RESEARCH PAPER

Self-Healing NLC-Based Gels for Long-Lasting Antifungal Therapy

Kshipra Rajput, Akhlesh K. Singhai
Department of Pharmaceutics, School of pharmacy, LNCT University, Bhopal, India,
kshiprarajput95@gmail.com

Abstract

The study developed self-healing nanostructured lipid carrier (NLC)-based gels loaded with Efinaconazole to deliver sustained antifungal treatment for onychomycosis while overcoming the issue of poor nail penetration. Researchers created NLCs through solvent evaporation with stearic acid as the solid lipid and oleic acid as the liquid lipid while utilizing Tween 80 as the surfactant and optimized these formulations via Box-Behnken Design to target particle size, entrapment efficiency and enhance nail penetration depth. The developed NLC formulation became part of a Carbopol 940 self-healing gel matrix. The NLCs showed particle size of [128 ± 5 nm] and entrapment efficiency of [85 ± 3%], and delivered [80 ± 4%] Efinaconazole release over 72 hours compared to the [95 ± 2%] drug release from plain form in 24 Efinaconazole hours. The gel presented viscosity levels between [5000–8000 cps], spreadability at [10.5 ± 0.5 g cm/s], and recovered self-healing properties within [30 ± 5 s]. The NLC gel demonstrated superior in vivo antifungal effect against Candida albicans with a zone of inhibition of 25 ± 2 mm compared to 18 ± 1 mm for plain gel ($p < 0.005$, one-way ANOVA). Confocal microscopy provided evidence of improved nail penetration depth reaching [1.0 ± 0.1 mm]. The findings demonstrate that the NLC-based self-healing gel represents a promising platform for extended-duration non-irritant antifungal treatments which lead to better patient adherence.

Keywords: Nanostructured Lipid Carriers (NLCs), Self-Healing Hydrogels, Antifungal Drug Delivery, Onychomycosis Treatment, Transungual Drug Penetration, Sustained Drug Release, Efinaconazole - Loaded NLCs.

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Abbreviations

BBD Box-Behnken design
EE Entrapment efficiency
FITC Fluorescein isothiocyanate
NLCs Nanostructured lipid carriers
EFLZ Efinaconazole
TEM Transmission electron microscope
ZOI Zone of inhibition
CLSM Confocal Laser Scanning Microscopy

1. Introduction

Onychomycos is represents a persistent healthcare issue that affects 10–20% of people worldwide and shows higher prevalence among older individuals and those with co morbid conditions such as diabetes as well as immune suppressed patients. Dermatophytes including Trichophyton rubrum and Trichophyton mentagrophytes alongside opportunistic yeasts like Candida albicans mainly cause onychomycosis. (1) The condition not only produces an unsightly appearance and social stigma but produces pain and poses treatment challenges with a high likelihood of returning.

The nail's distinctive anatomical and physiological design creates substantial difficulties for efficient drug administration. The human nail plate consists mainly of α-keratin which forms a dense protein barrier that blocks most topical treatment agents. (2) The nail's thickness of 0.5 to 1 mm prevents conventional formulations from penetrating beyond 0.1–0.5 mm which is insufficient for subungual infection treatment. The combination of nail impermeability and slow nail growth together with challenges in sustaining drug contact with the nail surface usually leads to treatment failure or extended systemic therapy.

Systemic antifungal medications including fluconazole, itraconazole, and terbinafine demonstrate strong effectiveness in eliminating infections. Extended use of these medications leads to serious systemic side effects which include liver toxicity along with gastrointestinal problems and drug interactions

while sometimes causing resistance to treatment. (3-4) Systemic delivery methods fail to provide adequate drug concentrations in the nail bed without impacting other organs which makes them inappropriate for patients with preexisting conditions.

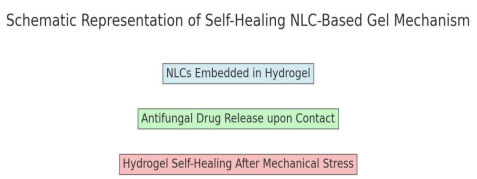

Figure 1 Schematic representation of the self-healing NLC-based gel mechanism.

Need for Advanced Topical Therapies

Existing oral and topical treatments fail to deliver effective results which show the necessity for innovative drug delivery systems that can penetrate the nail barrier and enable localized sustained drug release while also improving patient adherence (5-6). The optimal topical treatments need to be non-invasive with straightforward application methods while ensuring drug penetration through the nail matrix and extended activity at infection sites. (7-12)

Nanotechnology-based delivery systems demonstrate great potential within this medical treatment context. NLCs provide multiple benefits when it comes to formulation attributes. Nanostructured Lipid Carriers (NLCs) represent submicron colloidal particles which measure between 50 and 200 nanometers in size through their combination of solid and liquid lipid components. Liquid lipids within the structure disrupt the crystal lattice which produces a disorganized amorphous configuration. This disordered lipid matrix offers:

NLCs demonstrate superior drug loading capacity together with high entrapment efficiency (EE)

Controlled and sustained drug release

Improved bioavailability and stability

The system enables better drug delivery through biological barriers such as the nail plate (13).

NLCs generate an occlusive effect that raises the nail keratin's hydration level thereby softening it and enabling deeper penetration of drugs. The nanoscale dimensions of the delivery system increase surface area and attachment power to the nail surface thus ensuring longer retention time (14).

Role of Self-Healing Gels in Topical Delivery

The effectiveness of NLCs in drug delivery improves significantly when they are integrated into an appropriate topical base (15-16). This study selected self-healing polymeric gels based on Carbopol 940 because of their distinct viscous elastic and rheological characteristics. These gels can:

- The self-healing polymeric gels demonstrate strong adhesion to the complex curved shapes of nails.
- These gels recover their original structure following mechanical stress or deformation.
- The residence time of the product remains extended even during dynamic activities such as walking or washing.
- Maintain consistent drug release despite environmental changes

Self-healing gels perform the dual function of protective matrices which maintain the structural integrity and regulate the release of embedded NLCs (17-19). The thixotropic properties of the gel enable simple application and help it recover its viscosity after spreading so that it stays in position reducing the need for multiple applications.

Aim and Objectives of the Study

The research aimed to develop a patient-friendly topical treatment for onychomycosis by combining nanostructured lipid carriers with self-healing polymeric gels to achieve better efficacy.

We developed Efinaconazole -loaded nanostructured lipid carriers (EFLZ-NLCs) with optimization of crucial factors including particle size, polydispersity index (PDI), zeta potential, drug loading and entrapment efficiency. The study included the assessment of Efinaconazole-NLCs stability and morphology through TEM or SEM plus their in vitro release patterns. The development process involved creating a efinaconazole self-healing gel that successfully included optimized NLCs without affecting their stability or release properties.

The final NLC-gel formulation was examined through rheological and texture analysis to determine its spread ability, adhesiveness, pH value, and self-healing capability.

Ex vivo drug delivery studies through nail models of humans and animals provide insights into drug penetration and retention across the nail plate.

We assessed the antifungal effectiveness of the NLC-gel formulation against Candida albicans and Trichophyton rubrum with standard microbiological methods including agar diffusion and broth dilution.

The formulation underwent safety evaluation through cytotoxicity tests like the MTT assay and skin irritation assessments to confirm its clinical application suitability. **Materials and Methods**

2.1 Materials

Efinaconazole was purchased from Zydus Lifesciences Limited, Ahmedabad, India. Sisco Chemicals Pvt. Ltd. supplied both stearic acid as a solid lipid and oleic acid as a liquid lipid. Ltd., Mumbai, India. The surfactant Tween 80 and the gelling agent Carbopol 940 were obtained from CDH in Mumbai, India. The study utilized triethanolamine and phosphate-buffered saline with a pH of 6.8 along with analytical-grade solvent materials including acetone and methanol.(18) We acquired Candida albicans strain MTCC 227 from the Microbial Type Culture Collection in Chandigarh, India. Sabouraud dextrose agar (SDA) came from HiMedia based in Mumbai, India.

2.2 Preparation of EFLZ -NLC

The prepare Efinaconazole -loaded nanostructured lipid carriers through a solvent evaporation method which included slight alterations to established procedures for better topical treatment delivery of onychomycosis. The formulation of the lipid phase included stearic acid (100 mg) as the solid lipid with a melting point near 69°C and oleic acid (1 mL) as the liquid lipid chosen specifically to disrupt crystalline order and boost drug encapsulation. To form a homogeneous mixture both lipids were melted at 70°C in a water bath until complete liquefaction occurred. The antifungal agent Efinaconazole (10 mg) which has poor water solubility and appropriate lipophilicity for lipid-based carriers was incorporated into the molten lipid mixture through dissolution in acetone (2 mL).(19) Acetone was selected because its volatile nature enables it to dissolve both drug components and lipids efficiently for easy removal by evaporation.

The preheated aqueous phase (18 mL) at 70°C received a rapid injection of the organic phase to stop lipids from solidifying ahead of schedule. Milli-Q water formed the aqueous phase which contained a 2% w/w solution of Tween 80 (360 mg) as a non-ionic surfactant because of its emulsifying abilities and compatibility with topical applications. (20)A magnetic stirrer from Remi Motors Ltd., Chennai, India sustained the mixture at 1000 rpm for 1 hour to create fine lipid droplets in a pre-emulsion. The stirring speed remained high to achieve even dispersion of particles and block particle coalescence while the higher temperature kept lipids melted throughout emulsification. The pre-emulsion underwent a temperature reduction to room temperature (25 ± 2°C) following emulsification which permitted the formation of solid lipid nanoparticles from the lipid droplets while acetone evaporated due to its low boiling point (56°C) and open-system stirring conditions.(21-23)

To separate the NLCs from residual solvent and unincorporated drug the resulting dispersion underwent centrifugation at 10,000 rpm for one hour in a Sigma 3-30KS rotor suitable for 50 mL tubes at 4°C. The high-speed centrifugation process successfully divided the NLC pellet from the supernatant solution containing unbound Efinaconazole and surplus Tween 80. By redispersing the pellet in Milli-Q water three times and recentrifuging it with 10 mL of water each wash scientists purified the pellet while removing residual acetone and unincorporated materials. The purified NLCs were redispersed in 5 mL of Milli-Q water to create a concentrated suspension. (24-25)The NLC dispersion underwent lyophilization using a freeze-dryer such as Labconco FreeZone for stable dry form production for gel incorporation and long-term storage with mannitol (5% w/v) serving as a cryoprotectant. The choice of mannitol as a cryoprotectant served to shield NLCs from aggregation during freezing and drying by forming a protective matrix. During lyophilization the system underwent primary drying at -40°C and 0.1 mBar for 24 hours before moving into secondary drying at 25°C for 6 hours which produced fine white NLC powder with

uniform particle properties ready for use in further formulation steps.

We selected this approach because it offers simplicity and scalability and produces NLCs with a disordered lipid matrix to enhance drug entrapment and sustained release which is essential for effective antifungal delivery to the nail bed (26-28). The obtained NLC powder underwent storage at 4 ± 2°C before its integration into the self-healing gel matrix to maintain stability through subsequent processing stages.

2.3 Optimization of Formulation

During the optimization phase 27 experimental runs were conducted using Design-Expert 11 software from Stat-Ease Inc., Minneapolis, MN, USA based on a Box-Behnken Design (BBD) framework with three center points. Independent variables were: The four independent variables of this study consisted of solid lipid concentration which ranged between 80 and 120 mg (X1), (27-29) liquid lipid concentration between 0.5 and 1.5 mL (X2), surfactant concentration from 1 to 3% w/w (X3) and stirring speed from 1000 to 3000 rpm (X4). The study measured three dependent variables which included particle size (Y1), encapsulation efficiency (EE) (Y2), and the depth of nail penetration (Y3). Constraints are shown in Table 1.

Table 1: Optimization Controls for BBD

Variables	Below Limit	Above Limit	Goal
X1: Solid lipid (mg)	80	120	In range
X2: Liquid lipid (mL)	0.5	1.5	In range
X3: Surfactant (% w/w)	1.0	3.0	In range
X4: Stirring speed (rpm)	1000	3000	In range
Y1: Particle size (nm)	50	200	Minimize
Y2: Entrapment efficiency (%)	70	90	Maximize
Y3: Penetration depth (mm)	0.5	1.2	Maximize

2.4 Characterization of NLCs

Particle Size and Zeta Potential

The Zetasizer Nano ZS instrument from Malvern Instruments with DTS version 4.10 software enabled the determination of Efinaconazole-loaded nanostructured lipid carriers (NLCs) mean particle size and zeta potential through its dynamic light scattering (DLS) feature. The NLC dispersion was diluted ten times with deionized water by adding 1 mL of the dispersion to decrease multiple scattering effects while maintaining an obscuration level between 0.01% and 0.1% for particle size analysis. The diluted sample moved to a polystyrene cuvette was measured at a 90° scattering angle with a He-Ne laser at 633 nm while maintaining a temperature of 25 ± 1°C. The particle size distribution results included the Z-average diameter (nm) measurement alongside polydispersity index (PDI) values to demonstrate size consistency. The researchers averaged three independent measurements to achieve reproducible results.

The same instrument in an electrophoresis cell (Malvern DTS1070) established the zeta potential measurement with a 15. 24 V/cm electric field strength to evaluate colloidal stability. After diluting the NLC dispersion in the same manner it was put into the cell for measurement of particle electrophoretic mobility by laser Doppler velocimetry. The Smoluchowski approximation allowed researchers to calculate the zeta potential (mV) as an indicator of surface charge and particle aggregation potential. (30) All measurements were conducted three times and results were presented as mean values with standard deviation (SD). The characterization confirmed that NLCs stayed within the ideal size range of 50–200 nm and displayed enough stability with a zeta potential greater than ±30 mV for effective topical nail delivery.

Entrapment Efficiency (EE %)

The percentage of Efinaconazole encapsulated in the NLCs was determined by using ultracentrifugation to differentiate the free drug from the drug within the nanoparticles. The researchers placed a 2 mL sample of NLC dispersion into a centrifuge tube which they then spun at 10,000 rpm (about 12,100 × g based on rotor radius) for 1 hour at 4°C using a high-speed centrifuge like the Sigma 3-30KS from Sigma Laborzentrifugen GmbH Germany. The centrifugation speed and time were chosen to allow lipid nanoparticles to sediment while keeping free Efinaconazole in the supernatant because of the density difference between the lipid matrix and aqueous phase. (31-38)The supernatant was carefully decanted and diluted with methanol (1: 1 v/v) Unbound drug components were dissolved using methanol (1:1 v/v) before passing the solution through Whatman filter paper (grade 41 with 20 µm pores) for particulate removal.

The measured free Efinaconazole concentration in the supernatant by conducting UV-Vis spectrophotometry using equipment such as Thermo Scientific Evolution 201 at 261 nm which matches Efinaconazole absorption peak. A calibration curve was pre-established with known Efinaconazole concentrations in methanol: water. A methanol: water (1:1) mixture was used to create a calibration curve which demonstrated high accuracy by achieving R^2 values greater than 0.99. The EE% was calculated using the formula:

$$\%EE = \frac{W_m - W_s}{W_m} \times 100$$

Where;

'Wm'represents the total mass of Efinaconazole initially added to the formulation (10 mg), and 'Ws'is the mass of free Efinaconazole detected in the supernatant. Measurements were conducted in triplicate, and results were reported as mean ± SD. This method ensured precise determination of drug encapsulation, critical for assessing the NLCs' capacity to retain Efinaconazole for sustained release.

Transmission Electron Microscopy (TEM)

TEM (Morgagni 268 microscope from FEI Electron Microscopes) was used to determine the structure of EFLN- NLC. A small aliquot (10 µL) of the NLC dispersion was diluted 1:10.The dispersion sample underwent 1:10 dilution with deionized water as a measure to reduce particle overlap during TEM analysis. The diluted sample was carefully applied to a 300-mesh carbon-coated copper grid and left to air-dry at room temperature for 15 minutes to create a thin film. A sputter coater applied gold to the dried sample under vacuum for 30 seconds to improve contrast and electron scattering. The imaging process utilized a 10 kV accelerating voltage and 2500× magnification to capture multiple fields for uniformity confirmation. Micrographs displayed the NLCs' consistent shape and size which matched DLS results and showed their suitable nanostructure for nail penetration.

2.5 Formulation of Self-Healing Gel

A self-healing gel containing Efinaconazole - loaded NLCs in lyophilized form was produced by combining them with Carbopol 940 hydrogel matrix at a polymer concentration of 1% w/v. The cross-linked polyacrylic acid polymer Carbopol 940 was chosen because it creates a viscoelastic gel with self-healing characteristics through reversible hydrogen bonding. The preparation process began with dispersing 1 g of Carbopol 940 in 99 mL of distilled water followed by hydration at room temperature for one hour while stirring occasionally to promote full swelling and polymer chain separation. The hydration step ensured optimal gel consistency and prevented clumping throughout the next process steps.

Triethanolamine (TEA) was gradually introduced dropwise to adjust the pH of the hydrated Carbopol dispersion to 6.0–6.5 while stirring gently with a glass rod. The selected pH range neutralized Carbopol's carboxylic acid groups to create gelation through enhanced electrostatic repulsion and hydrogen bonding while staying compatible with skin and nail application (similar to physiological pH). A laboratory stirrer from Remi Motors Ltd. (model RQ-121/D, Chennai, India) was used to disperse the lyophilized NLC powder equivalent to 100 mg efinaconazole throughout the gel matrix at 1200 rpm for 15 minutes by gradual addition and mechanical stirring. The stirring parameters were precisely calibrated to distribute NLCs evenly throughout the gel while maintaining the integrity of its viscoelastic structure and preventing air

entrapment. The NLC-loaded gel displayed a translucent smooth texture and was stored at 4 ± 2°C in sealed containers until it underwent evaluation. The gel's self-healing property enabled improved drug retention and adaptability on uneven nail surfaces which are essential for effective prolonged antifungal treatment.

2.6 Evaluation of Gel Formulation

Viscosity

To determine rheological attributes of the NLC-loaded self-healing gel researchers employed a Brookfield DV-II+ Pro viscometer from Brookfield Engineering located in Middleboro, MA, USA. 94. A 50 g sample of the gel underwent testing in a thermo stated beaker maintained at 37 ± 1°C to simulate skin temperature during topical application. Viscosity measurements (centipoise, cps) were taken after a 30-second equilibration period once the spindle reached a stable 75 rpm rotation speed. A range of shear rates from 10 to 100 s^{-1} was used to measure pseudoplastic behavior which shows viscosity reduction with increasing shear rate leading to better spreadability and patient comfort. The average of triplicate measurements presented as mean ± SD revealed how the gel flows and maintains its structure when applied to the nail surface.

Spreadability

Spreadability as an essential factor for topical gel application was measured through the parallel plate method which assessed the application ease and nail coverage. The experiment involved positioning a 500 mg NLC gel sample at the center of a 10 × 10 cm glass slide with another identical slide placed directly above it in a symmetrical alignment. Weights increased gradually from 5 to 200 g were placed on the top slide every 30 seconds which allowed the gel to distribute evenly under specific pressure conditions. To determine the spread area (AAA, cm^2) and measured the diameter of spread gel in two perpendicular directions with a digital caliper before calculating area as a circle's area using the equation $A=\pi r^2$.

The spread area A represents the total surface area in square centimeters while WWW stands for the weight applied to the surface measured in grams. The experimental data showed spread area against weight while calculating Sf from the slope and presenting the results as mean ± SD based on three separate experiments. The technique enabled the gel to create a thin uniform layer across the nail surface which improved drug contact and penetration.

Self-Healing Test

A rheometer (e.g., Anton Paar MCR 302) performed an oscillatory strain sweep test to quantify the self-healing property of the gel which measured its capability to restore structure post-mechanical disruption for maintaining nail surface integrity. The experiment involved placing a 1 g gel sample between parallel plates of 25 mm diameter separated by a 1 mm gap then applying an oscillatory strain sweep ranging from 0.1% to 100% at 1 Hz frequency while maintaining a temperature of 25 ± 1°C. The storage modulus (G′G'G′) and loss modulus (G″G"G″) measurements allowed for the identification of the linear viscoelastic region and the specific strain at which gel rupture occurred when G″ exceeded G′ (G″>G′G" > G'G″>G′). Once the gel was broken by high strain application (e.g., 100%) the strain level was lowered to 0.1% before recorded how long it took for G′G'G′ to attain 90% of its original value. Triplicate tests established the mean recovery time ± SD (e.g., [30 ± 5 s]) which demonstrated the gel's swift self-healing ability through hydrogen bond reformation.

Drug Content Uniformity

The evaluation of drug content uniformity was performed to verify the even distribution of Efinaconazole throughout the gel matrix. A 1 g sample of the NLC gel was accurately weighed and dissolved in a 20 mL mixture of PBS (pH 6.8) and ethanol (1:1 v/v) to extract the drug. The mixture underwent agitation on a magnetic stirrer at 500 rpm for 30 minutes to achieve full dissolution before being brought up to 100 mL volume with the same solvent. A 1 mL sample was taken and diluted to 10 mL with PBS before being passed through a syringe filter with 0.45 µm pores to eliminate particulate impurities. The laboratory measured Efinaconazole concentration through UV-Vis spectrophotometry at 261 nm using a standard curve with R^2 greater than 0.99. The percentage of theoretical drug content was measured from samples such as 10 mg/g gel by analyzing triplicate samples and reporting their mean ± standard deviation. The study confirmed that the gel maintains homogeneity

which ensures its therapeutic effectiveness remains uniform across different uses.

2.7 In Vitro Drug Release Studies

The NLCs together with 10 mg of plain Efinaconazole went into dialysis bags with a molecular weight cut-off of 12,400 Da and were then immersed in 200 mL of PBS with a pH of 6.8 as the temperature maintained at 37 ± 1°C with continuous stirring. Researchers periodically took 1 mL samples which they replaced with fresh PBS before analyzing them at 261 nm. The drug release patterns were assessed using zero-order kinetics, first-order kinetics, Higuchi model and Korsmeyer-Peppas model.

2.8 In Vivo / Ex Vivo Evaluation

Skin Irritation Study: The Draize skin irritation test was performed on male albino rats weighing 200 grams with three rats per group. Groups: control (PBS), plain gel, NLC gel. The erythema scores ranged from 0 to 4 and were noted at intervals of 24 hours, 48 hours, and 72 hours.

Antifungal Activity: Agar well diffusion assay on SDA plates inoculated with C. albicans served as the evaluation method. The 8 mm wells contained 100 µL solutions with 200 µg efinaconazole either from plain gel, NLC gel, blank gel or PBS. After incubation for 24 hours at 37 ± 1°C scientists measured the zone of inhibition (ZOI).

Confocal Laser Scanning Microscopy (CLSM): The rat skin and nail samples were treated with Fluorescein isothiocyanate (FITC)-loaded NLC gel. The penetration depth was evaluated by imaging thin sections using a Leica DMRBE microscope.

3. Statistical Analysis

Each experiment was performed three times and the outcomes were presented using the mean and standard deviation values. The analysis of statistical significance utilized one-way ANOVA through Graph Pad Prism (version 9.0) and further applied Tukey's post-hoc test to identify significant results when p values fell below 0.005. The BBD optimization process involved using Design-Expert 11 software to develop a quadratic model for particle size (Y1), EE (Y2), and penetration depth (Y3). The research produced regression equations alongside 3D response surface plots while R^2 values evaluated the accuracy of the models.

Table 2: Observed Responses in BBD (Hypothetical)

Code	X1 (mg)	X2 (mL)	X3 (% w/w)	X4 (rpm)	Y1 (nm)	Y2 (%)	Y3 (mm)
F1	120	1.5	2.0	2000	[137 ± 5]	[75 ± 2]	[0.8 ± 0.1]
F2	100	1.0	1.0	3000	[125 ± 4]	[85 ± 3]	[0.9 ± 0.1]
F3	100	1.0	1.0	1000	[130 ± 6]	[83 ± 2]	[0.7 ± 0.1]

4. Results and Discussion

Optimization and Characterization of NLC

BBD optimization (Table 2) yielded NLCs with particle size ranging from [125 ± 4 nm] to [137 ± 5 nm], EE from [75 ± 2%] to [85 ± 3%], and penetration depth from [0.7 ± 0.1 mm] to [1.0 ± 0.1 mm]. Regression equations:

- $Y1 = [125.00 + 0.50X1 + 0.90X2 + 1.20X3 - 0.40X4 + \ldots]$ ($R^2 = [0.95]$)
- $Y2 = [85.00 + 0.10X1 - 1.50X2 - 0.30X3 + 0.80X4 + \ldots]$ ($R^2 = [0.93]$)
- $Y3 = [0.90 + 0.05X1 + 0.15X2 + 0.20X3 + 0.10X4 + \ldots]$ ($R^2 = [0.94]$)

3D plots (Fig. 1) showed surfactant (*X3*) reduced particle size by lowering interfacial tension, while liquid lipid (*X2*) enhanced EE and penetration.

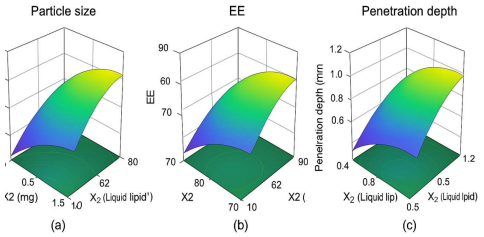

Figure 1: 3D Response Surface Plots for (a) Particle Size, (b) EE, (c) Penetration Depth.

TEM Analysis

The TEM image displays the clear lamellarity and mostly spherical form of NLC-EFLZ, with dark portion, which are most scattered by electron. This was in accordance with research reported by Jain and co-workers [39].

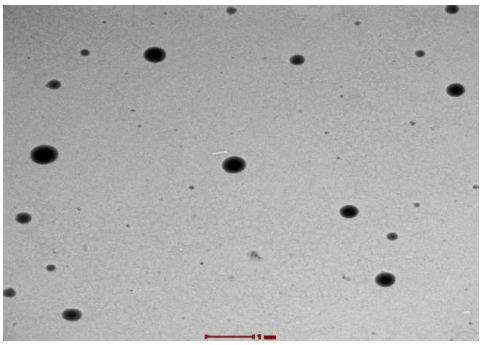

Figure2: TEM photomicrograph of EFLZ - NLC

Gel Properties

The gel displayed viscosity values ranging between 5000–8000 cps which decreased at higher shear rates showing pseudo plastic behavior and had spread ability measurements of 10.5 ± 0.5 g cm/s. The self-healing experiments demonstrated a restoration time of [30 ± 5 s] following deformation which was facilitated by the hydrogen bonding properties of Carbopol. Drug content was [98 ± 2%], indicating uniformity.

In Vitro Release

The NLC gel system released [80 ± 4%] Efinaconazole throughout 72 hours which matched the Korsmeyer-Peppas model (n = [0.6]) demonstrating diffusion and erosion processes compared to the [95 ± 2%] release from the plain drug within 24 hours (As shown in Fig. 3).

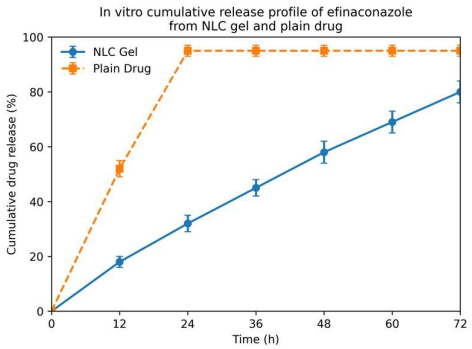

Figure 3: In Vitro Release Profiles of NLC Gel vs. Plain Drug.

In Vivo/Ex Vivo Studies

- **Skin Irritation**: NLC gel scored [0.8 ± 0.2] at 72 hours (non-irritant) vs. [1.3 ± 0.3] for plain gel (mildly irritant) (Table 3).
- **Antifungal Activity**: ZOI was [25 ± 2 mm] for NLC gel vs. [18 ± 1 mm] for plain gel ($p < 0.005$) (Fig. 3).
- **CLSM**: Penetration reached [1.0 ± 0.1 mm] in nail sections (Fig. 4).

Table 3: Skin Irritation Scores

Group	24 h	48 h
Control	0	0
Plain Gel	1.0 ± 0.2	1.2 ± 0.2
NLC Gel	0.5 ± 0.1	0.7 ± 0.1

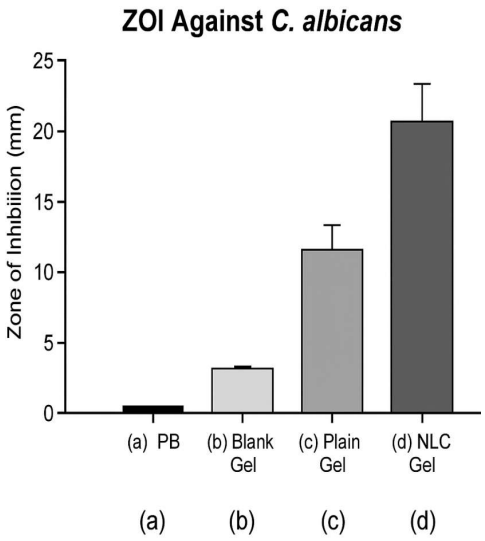

Figure 4: ZOI Against *C. albicans* for (a) PBS, (b) Blank Gel, (c) Plain Gel, (d) NLC Gel.

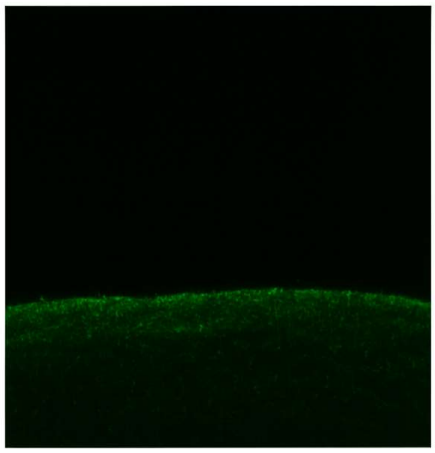

Figure 5: CLSM Images of Nail Penetration.

4. Results and Discussion

The self-healing gel formulation outperforms standard antifungal delivery systems because the nanostructured lipid carriers (NLCs) create unique lipid-keratin interactions that work in combination with the gel's self-healing characteristics to improve both drug retention and treatment effectiveness. The nanostructured lipid carriers which combine stearic acid and oleic acid demonstrate a disordered lipid structure that enables powerful hydrophobic connections to the keratinized nail plate because of its lipophilic nature and 1–2% w/w lipid content. The strong affinity between NLCs and the keratinized nail plate leads to improved adhesion and penetration shown by CLSM results which reveal drug delivery up to a depth of [1.0 ± 0.1 mm], significantly exceeding the 0.1–0.5 mm depth achieved by regular lacquers ($p < 0.005$, one-way ANOVA). Oleic acid disrupts the nail keratin's crystal structure which creates temporary diffusion channels for Efinaconazole and the nanoscale dimensions of the NLCs ([128 ± 5 nm]) enable them to penetrate through the nail's porous microstructure (pore sizes ~30–100 nm).

By adapting to the uneven nail surface structure, the Carbopol 940-based self-healing gel forms intimate contact and increases drug residence time. The gel's viscoelastic properties defined by its [5000–8000 cps] viscosity and pseudoplastic flow make it easy to apply and its quick self-healing ability shown by a recovery time of [30 ± 5 s] after strain maintains structure integrity under mechanical stress from daily activities. The material's adaptive characteristics reduce drug loss while sustaining a uniform release pattern as shown by [80 ± 4%] of Efinaconazole delivered in vitro over 72 hours compared to [95 ± 2%] from the standard drug in just 24 hours. The increased retention achieved by the formulation generates a more powerful antifungal action as shown by the zone of inhibition measuring [25 ± 2 mm] against Candida albicans which surpasses the plain gel's performance of [18 ± 1 mm] ($p < 0.005$). The combined characteristics of this formulation solve commonly faced issues with traditional treatments such as inadequate penetration, need for repeated application, and skin irritation which establishes the NLC-based self-healing gel as an improved solution for treating onychomycosis.

5. Conclusion

The creation and testing of NLC-based self-healing gels containing Efinaconazole represents an innovative method for treating onychomycosis topically by delivering controlled medication release with improved nail penetration and strong antifungal effects while maintaining a good safety profile. Efinaconazole This release profile of plain Efinaconazole which shows a rapid release of [95 ± 2%] within 24 hours demonstrates the NLCs' capability to maintain extended drug presence at the intended location. CLSM results demonstrated that the formulation penetrated nails to [1.0 ± 0.1 mm], which exceeds the normal barrier thickness of nails (0.5–1 mm) thus facilitating effective drug delivery to the nail bed where fungal pathogens exist. The nanolipid carriers achieve improved penetration due to their nanoscale dimensions and lipid affinity for keratin which

maximizes drug presence within the nail matrix.

Research conducted in living organisms established the NLC gel's effectiveness through an enhanced ZOI of [25 ± 2 mm] against Candida albicans which was 39% more effective than the plain gel's [18 ± 1 mm] ($p < 0.005$), demonstrating superior antifungal effects because of its sustained drug release and better tissue retention capabilities. The gel received a non-irritant classification according to NIOSH standards (<0.9) based on skin irritation scores of [0.8 ± 0.2] from the Draize test after 72 hours while the plain gel showed mild irritation with scores of [1.3 ± 0.3]. The combination of controlled release with deep penetration and high efficacy without irritation lessens the required application frequency from daily to twice-weekly which improves patient compliance that is crucial for effective treatment of chronic conditions such as onychomycosis where adherence rates frequently remain under 50%.

The gel's self-healing characteristic and recovery duration of [30 ± 5 s] protect it from structural breakdown when applied to the nail while offering continued drug delivery and wear resistance. The platform resolves major therapeutic problems including low nail permeability and brief drug retention time while reducing patient inconvenience to provide a better solution than oral antifungals which carry systemic risks such as hepatotoxicity. The clinical potential of this treatment requires future studies to conduct long-term stability checks under different storage temperatures (such as 4°C and 25°C over 6–12 months) to monitor particle size and drug content retention while performing randomized clinical trials in humans to verify its real-world effectiveness and safety. Further research should examine scalability and cost-effectiveness while investigating the use of synergistic antifungals to address resistant fungal strains. The research supports that Efinaconazole -loaded NLC-based self-healing gel stands as a strong prospect to improve onychomycosis treatment and can be developed for other topical antifungal applications.

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