Terbinafine hydrochloride exhibits encouraging antifungal action in addition to the antifungal drugs mentioned previously [5]. In nail lacquer, it serves as an antifungal agent. Enhancing terbinafine hydrochloride permeability and extending its release are the objectives of this effort. There is a noteworthy decrease in fungal infection if terbinafine hydrochloride is administered once or twice a week, according to reports [6].

MATERIALS AND METHODS

Materials

Span 60, cholesterol, triacetin, nitrocellulose, ethyl acetate, and Eudragit RL 100 from LOBA Chemie in India and Sigma Aldrich. Terbinafine hydrochloride was obtained from Swapnroop drugs and solvents of analytical-grade ethanol and ethyl acetate.

Methods

Formulation of Niosomes by Thin Film Hydration Method

An amount of 10 ml of ethanol: Chloroform mixture was used to dissolve TBH and precisely weighed Span 60 and cholesterol, at 60°C, an organic solvent is evaporated in a rotary evaporator under reduced pressure and creates a thin layer. Dried films hydrated by 10 ml of PBS (pH 7.4), shaken for 1 hour or sonicated at room temperature. After that, allowed it to mature overnight at 4ºC. For subsequent use, the resultant niosomal formulation was stored in the refrigerator [7, 8].

Formulation of Medicated Nail Lacquer

A simple mixing procedure was used to create nail lacquer. Nitrocellulose, triacetin, ethyl acetate, ethanol, and Eudragit RL 100 are used [9, 10]. The solvent system, including nitrocellulose, triacetin, ethyl acetate, and ethyl alcohol in a proportion of 5:8:3:1 was used to dissolve the polymer Eudragit RL 100. Also, add oleic acid as a penetration enhancer to it. Subsequently, niosomal preparation was added concurrently and continuously stirred until the required consistency was reached, are shown in Table 1.

Table 1. Composition of niosomal batch.

Ingredients (mg)	FTN3
Terbinafine HCL	50
Span 60	215
Cholesterol	40
Chloroform: methanol	10
Phosphate buffer solution pH (7.4) (Make up to10ml)	10

FTIR Spectroscopy

FTIR Spectrum of the pure terbinafine hydrochloride medication and excipients were obtained [11]. By using the potassium bromide compression technique (5 mg of sample and 600 mg of KBr) scanned at 400-4000 cm-1 range. The acquired spectra were presented as % transmittance versus wavenumber (cm^{-1}) [12–14].

Differential Scanning Calorimetry

Using DSC-50 probe from Shimadzu, Kyoto, Japan-based Company, the DSC data were obtained for the terbinafine hydrochloride and optimized niosomal formulations. Standard 40 ml aluminum crucible pans were filled with approximately 5 mg of each sample, covered by perforated lids, and heated to a temperature between 0 and 400°C. The procedure is carried out with a 40 ml/min nitrogen-gas purging flow rate [15].

X-ray Diffraction (XRD)

BRUKER ADVANCE is used to acquire X-ray diffraction (XRD) profiles for the optimized niosomal batch, terbinafine hydrochloride, and physical formulation. Monochromatized cu-Kα radiation (1.54184 A°) was applied to approximately 5 mg of each material, and the samples of terbinafine hydrochloride and physical mixture are scanned at 40 ml/min to studied within 40–1000 A° range. The settings for voltage and current were 35 kV along with 15 mA, respectively [16, 17].

Table 2. Different factors with assigned coded value.

Value	Factors	
	X1 (Non-Ionic Surfactant Concentration) (mg)	X2 (Cholesterol Concentration) (mg)
+1	215	60
0	200	50
–1	185	40

Table 3. 32 factorial design layouts.

Formulation Batches	Variable (X1)	Variable (X2)
FTN1	+1	+1
FTN2	+1	0
FTN3	+1	–1
FTN4	0	+1
FTN5	0	0
FTN6	–0	–1
FTN7	–1	+1
FTN8	–1	0
FTN9	–1	–1

Note: The independent variable has three levels: +1 for higher, 0 for mid-level, and –1 for lower.

Factorial Design

To optimize the suggested work, a 3^2-FFD methodology is utilized to execute trials using Software Trial version 7.0.0. There were nine experimental runs for this design. The value of the Span 60 concentration (X1) as well as the value of con. Of cholesterol (X2) are independent factors or variables chosen for analysis. Zeta potential (Y2), size of particles (Y1), and % entrapment efficiency (Y3) are the dependent factors or variables for evaluation. This methodology shows how changing both variables affect the responses. The response surface methodology was utilized in the present optimization study for the purpose of carrying out several calculations utilizing Design Expert software 7.0 is shown in Table 2. Multiple linear regression analysis was used in this work to generate polynomial models including interactions for individual response variables. ANOVA as well as the software called Design Expert (version 7.0.0) are two statistical methods used for evaluating the

impact of independent variables upon results which are shown in Table 2. A statistically significant level of $p < 0.05$ is considered an indicator. When analyzing the simultaneous effects of two components on the solution, 3D response surface plot diagrams are helpful. They provide a graphic representation of how independent variables affect outcomes, as shown in Table 3 [18].

Particle Size and Polydispersity Index Measurements

By utilizing a particle sizer of HORIBA, applying scattering light principles, at 25.0°C. Average particle size was measured in triplicate. Before measurement, the samples were diluted using dist. H_2O (Z-average) average diameter of the particles is displayed because of the analysis. Additionally, an indication of dispersion uniformity or homogeneity called polydispersity index (PDI) was determined. PS and PDI are measured in triplicates [19, 20].

Zeta Potential Measurements

The zeta sizer is used to determine the charge on the particles at 3.3 V electrode voltage. The dispersion medium has a viscosity of 0.894 m Pa. s. The average zeta potential of each sample of each formulation is determined.

Percent Entrapment Efficiency

The centrifugation procedure is used to determine the niosomes' % EE. Freshly prepared niosomal formulation was added to a centrifuge tube. PBS is taken for diluting each batch's supernatant. The centrifuge tube rotates to 10,000 rpm. By using a centrifuge (REMI INSTRUMENT) for 30 min study is carried out. Next, a centrifugation was performed on the niosomal formulation. Every time collected; 1 ml supernatant analyzed on a UV spectrophotometer (SHIMADZU UV-1900) at 224 nm [21].

Entrapment efficiency was calculated by applying the given formula:

$$\text{Entrapment efficiency (EE \%)} = \frac{\text{Initial drug-final drug}}{\text{Initial drug}} \times 100$$

Transmission Electron Microscopy

The niosomes shape was evaluated using TEM. After being diluted 10 times, the optimized batch (FTN-3) batch is carefully placed on the copper grid, which is coated with carbon for one minute. Any excess was then carefully removed. The staining agent employed was a solution consisting of 1% phosphotungstic acid; the excess of solution was removed before the grid allowed drying. The TEM instrument used 200 kV, images are captured by the device, which were then analyzed using imaging viewer software [22].

CHARACTERIZATION OF NAIL LACQUER

Drug Content

An amount of 200 ml was PBS used for dissolving about 200 mg of nail lacquer. A 15-min ultrasonication of the fluid was conducted. After filtering the resultant solution, PBS (pH 7.4) was added to get up to 100 ml volume [23]. Drug content within the diluted solution was evaluated using spectrophotometry at a wavelength of 224 nm.

Studies on *In Vitro* Release Using Artificial Membranes

Diffusion tests were conducted using a dialysis membrane as an artificial membrane used to determine the *in-vitro* drug release from niosomal nail lacquer at 37°C. After applying the composition to the dialysis membrane, it was let dry. Between the donor & receptor compartments, the manufactured membrane was positioned on the cell. Around 200 ml of PBS was added into the receptor. The entire setup was maintained at 37°C while stirring [24]. An amount of 5 ml aliquots was taken out using the syringe and the same volume of brand-new receptor medium is added back in right away. Terbinafine hydrochloride-loaded niosomes releases were also carried out using *in vitro* release tech. Diffusion experiments were conducted on the produced niosomes using a dialysis bag. About

200 ml of PBS with a pH of 7.4 was used as the diffusion medium, and the niosomes sample was put into the dialysis bag [25]. The diffusion investigations were conducted at 37 ± 1°C. An amount of 5 ml is taken out every 60 minutes, 120 minutes, and so on for up to 24 hours. Each sample was then replaced along with an equivalent volume of completely fresh diffusion medium. Drug release is measured using an ultraviolet visible spectrophotometer at 224 nm [26].

In Vitro Antifungal Activity

Employing the agar-cup plate technique, the antifungal activity of the optimized lacquer composition which is assessed along with the marketed formulation (Terbinaforce 1% W/W). On the Sabouraud Dextrose Agar, formulation is investigated over strain *Candida albicans*. After filling sterile plates with Sabouraud agar medium, the plates were left to cool and solidify [27]. Using a spreading rod, uniformly distribute 100 µl of the fungal strain broth over the medium and dried completely. The control solution was made in water for injection and wells are filled with 100 µl of the test solutions and standard. For 24 hours, the petri plates were incubated at 37°C. The zone of inhibition (ZI) diameters was used to measure the antifungal activity. All measurements were made in triplicate [28].

- Control.
- Commercial formulation (Terbinaforce).
- Nail lacquer (FTN3) loaded with terbinafine hydrochloride niosomes (100 µl).

Stability Studies

In accordance with ICH requirements, tests on stability for nail lacquers were conducted. The ideal mixture was kept for one month for about 1 month at 40 ± 2°C/75 ± 5% RH. The samples' nonvolatile content, drying duration, and diffusion through an artificial membrane were then examined. Over the course of one month, the niosomal formulation was stored in colored glass, and the stability of the optimal batch of niosome produced using the thin film hydration technique was examined. Each month, samples from optimized batch were taken and terbinafine hydrochloride entrapment efficiency was examined using spectroscopy [29].

RESULTS AND DISCUSSION

FTIR Spectroscopy

Fourier Transform Infrared Spectroscopy (FTIR) was employed to investigate the possible interactions between terbinafine hydrochloride (TBH) and excipients in both the physical mixture and final formulation. The FTIR spectra of the pure drug, physical mixture, and formulation were compared, and their characteristic functional group absorption peaks are summarized in Table 4(a–c) and Figure 1(a–c). The NH_3 stretching vibration, indicative of primary amine groups, was observed at 3042.64 cm^{-1} in pure terbinafine HCl. In the physical mixture and final formulation, this band shifted to 3420.62 cm^{-1} and 3436.05 cm^{-1}, respectively. These shifts, although within the standard range of 3500–3100 cm^{-1}, suggest a potential interaction or hydrogen bonding involving the NH_3 group during formulation. The C=C aromatic stretching vibration appeared at 1636.3 cm^{-1} for pure TBH. In the physical mixture, a slight shift to 1632.93 cm^{-1} was observed, while in the final formulation it further shifted to 1670.05 cm^{-1}. These values lie within the standard range of 1680–1600 cm^{-1}, indicating that the aromatic system remains largely intact. However, the observed shifts may point toward minor interactions affecting the π-electron cloud during formulation. The alkyl region, which typically includes C≡C or C≡N groups, z 2862.81 cm^{-1} for both TBH and the physical mixture. In the formulation, this band shifted slightly down to 2720.58 cm^{-1}, indicating a potential reduction in bond polarity or molecular interactions in the formulation matrix. The expected standard range is 2975–2850 cm^{-1}, suggesting that this deviation in the formulation could be due to structural changes or excipient interaction. The C–N stretching vibration, typically found in the 1020–1250 cm^{-1} range, was observed at 1317.14 cm^{-1} for TBH, indicating a higher frequency than expected, possibly due to conjugation or ring structure effects. In the physical mixture, the C–N stretch was significantly lower at 1106.46 cm^{-1}, aligning better with standard values. In the formulation, it shifted to 1365.63 cm^{-1}, which again is slightly above the expected range, suggesting possible chemical changes or altered bonding environment of the amine group due to the formulation are shown in Table 4.

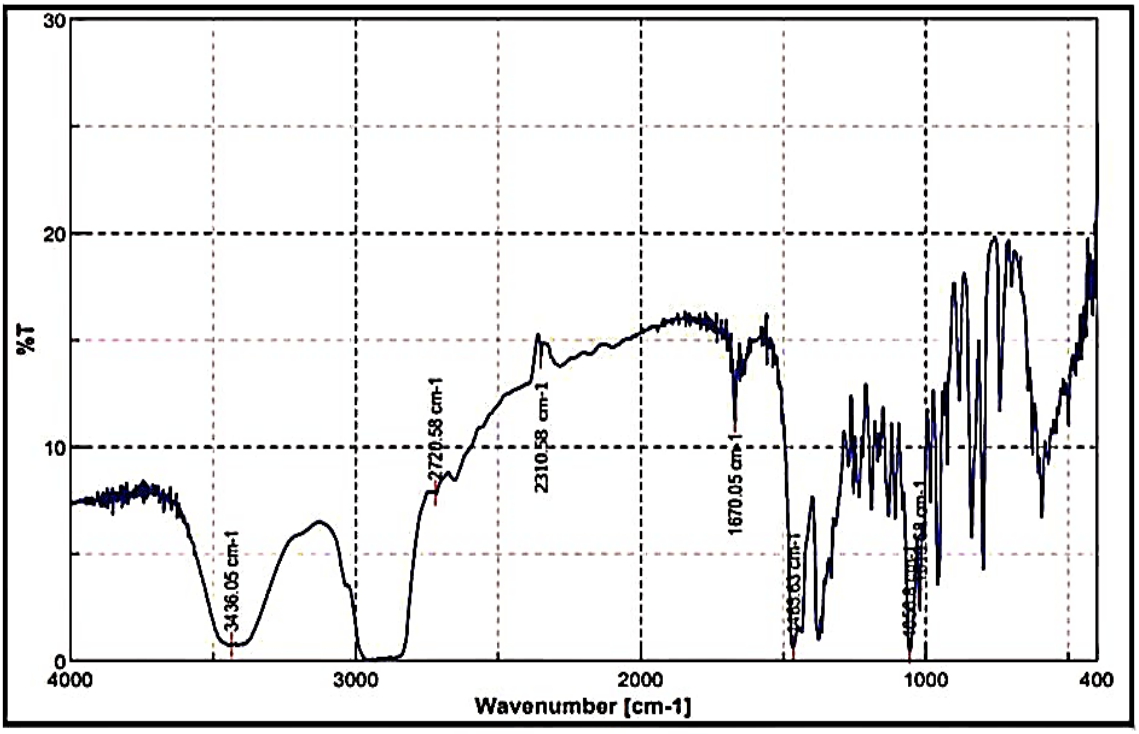

Figure : FTIR layout of Formulation

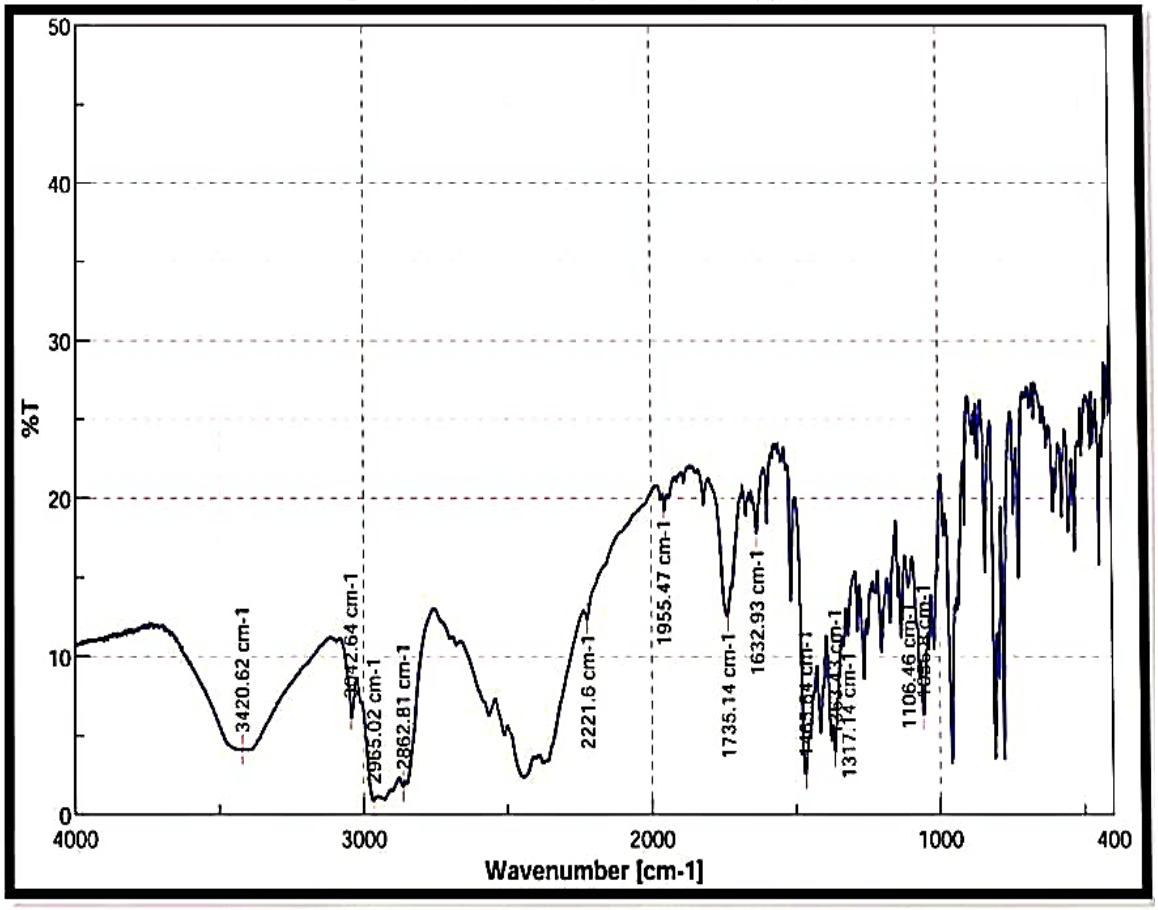

Figure : FTIR layout of Physical mixture

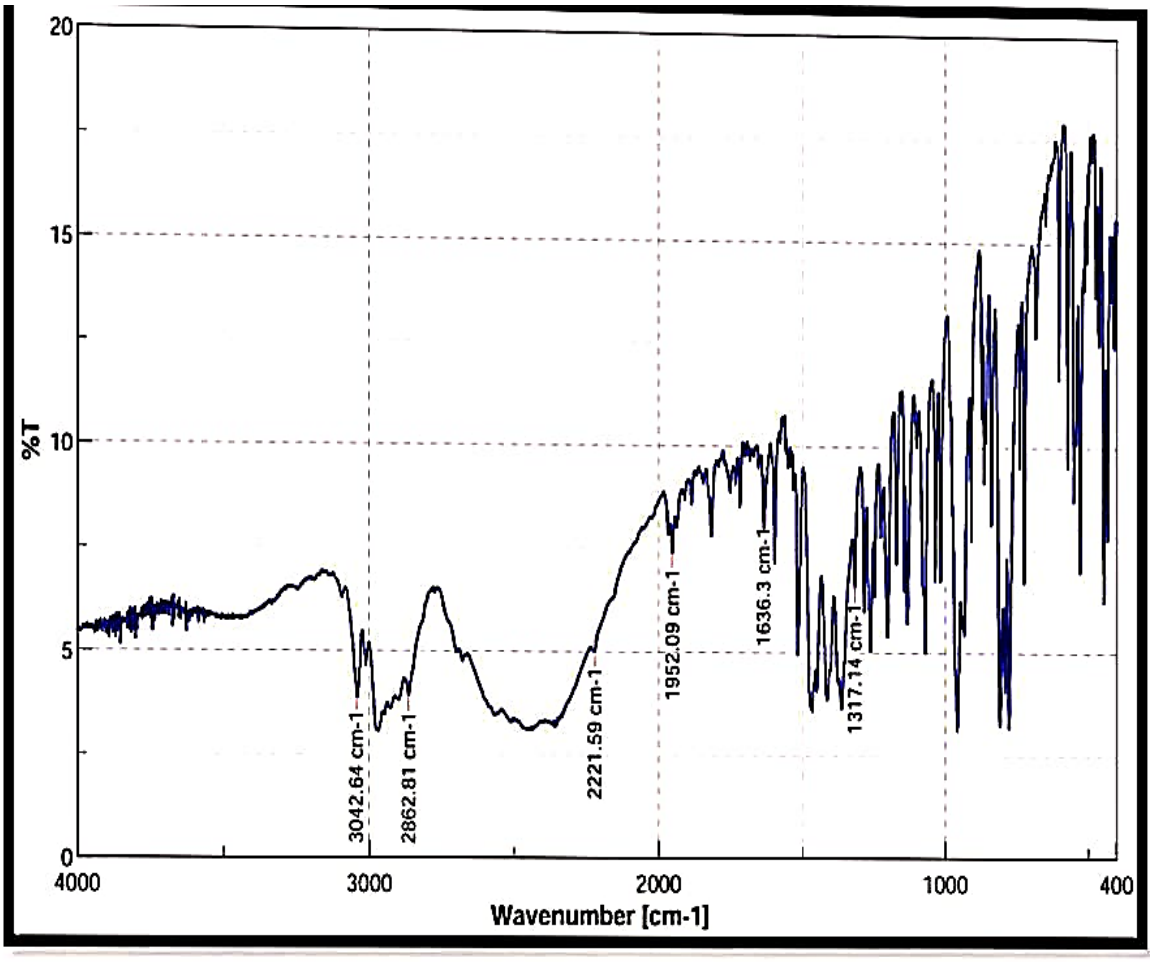

Figure : FTIR layout of Terbinafine hydrochloride

Figure 1. FTIR spectrum of (a) terbinafine HCL, (b) physical mixture, and (c) formulation.

Table 4. FTIR ranges of (a) TBH, (b) physical mixture, and (c) formulation.

Functional Group	Terbinafine HCL	Physical Mixture	Formulation	Standard Range
NH3	3042.64	3420.62	3436.05	3500–3100
C=C Stretch	1636.3	1632.93	1670.05	1680–1600
Alkyl	2221.59	2221.6	2310.58	2250–2100
Aliphatic-C–H stretch	2862.81	2862.81	2720.58	2975–2850
C–N	1317.14	1106.46	1365.63	1020–1250

Differential Scanning Calorimetry

By using DSC thermal profile of pure TBH demonstrated a strong peak at 207°C, it was caused by melting transition of TBH during test. The DSC thermal profile of drug-loaded niosomes revealed that TBH peaked at 205°C. The presence of a change or modest shift in drug peaks with lower intensity suggested that TBH entrapment in niosomes was caused by a modest reduction in crystallinity, which might be attributable to molecular dispersion or a soluble form of drug in the hydrophilic center of the niosomes. The enthalpy change value for pure TBH was greater in niosomal, suggesting that the medication was molecularly disseminated in niosomal nanoparticles and transformed to amorphous state [30]. So, the thermal behavior of the medicament in formulation was investigated using DSC analysis are summarized in Figure 2(a–b).

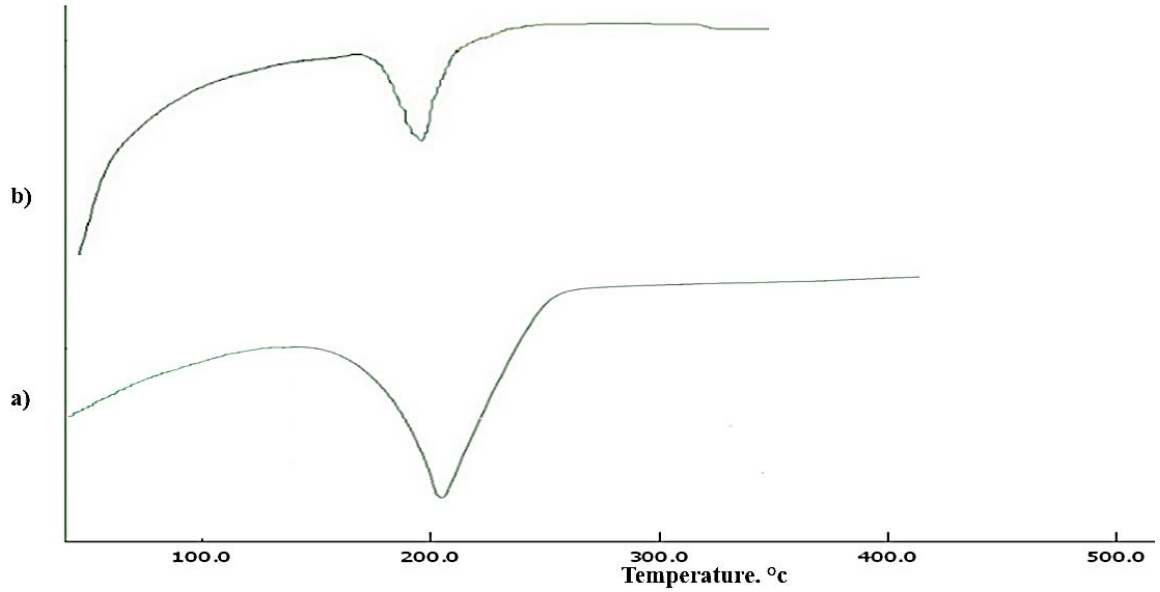

Figure 2. DSC spectra of (a) terbinafine HCL and (b) formulation.

XRD

XRD patterns of the produced niosomal formulation, as well as pure TBH and physical mixture, were acquired by utilizing an X-ray Diffractometer. To confirm the nature and physical state of TBH, XRD patterns of produced TBH containing niosomes, also with the pure drug was acquired. The diffractogram of pure TBH clearly showed strong characteristic peaks in the 5–30° range; however, those characteristic peaks vanished in TBH-loaded niosomal formulation, demonstrating medicament is either dispersed molecularly in niosomes and has become amorphous, are shown in Figure 3(a–c).

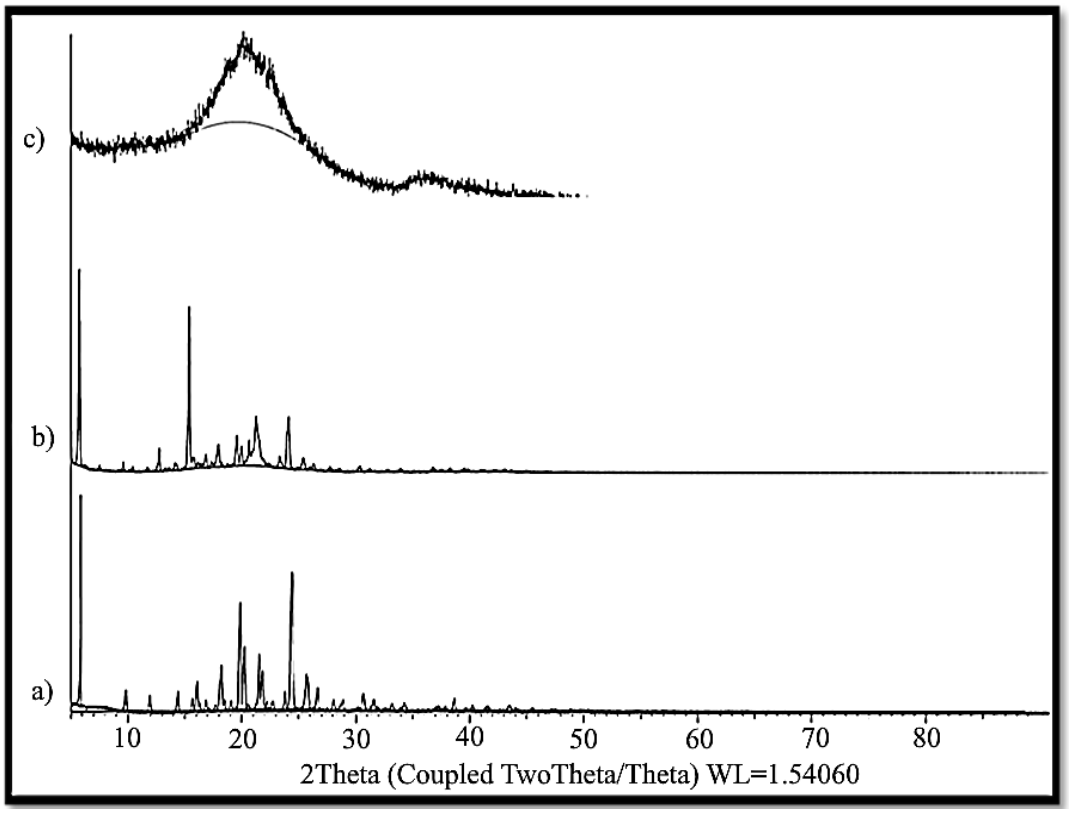

Figure 3. XRD layout of (a) terbinafine hydrochloride, (b) physical mixture, and (c) formulation.

Transmission Electron Microscopy

Transmission electron microscopy (TEM) images revealed that the prepared niosomes exhibit a spherical morphology with a relatively uniform structure. The average particle size was found to be approximately 200 nm, confirming the nanoscale nature of the vesicles. This size range is suitable for enhancing drug delivery, particularly for topical or transdermal applications. The well-defined spherical shape further indicates successful niosome formation, and structural integrity are shown in Figure 4.

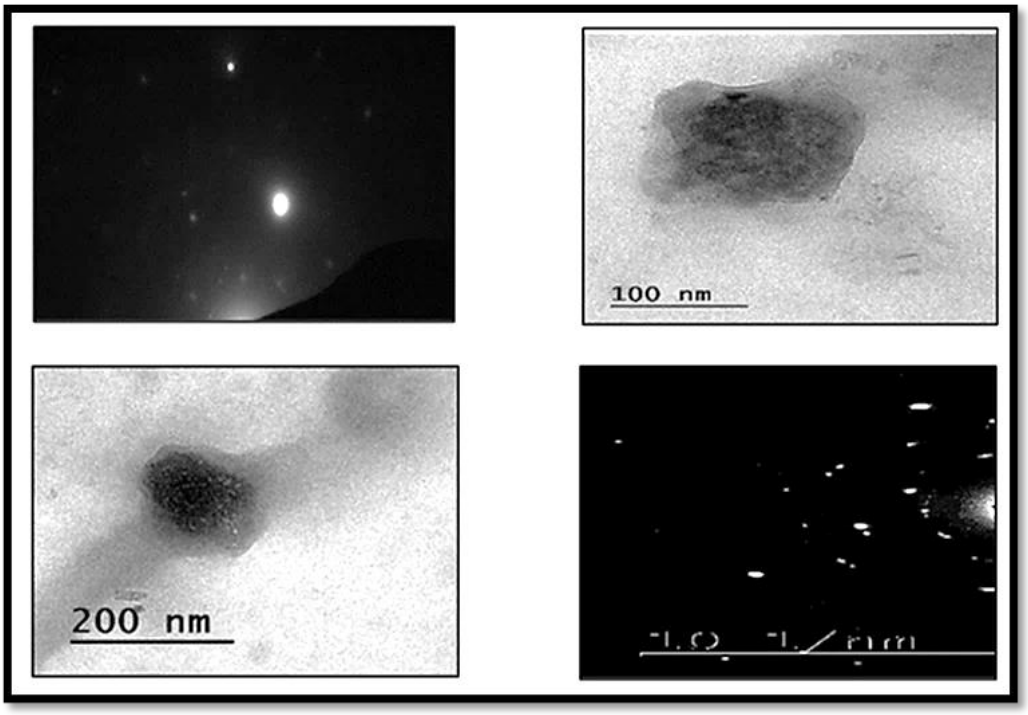

Figure 4. FTN3 niosome batch under TEM.

Particle Size, Zeta Potential, Percent Entrapment Efficiency

By utilizing a particle sizer of HORIBA, applying scattering light principles, at 25.0°C. Average particle size was measured in triplicate. Before measurement, the samples were diluted using dist. H_2O, (Z-average) average diameter of the particles is displayed because of the analysis. Additionally, an indication of dispersion uniformity or homogeneity called PDI was determined. PS and PDI are measured in triplicates. The Zeta sizer is used to determine the charge on the particles at 3.3 V electrode voltage. The dispersion medium has a viscosity of 0.894 mPa. The average zeta potential of each sample of each formulation is determined and is shown in Table 5.

Table 5. Formulation variable and response of optimized batch.

Batch Code	Formulation Variable S		Formulation Response		
	Conc. of Span 60 (mg) (X1)	Conc. of Cholesterol (mg) (X2)	Particle Size (nm) (Y1)	Zeta Potential (mV) (Y2)	Entrapment Efficiency (%) (Y3)
TN1	215	60	169±0.01	–33.7±0.01	78.26±0.02
TN2	215	50	154.3±0.01	–31.7±0.01	78.52±0.02
TN3	215	40	126±0.02	–31.4±0.02	82.69±0.01
TN4	200	60	272.1±0.01	–29.3±0.01	75.92±0.02
TN5	200	50	269.7±0.02	–27.4±0.01	76.18±0.01
TN6	200	40	238.4±0.02	–25.8±0.05	77.48±0.01
TN7	185	60	299.2±0.01	–24.2±0.01	74.67±0.01
TN8	185	50	294.6±0.02	–22.4±0.02	71.75±0.01
TN9	185	40	280.4±0.01	–21.9±0.01	70.97±0.01

FACTORIAL DESIGN

Particle Size

The 3D response surface plots illustrate the effect of surfactant concentration and cholesterol concentration on particle size of the niosomes. The statistical model applied to the data was found to be highly significant with a p-value of 0.0001, indicating a strong correlation between the formulation variables and the particle size. The coefficient of determination ($R^2 = 0.9989$) suggests an excellent fit of the model, with 99.89% of the variability in particle size explained by changes in surfactant and cholesterol concentrations. This demonstrates that both variables play a critical role in controlling the size of the niosomal vesicles, are shown in Figure 5 and Table 6.

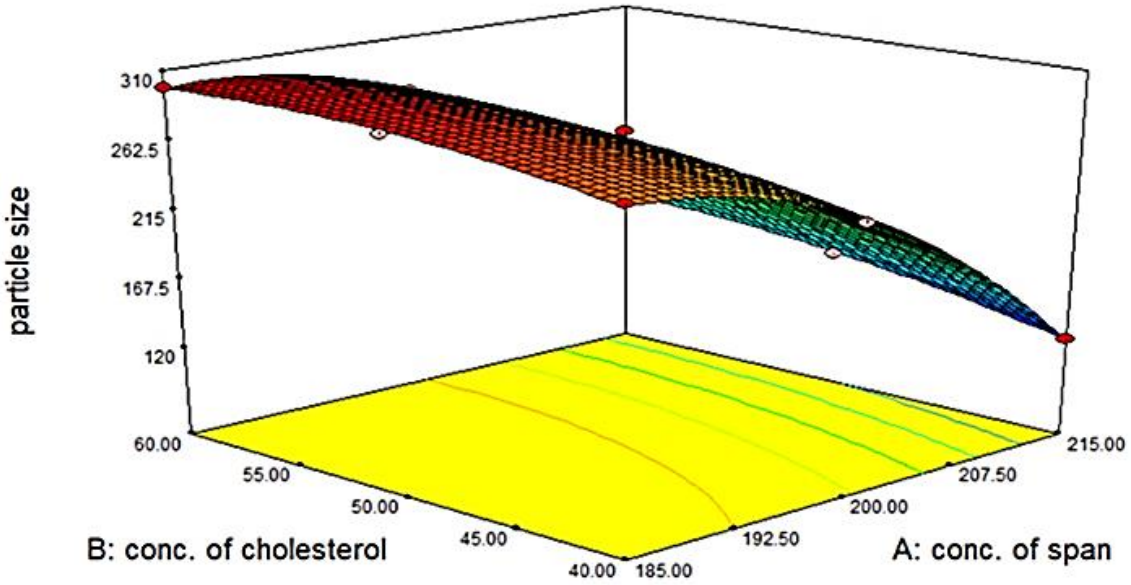

Figure 5. 3D response of particle size.

Table 6. 3D response surface plots showing concentration of surfactant and concentration of cholesterol effect on particle size.

Response	Sources		Significant
	Model p Value	R^2	
Particle size	0.0001	0.9989	

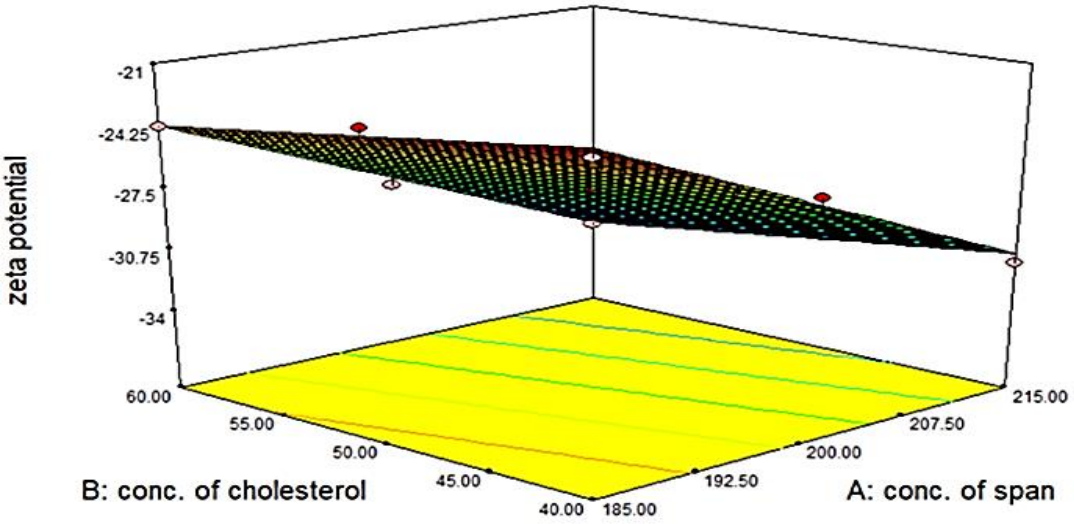

Figure 6. 3D response of zeta potential.

Zeta Potential

The 3D response surface plots demonstrate the impact of surfactant concentration and cholesterol concentration on the zeta potential of niosomal formulation. The statistical analysis shows that the model is highly significant with a p-value of 0.0001, indicating a strong influence of the independent variables on zeta potential. The R^2 value of 0.9913 confirms a very high degree of model accuracy, with 99.13% of the variation in zeta potential explained by changes in surfactant and cholesterol levels. These results suggest that both components are key factors in determining the surface charge and stability of the niosomes, which are shown in Figure 6 and Table 7.

Table 7. 3D response surface plots showing concentration of surfactant and concentration of cholesterol effect on zeta potential.

Response	Sources		Significant
	Model p Value	R^2	
Zeta potential	0.0001	0.9913	

3% Entrapment Efficiency

A 3D response surface plot was constructed to evaluate the combined effects of surfactant concentration and cholesterol concentration on the % entrapment efficiency of the formulation. The statistical analysis indicated that the model was significant, with a model p-value of *0.0007*, suggesting a strong relationship between the independent variables and the response. The coefficient of determination ($R^2 = 0.9586$) indicated an excellent fit of the model, explaining approximately 95.86% of the variability in the entrapment efficiency. This demonstrates that the selected concentrations of surfactant and cholesterol significantly influence the entrapment efficiency, and the model can be reliably used to predict outcomes within the studied range, are shown in Figure 7 and Table 8.

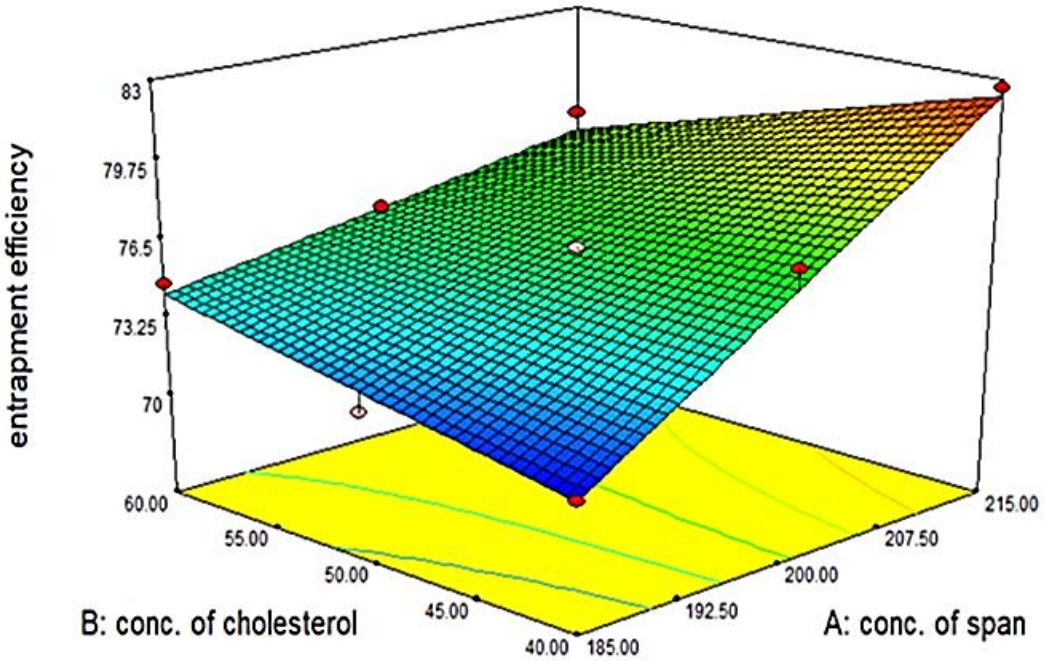

Figure 7. 3D response of % entrapment efficiency.

Table 8. 3D response surface plots showing concentration of surfactant and concentration of cholesterol effect on % entrapment efficiency.

Response	Sources		Significant
	Model p Value	R^2	
% Entrapment efficiency	0.0007	0.9586	

In-Vitro Release Study

In vitro release study is carried out for all batches. The optimized batch TN3 shows 74.71% of drug release in 24 hours. Which follows diffusion mechanism because it follows because it follows Korsemeyer Peppas release mechanism with "n" or exponent value of 0.601 is shown in Table 9 and Figure 8.

Table 9. In-vitro drug release study of niosomal batches.

Time (hr.)	FTN 1	FTN 2	FTN 3	FTN 4	FTN 5	FTN 6	FTN 7	FTN 8	FTN 9
0	0	0	0	0	0	0	0	0	0
1	11.17	11.59	12.21	6.67	8.57	9.82	10.29	8.99	7.53
2	18.36	18.57	20.13	10.40	13.26	16.48	16.99	13.47	10.76
3	24.71	24.92	27.01	18.02	20.96	22.01	22.77	20.99	18.88
4	28.88	29.30	30.23	20.76	24.82	26.90	27.90	25.82	22.73
5	32.01	32.94	34.30	27.84	28.26	30.96	31.86	29.23	24.09
6	39.30	39.71	41.38	31.28	35.96	37.53	38.35	36.86	33.88
7	42.42	42.84	44.82	33.78	39.82	40.03	41.20	39.92	37.63
8	48.67	48.78	50.13	36.28	45.44	46.07	47.29	46.53	43.36
16	58.46	59.40	60.65	53.67	56.28	57.42	58.37	57.19	54.19
24	72.11	72.94	74.71	65.76	69.92	70.96	71.99	69.99	67.84

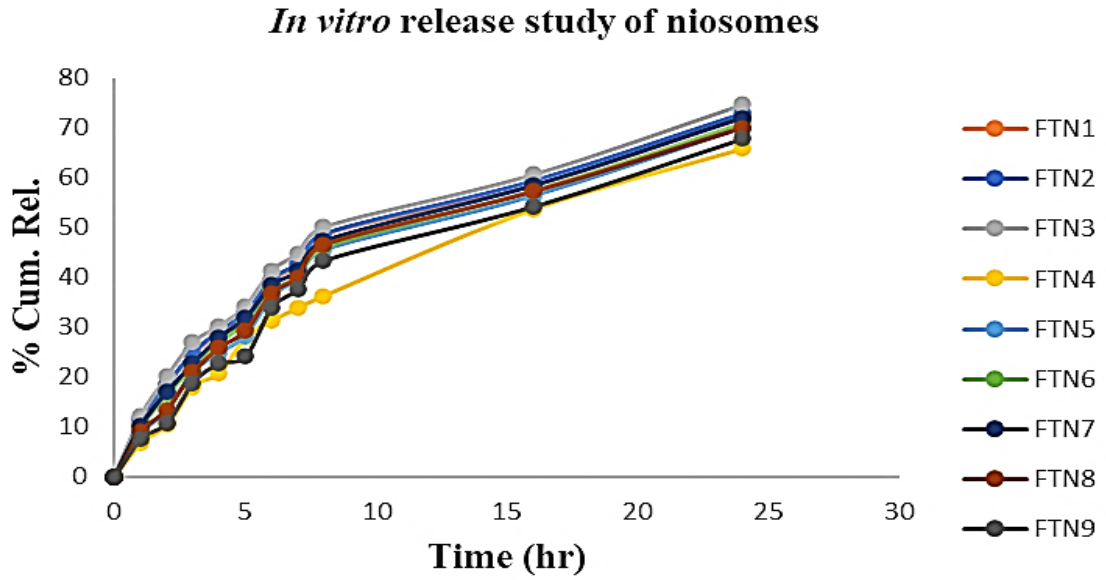

Figure 8. *In-vitro* release study of optimized batches.

CHARACTERIZATION OF NIOSOMAL NAIL LACQUER

Drying Time

It was discovered that the drying time of the nail lacquer is 180 seconds.

Flow Smoothness

It demonstrates adequate that flow properties also produce a smooth coating that is uniform when poured on the glass plate.

Nonvolatile Content

- Initial wt. of petri plate containing sample = 30.549 gm.
- Final wt. of petri plate containing after drying = 30.386 gm.
- = 30.549–30.386/30.549.
- = 0.53%.

Water Resistance

An assessment of nail lacquer's water resistance was conducted. After being submerged in water for a whole day, the nail lacquer was shown to absorb less water. Oleic acid-prepared formulation demonstrated exceptional water resistance. Oleic acid-prepared formulations produced outstanding outcomes, are shown in Table 10 and Figure 9.

Table 10. Water resistance test.

W^1 (gm)	W^2 (gm)	Difference in weight (gm)
5.35	5.25	0.10

Figure 9. Water resistance test for nail lacquer.

Estimating Drug Content

A formulation indicates a high concentration of drug when the drug content 85%. This guarantees an improved therapeutic outcome.

Comparative *in Vitro* Release Study

Release studies using a synthetic membrane (dialysis) were carried out. Nail lacquer composition is evenly applied to the membrane's surface. We carried out the diffusion investigation for a whole 24 hours. The formulation for nail lacquer had the maximum release, at 60.65%. It was discovered that the addition of oleic acid, a permeability enhancer, promotes medication release. Furthermore, nitrocellulose maintains terbinafine hydrochloride release for up to 48 hours, are shown in Table 11 and Figure 10.

Table 11. Values of Comparative In-vitro release Study.

Time (hr.)	TN3 Loaded Nail Lacquer	Marketed FORMULATION TERBINAFORCE (1% w/w)
1	6.07	24.77
2	12.32	70.04
3	17.84	82.70
4	23.67	99.04
5	25.76	–
6	29.30	–
7	31.17	–
8	34.61	–
16	51.48	–
24	60.65	–

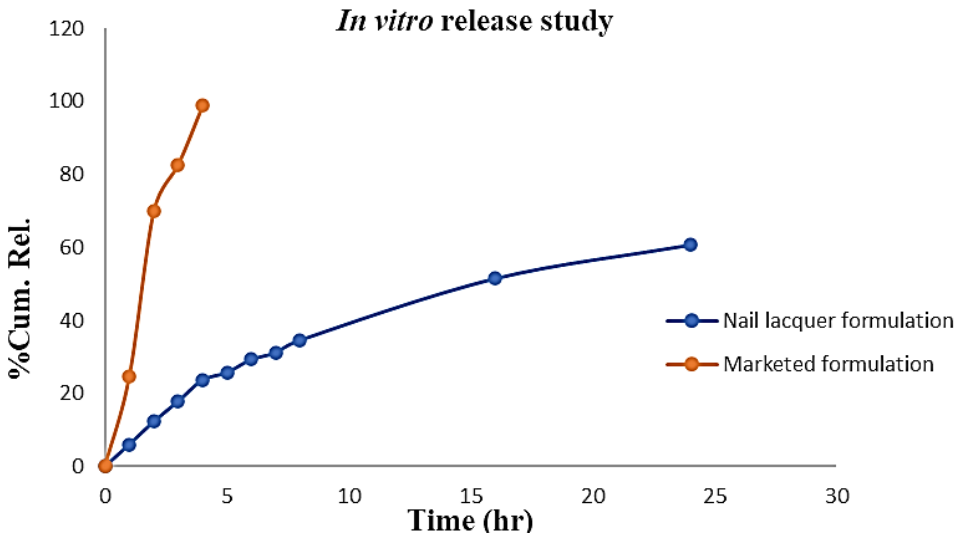

Figure 10. Comparative *in-vitro* release study of optimized batch and marketed formulation.

Antifungal Activity Against *Candida Albicans*

The antifungal activity of the optimized nail lacquer formulation was evaluated using the ZI method, and results were compared with a marketed formulation and a control.

- *The control showed no antifungal activity (ZI: 0 mm*), confirming the absence of inherent antifungal properties.
- The *marketed formulation* exhibited a ZI of *10 ± 0.01 mm*, indicating moderate antifungal activity.
- The *optimized nail lacquer formulation* demonstrated a significantly higher ZI of *14 ± 0.01 mm*, indicating superior antifungal efficacy, is shown in Figure 11(a–c) and Table 12.

Figure 11. *In-vitro* antifungal activity of Nail lacquer compared with marketed formulation.

Using the agar well diffusion, the ZI over the strain *Candida albicans* was measured to assess the antifungal profile of samples 1, 2, and 3. The compounds 2 and 3 had effective antifungal action.

Table 12. Antifungal activity study of optimized batch.

Sr. No.	Solution	Zone of Inhibition (mm)
1.	Control	1.0
2.	Marketed formulation	2.10 ± 0.01
3.	Nail lacquer formulation	3.14± 0.01

Stability Studies

For the formulated optimized batch TN3 a 1 month stability study was carried out at controlled temperature (4°C ± 2°C) niosome formulation was tested for %EE, particle size, also for zeta potential during a one-month period. And the result shows formulation was stable after 1 month. Findings demonstrated that nail lacquer had ideal stability after 1 month of storage. There were no notable changes to the color, nonvolatile content, drying time, or smoothness to flow are shown in Table 13.

Table 13. Stability study of FTN3 niosomes.

Sr. No.	Evaluation parameter	Time Interval	
		0 Day (Initial)	30 Days (After 1 Month)
1	Entrapment efficiency (%)	82.69	82.75
2	Particle size (nm)	126.0	128.9
3	Zeta potential (mV)	–31.4	–31.7

CONCLUSIONS

According to the data, niosomal formulations increased the medicine's solubility and permeability. Because the medicine had poor solubility, it overcomes and produces like superior outcomes in the form of niosomes, which considerably increases the drug's solubility and permeability. It is concluded that the efficiency of terbinafine hydrochloride for the treatment of onychomycosis fungal infection can be cured in a small dose when applied in the form of niosomal lacquer with an increase in patient compliance and targeted mode of treatment. In the future, *in vivo* research studies can be conducted to acquire a better understanding of the formulations and their characteristics.

Acknowledgment

I would like to thank Prof. D. D. Chougule, Dr. Shivajirao Kadam College of Pharmacy, Kasabe Digraj, Sangli, for providing the infrastructure and facility to complete the research work.

Conflict of Interest

There is no conflict of interest.

REFERENCES

1. Bhowmik D, Gopinath H, Kumar BP, Duraivel S, Aravind G, Kumar KS. Nail drug delivery system-a novel approaches for drug delivery system. The pharma innovation. 2013;1(11, Part A):3–16.
2. Saner MV, Kulkarni AD, Pardeshi CV. Insights into drug delivery across the nail plate barrier. J Drug Target. 2014;22(9):769–789. doi:10.3109/1061186X.2014.929138.
3. Murdan S. Enhancing the nail permeability of topically applied drugs. Expert Opin Drug Deliv. 2008;5(11):1267–1282. doi:10.1517/17425240802497218.
4. Šveikauskaitė I, Briedis V. Effect of film-forming polymers on release of naftifine hydrochloride from nail lacquers. Int J Polym Sci. 2017;2017(1). doi:10.1155/2017/1476270.
5. Vikas A, Rashmin P, Mrunali P, Chavan RB, Kaushik T. Mechanistic insights of formulation approaches for the treatment of nail infection: Conventional and novel drug delivery approaches. AAPS PharmSciTech. 2020;21(2):67. doi:10.1208/s12249-019-1591-9.
6. Jan S, Bora D, Bhise K. Preungual drug delivery systems of terbinafine hydrochloride nail lacquer. AJP. 2008;2(1). doi:10.22377/ajp.v2i1.175.
7. Ravalika V, Sailaja AK. Formulation and evaluation of etoricoxib niosomes by thin film hydration technique and ether injection method. Nano Biomed Eng. 2017;9(3):242–248. doi:10.5101/nbe.v9i3.p242-248.
8. Morteza-Semnani K, Saeedi M, Akbari J, Hedayati S, Hashemi SM, Rahimnia SM, et al. Green formulation, characterization, antifungal and biological safety evaluation of terbinafine HCl niosomes and niosomal gels manufactured by eco-friendly green method. J Biomater Sci Polym Ed. 2022;33(18):2325–2352. doi:10.1080/09205063.2022.2103626.
9. Marty JP. Amorolfine nail lacquer: A novel formulation. J Eur Acad Dermatol Venereol. 1995;4:S17–S21. doi:10.1016/0926-9959(94)00075-B.

10. Shirwaikar AA, Thomas T, Shirwaikar A, Lobo R, Prabhu KS. Treatment of onychomycosis: An update. Indian J Pharm Sci. 2008;70(6):710–714. doi:10.4103/0250-474X.49088.
11. Salve PS. Development and evaluation of topical drug delivery system for terbinafine hydrochloride using niosomes. Res J Topical and Cosmetic Sci. 2011;2(2):52–63.
12. Shi H, Xie Y. Solubility and thermodynamics of terbinafine hydrochloride in different neat and binary solvents: Measurement, correlation and molecular interactions. J Mol Liq. 2017;243:293–301. doi: 10.1016/j.molliq.2017.08.052.
13. Thavva VE, Baratam SR. Formulation and evaluation of terbinafine hydrochloride microsponge gel. Int J Appl Pharm. 2019;11(6):78–85. doi:10.22159/ijap.2019v11i6.32502.
14. Bargir TN, Aj AD, Sa PA. Composition of terbinafine HCL polymeric gel for mucosal drug delivery. IJBPAS. 2016;5(9):2146–2168.
15. Van Dooren AA, Müller BW. Purity determinations of drugs with differential scanning calorimetry (DSC)—a critical review. Int J Pharm. 1984;20(3):217–233. doi:10.1016/0378-5173(84)90170-4.
16. Kuminek G, Rauber GS, Riekes MK, de Campos CE, Monti GA, Bortoluzzi AJ, et al. Single crystal structure, solid state characterization and dissolution rate of terbinafine hydrochloride. J Pharm Biomed Anal. 2013;78–79:105–111. doi:10.1016/j.jpba.2013.02.001.
17. Atici EB, Karlığa B. Quantitative determination of two polymorphic forms of imatinib mesylate in a drug substance and tablet formulation by X-ray powder diffraction, differential scanning calorimetry and attenuated total reflectance Fourier transform infrared spectroscopy. J Pharm Biomed Anal. 2015;114:330–340. doi:10.1016/j.jpba.2015.06.011.
18. Gunst RF, Mason RL. Fractional factorial design. Wiley Interdisciplinary Reviews: Computational Statistics. 2009;1(2):234–244. doi:10.1002/wics.27.
19. Olii AT, Nugroho AK, Martien R, Riyanto S. Effect of ratio Span 60-Cholesterol on the characteristic of niosomes vitamin D3. RJPT. 2022;15(12):5551–5554. doi:10.52711/0974-360X.2022.00937.
20. Nowroozi F, Almasi A, Javidi J, Haeri A, Dadashzadeh S. Effect of surfactant type, cholesterol content and various downsizing methods on the particle size of niosomes. Iran J Pharm Res. 2018;17(Suppl2):1–11.
21. Lv Y, He H, Qi J, Lu Y, Zhao W, Dong X, et al. Visual validation of the measurement of entrapment efficiency of drug nanocarriers. Int J Pharm. 2018;547(1–2):395–403. doi:10.1016/j.ijpharm.2018.06.025.
22. Nordström R, Zhu L, Härmark J, Levi-Kalisman Y, Koren E, Barenholz Y, et al. Quantitative cryo-TEM reveals new structural details of doxil-like PEGylated liposomal doxorubicin formulation. Pharmaceutics. 2021;13(1):123. doi:10.3390/pharmaceutics13010123.
23. Puri V, Savla R, Chen K, Robinson K, Virani A, Michniak-Kohn B. Antifungal nail lacquer for enhanced transungual delivery of econazole nitrate. Pharmaceutics. 2022;14(10):2204. doi:10.3390/pharmaceutics14102204. doi: 10.3390/pharmaceutics14102204.
24. Aggarwal R, Targhotra M, Sahoo PK, Chauhan MK. Efinaconazole nail lacquer for the transungual drug delivery: Formulation, optimization, characterization and in vitro evaluation. J Drug Deliv Sci Technol. 2020;60(2):101998. doi:10.1016/j.jddst.2020.101998.
25. Thatai P, Sapra B. Terbinafine hydrochloride nail lacquer for the management of onychomycosis: Formulation, characterization and in vitro evaluation. Ther Deliv. 2018;9(2):99–119. doi:10.4155/tde-2017-0069.
26. Mehta SK, Jindal N, Kaur G. Quantitative investigation, stability and in vitro release studies of anti-TB drugs in Triton niosomes. Colloids Surf B Biointerfaces. 2011;87(1):173–179. doi:10.1016/j.colsurfb.2011.05.018.
27. Singh CH, Jain CP, Kumar BN. Formulation, characterization, stability and invitro evaluation of nimesulide niosomes. Pharmacophore. 2011;2(3):131–148.
28. Thavva VE, Baratam SR. Formulation and evaluation of terbinafine hydrochloride microsponge gel. Int J Appl Pharm. 2019;11(6):78–85.
29. Valdes BS, Serro AP, Gordo PM, Silva A, Gonçalves L, Salgado A, et al. New polyurethane nail lacquers for the delivery of terbinafine: formulation and antifungal activity evaluation. J Pharm Sci. 2017;106(6):1570–1577. doi: 10.1016/j.xphs.2017.02.017.
30. Ceren Ertekin Z, Sezgin Bayindir Z, Yuksel N. Stability studies on piroxicam encapsulated niosomes. Curr Drug Deliv. 2015;12(2):192–199. doi: 10.2174/1567201811666140723115852.

