RESEARCH ARTICLE

Antifungal Niosomal Nail Lacquer for Enhanced Transungual Delivery of Efinaconazole in the Treatment of Onychomycosis

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ABSTRACT

Niosomes, multilamellar vesicles, efficiently transfer active substances into the epidermis or systemic circulation. Topical medication delivery techniques increase skin permeability to active compounds. Onychomycosis, a common nail ailment caused by fungus, requires efficient topical therapies due to the risks of systemic antifungal therapy. This research aimed to make a nail polish with efinaconazole (EFN) to treat onychomycosis. The spherical Niosomes contained efinaconazole and had a 100 to 130 nm diameter. In the 24-hour *in-vitro* experiment, drug trapping ranged from 40 to 90% and release from 25 to 86%. The 1:2 mixtures of efinaconazole niosomes, Span 60, and CHO produced nail paint with good results. Efinaconazole-loaded niosomal nail polish had better drug release, antifungal effectiveness, and smoothness over other formulations. Topical nail polish can help low-bioavailability medicines. This method helps the medication enter the body through the nail. The ENNL can deliver onychomycosis drugs topically.

Keywords: Efinaconazole, Onychomycosis, Niosomal, Nail lacquer, Drug delivery system.

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INTRODUCTION

Efinaconazole is applied topically to treat toenail fungus or yeast infections. This drug either eradicates the detrimental yeast or fungus or inhibits its proliferation. Efinaconazole has been approved by the United States Food and Drug Administration (USFDA) for the topical treatment of toenail onychomycosis caused by the fungus *Trichophyton rubrum* and *T. mentagrophytes*.[1] It is classified as an azole antifungal medication. Chemical structure of Efinaconazole is shown in Figure 1.

Niosomes, which are small lamellar particles, are formed by combining a non-ionic surfactant with a charge-inducing substance such as cholesterol. "The compounds in question possess hydrophilic and hydrophobic functional groups that engage in interactions with different soluble herbal components. Advancements in vaccination and the management of infectious diseases have made significant progress in the past few decades. Biotechnology and genetic engineering have enhanced the effective administration of bioactive substances that specifically target diseases, while also generating a wide range of these compounds which is shown in Figure 2.

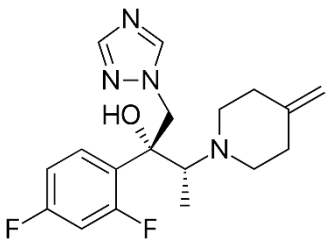

Figure 1: Chemical structure of efinaconazole

Niosomes are lipid vesicles composed of non-ionic surfactants. Liposomes are inferior to them due to their better stability, biodegradability, economy, and absence of toxicity. This work explores the increasing interest in niosomes in several scientific disciplines, with a particular focus on their potential medical uses.[2, 3] Onychomycosis is the predominant type of nail fungus. It alters the distance between the toes and fingers. For the treatment of onychomycosis, a combination of oral and topical therapies can be employed either concurrently or independently. Empirical data indicates that oral antifungal medicines has the capacity to induce adverse reactions and exhibit suboptimal absorption in the gastrointestinal tract and other bodily regions. Onychomycosis refers to a fungal infection that mostly affects the nail plate. The problem can be attributed to yeasts, dermatophytes, or non-dermatophytes fungus. This condition is frequently observed. It is held by approximately 10 to 12% of the American population". This study aimed to

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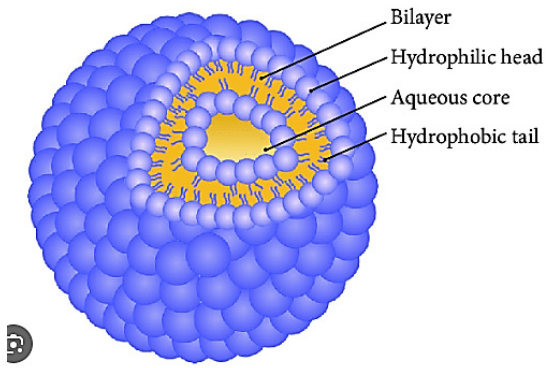


Figure 2: Structure of niosomes

assess the viability of utilizing niosomes, which are lipid-based vesicles carrying efinaconazole in nail polish, as a potential treatment for onychomycosis, a fungal infection of the nails.[4-6]

MATERIALS AND METHODS

Materials

Efinaconazole was marketed and provided by Sun Pharma Ltd, an Indian corporation situated in Mumbai. The Span 60, nitrocellulose, and ethyl cellulose were procured from the Mumbai-based SD Fine Chemicals Ltd. Sigma-Aldrich of Mumbai was the source of the cholesterol. A Merck plant in Bombay dispatched Pluronic L121, diacetyl phosphate, and two doses of salicylic acid. SD Fine Chemicals Ltd. provided the sodium dihydrogen phosphate, methanol, and ethanol. The remaining commodities met the analytical standards for excellent grade.

Methods

Pre-formulation study

- *Drug excipient interaction studies*

Investigating the compatibility of drugs and excipients is a crucial step during the pre-formulation phase of drug development. The possible interactions between medications and excipients can impact the chemical composition, physical properties, bioavailability, and stability of the dosage form.[7-9]

- *Preparation of efinaconazole niosomes*

The probe sonication method was employed to combine 15 mL of water and 100 mg of efinaconazole, resulting in the formation of niosomes. This was accomplished using a magnetic stirrer. This was followed by the addition of Span 60, cholesterol, Pluronic L121, and diacetyl phosphate. The most advanced niosomes were produced using a variety of concentrations of Pluronic L121 and DCP. The primary composite component was identified as 1-mg of diacetyl phosphate and 290 mg of Pluronic L121, as per the initial analysis results. Then, the batch was subjected to a Vibra cell sonication procedure for 5 minutes at a probe temperature of 57°C and an amplitude of 30% (Table 1). The niosomes were stored at 4°C in anticipation of a physicochemical investigation following their synthesis through probe sonication.[10–13]

Table 1: Various concentrations of surfactants for niosomes preparation

Formulations	*Drug (mg)*	*Span 60 (mg)*	*Pluronic L121 (mg)*	*Cholesterol (mg)*	*DCP (mg)*	*Milli-Q H2O (mL)*
EFN1	100	430	246	773	1	15
EFN2	100	430	290	773	1	15
EFN3	100	430	290	773	2	15
EFN4	100	430	246	773	0	15
EFN5	100	430	334	773	1	15
EFN6	100	430	318	773	1	15

Characterization of Efinaconazole Niosomes

Morphology

The dimensions, morphology, and surface topography of the niosomes were assessed using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). A silicon chip was covered with a solitary particle of niosome solution to create a specimen". The sample was dried thoroughly before being subjected to scanning electron microscopy (SEM) investigation.[14-17]

Size and zeta potential measurements

The Niosomes in each formulation were analyzed using the Zetasizer Nano ZS by Malvern Instruments Ltd. to measure their zeta-potential, polydispersity index (PDI), and average diameter (z-average). The zeta potential, also known as the surface charge of a vesicle, can be measured by observing the movement of particles in an electrophoretic field.[18-20]

Fourier-transform infrared spectroscopy

Scientists employ fourier-transform infrared spectroscopy (FTIR), commonly referred to as FTIR, to investigate the interaction between matter and infrared radiation. This method quantifies the absorption and transmission of infrared energy. The FTIR scanning was conducted at room temperature with a resolution of 4 cm^{-1} and a scanning range from 4000 to 400 cm^{-1}.[21, 22]

Entrapment efficiency

The process of centrifugation is employed at a speed of 5,000 rpm for a duration of 30 minutes at a temperature of 4°C in order to eliminate the drug that is not linked to the efinaconazole niosomes. After being washed in 10 mL of PBS, the niosomal granules were subjected to a second centrifugation. We employed a Millipore 0.22 m filter, manufactured in the United States, to isolate the supernatant. A method to quantify the quantity of a pharmaceutical agent in niosomes is by assessing their absorbance at a wavelength of 230 nm.[23,24]

Percent drug entrapment = Total drug-drug in supernatant/ Total drug × 100

Formulation of Niosomal Nail Lacquer

A rudimentary blending procedure was employed to produce nail lacquers. The inclusion of ethanol resulted in the dissolution of the film-forming agent. The process of adding a niosomal solution, which contained 100 mg of the medication, to the previously indicated combination was carried out

with constant stirring. After adding keratolytic chemicals and propylene glycol, the mixture was stirred for a further 30 minutes. There were a total of six distinct formulas that were created and subsequently evaluated which is shown in Table 2.

Evaluation of Niosomal Nail Lacquer[25]

Folding endurance

Folding endurance refers to the greatest number of times a film may be folded before it tears. To determine the flexibility of the polymer film, one can measure its duration of foldability". The flexibility of the films was assessed by subjecting them to repeated folding to measure their durability.

Non-volatile content

A glass petri dish with a diameter of 8 cm contained the sample. The utilization of wire coated with tar ensured that the samples would be uniformly dispersed. Following one hour of baking at a temperature of 105°C, the dish was removed from the oven, allowed to cool, and subsequently weighed. After the sample had undergone the process of drying, the change in weight, whether it decreased or increased, was determined.

Drying time

A film specimen was deposited onto a glass petri dish. A timer was established to ascertain the duration required for the film to fully solidify.

Stability studies Niosomal Nail Lacquer

We followed the rules specified by the International Council for Harmonization (ICH) when we conducted stability tests of manicure lacquers. Temperatures of 25 ± 2°C with 60% relative humidity were used to preserve the samples for 6 months, followed by a month at 40 ± 2°C with 75% relative humidity.[26]

Antifungal Activity Niosomal Nail Lacquer[27]

In-vitro studies by agar diffusion methods

Comparative studies were conducted to assess the antifungal effectiveness of the niosomal formulation in comparison to conventional efinaconazole niosomal nail lacquer and commercially available antifungal nail lacquer. *Candida albicans* was used as the test microorganism. The findings from an agar diffusion test conducted using the "Cup plate" technique validate this.[26, 27]

Table 2: Formulation of efinaconazole niosomal nail lacquer

Ingredients (%)	*ENNL -1*	*ENNL -2*	*ENNL -3*	*ENNL -4*	*ENNL -5*	*ENNL -6*
Efinaconazole niosomes	10	10	10	10	10	10
Nitrocellulose	4	4	5	5	6	6
Salicylic acid	-	4	8	16	20	20
2-HPβ-CD	-	-	6	8	10	12
Ethylcellulose	-	-	-	0.3	0.6	0.9
Propylene glycol	12	12	12	12	12	12
Ethanol q.s	100	100	100	100	100	100

Histopathology of the skin of animal post-treatment

This is the hide of a processed animal. The efficacy of efinaconazole niosomal nail lacquer was evaluated using Periodic acid Schiff's staining (PAS), a histology technique utilized to detect fungal hyphae. In order to gain a deeper comprehension of the alterations that occurred in the dermis and epidermis of the skin over a period of time, the application of hematoxylin and eosin (H&E) staining was employed.[25-27]

RESULT AND DISCUSSION

Pre-formulation Study

Researchers employed FTIR and DSC analysis to determine the physical compatibility of the drugs and excipients.

FTIR spectroscopy

It was concluded that efinaconazole had comparable infrared, sample, and standard spectra. All of the unique summits were discovered to be inside the appropriate region. The integrity of the final sample was verified using infrared spectroscopy. Upon analyzing the infrared spectra of both the drug and its formulation, it is observed that the characteristic peaks of the formulation correspond to those of the pure drug. The results can be observed in Figure 3.

Differential scanning colorimetry

The DSC analysis was conducted to characterize both the Efinaconazole. The undiluted medication exhibited a distinct exothermic spike at a temperature of ^{o}C. Identical exothermic peaks were seen at the same temperature of 209^{o}C in the nail lacquer that was made. The aforementioned analysis verifies the absence of any interaction between the medicine and excipients. Figure 4 displays the results.

Characterization of Efinaconazole Niosomes

Morphology

To examine multiple efinaconazole-loaded niosome formulations (EFN2) and one EFN2, scanning electron microscopy (SEM) images were captured at a magnification of 5000X. The SEM image of the novel formula revealed vesicles that exhibited a near-spherical shape and displayed a uniform size. The results can be observed in Figure 5.

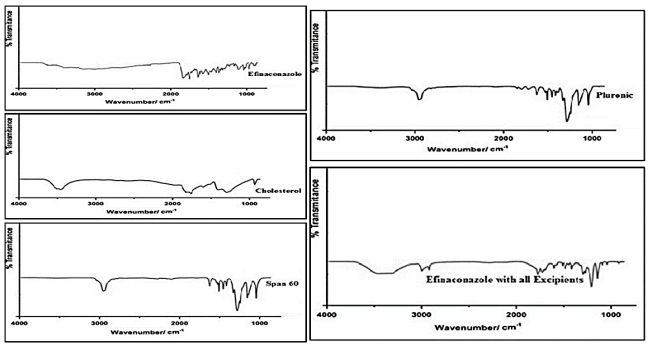


Figure 3: FTIR spectra of efinaconazole drug with excipient

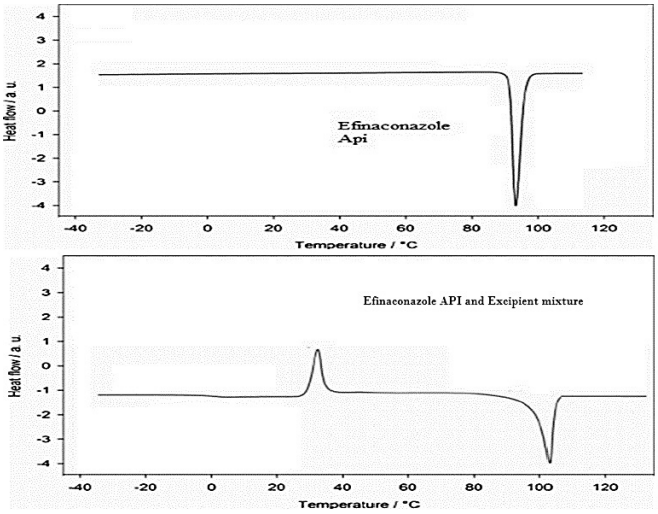


Figure 4: DSC Thermograms of efinaconazole drug with excipient

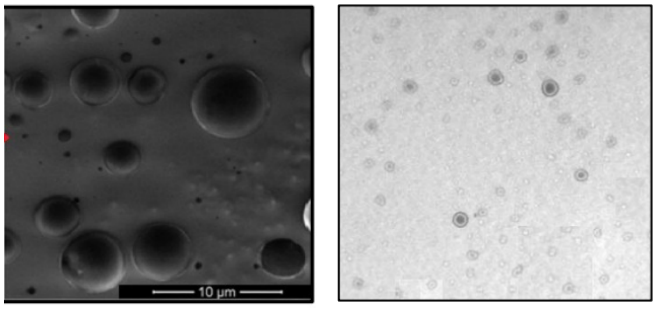


Figure 5: SEM and TEM of Efinaconazole niosomes

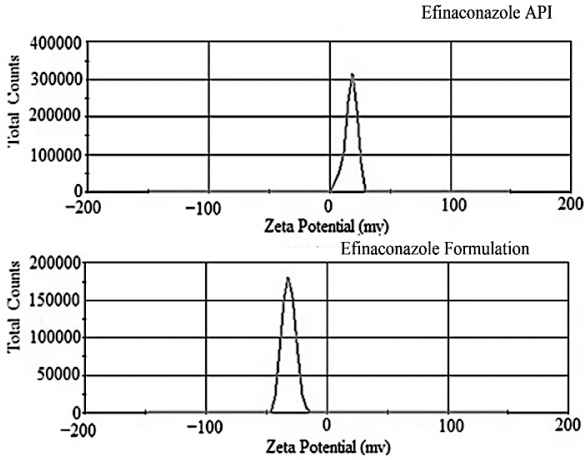


Figure 6: Zeta potential of efinaconazole niosomes

Size and zeta potential measurements

According to Figure 6, the zeta potential of niosomes produced from Span 80 and 60 exceeded -30 mV, indicating that the systems were stable.

Entrapment efficiency

The entrapment efficacy of a formulation can be used to determine the frequency at which dosage should be administered, which is a crucial aspect of drug delivery. It is customary to utilize this criterion for the purpose of ascertaining the concentration of the medicine in the formulation. The outcomes were shown in Table 3. Therefore, increasing the amount of the medicine in the formulation may result in a decreased frequency of administering the therapeutic component.

Table 3: Evaluation parameters of efinaconazole niosomes

Formulation	*Percentage yield*	*Entrapment efficiency*	*Particle size (nm)*	*Zeta potential (mV)*
EFN1	65.77 ± 0.17	45.25 ± 0.87	130.13	-5.0
EFN2	89.22 ± 1.12	90.21 ± 0.67	98.21	-4.4
EFN3	73.82 ± 0.74	75.55 ± 0.82	120.82	-5.2
EFN4	78.14 ± 0.53	80.23 ± 0.85	124.21	-4.1
EFN5	93.82 ± 0.74	92.55 ± 0.82	125.82	-5.4
EFN6	72.82 ± 0.74	70.55 ± 0.82	110.82	-4.2

Table 4: Physical appearance and water resistance of efinaconazole niosomal nail lacquer

Formulation code	*Gloss*	*Blush test*	*Smoothness to flow*	*Water resistance test*
F1	Pass	Pass	Pass	Poor
F2	Pass	Pass	Pass	Poor
F3	Pass	Pass	Pass	Poor
F4	Pass	Pass	Pass	Excellent
F5	Pass	Pass	Pass	Excellent
F6	Pass	Pass	Pass	Excellent

Evaluation of Niosomal Nail Lacquer

Smoothness to flow and gloss

By elevating the glass plate, a consistent and sleek layer was created through the application of nail lacquer. A comparison was conducted between the commercially produced nail lacquer and the sheen of a cosmetic sample that was sold. The prepared nail lacquer had a comparable luster.

Water resistance and blush test

A water resistance test was conducted to assess the durability of the manicured lacquer in water. The experimental findings demonstrated that the nail polish exhibited reduced water absorption after being immersed in water for a duration of 24 hours. Unlike formulations containing thioglycolic acid, which exhibited exceptional water resistance, formulations containing salicylic acid and urea did not possess sufficient water resistance. The results obtained from the flush test were quite comparable. The outcomes are shown in Table 4.

Drying time

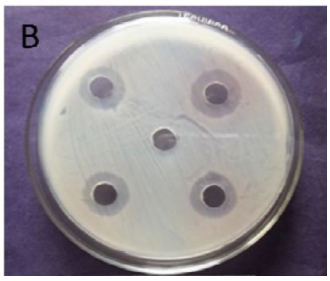
The drying time of nail lacquer was shown to vary between sixty-four and ninety seconds. The discovery that a curing duration of one to two minutes is optimal for nail lacquer led to the monitoring of all formulations". The range consists of values ranging from F1 to F9. Formulations containing thioglycolic acid dry at the fastest rate. Formulations containing salicylic acid need the most time to dry.

Table 5: Characterization of efinaconazole niosomal nail lacquer

Formulation code	*Drying time*	*Non-volatile content*	*Adhesion (%Peel off)*	*Hydration enhancement factor (HEF) %*	*%Drug content*	*Zone of inhibition (mm)*
F1	82	15	4.5	2.6	85	15
F2	87	18	6.5	3.9	86	18
F3	90	22	8.24	4.4	92	20
F4	64	10	2.53	5.8	96	21
F5	64	13	2.87	7.0	98	28
F6	69	18	3.01	6.4	94	25

Table 6: Antifungal activity of efinaconazole niosomal nail lacquer

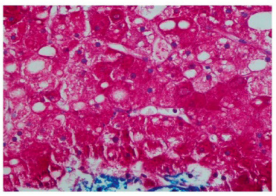
Antifungal activities (Zone of inhibition)		
Samples	*Concentration in (µL/mL)*	*Zone of inhibition in mm*
Marketed antifungal Nail Lacquer 85% W/V	100	26
Efinaconazole API	100	27
ENNL (Placebo)	100	22
ENNL	50	27
ENNL	100	28



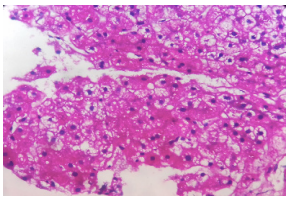
1 = ENNL (Placebo) 2 = Nailon Nail Lacquer %W/V 3 = ENNL (50 µg/mL) 4 = ENNL (100 µg/mL) 5 = Efinaconazole API

Figure 7: Antifungal activity of efinaconazole niosomal nail lacquer

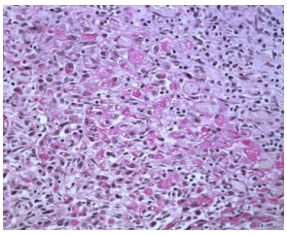
Figure 8: Histopathology PAS staining of the skin sections of before and after treatment with ENNL



The skin appears typical, displaying hair follicles, subcutaneous fat deposits, and a noticeable epidermis.



The presence of periodic acid is the cause. Based on Schiff's assessment, the ENNL-5 formulation effectively eliminated the fungal filaments within four days. Additionally, the hair follicle and shaft began to regenerate, the epidermis mended, and the epidermal cells started to enlarge.



The application of the ENNL-5 formulation resulted in complete regeneration of the hair follicle, shaft, and epidermis, as indicated by the findings of the Periodic Acid Schiff (PAS) test. The fungal hyphae have become invisible.

Non-volatile content

The non-volatile component percentage varied between 10 and 36% across all nine formulations. The formulations containing thioglycolic acid had the lowest number of volatile components. The concentration of volatile compounds was greatest in the formulation using urea.

In-vitro adhesion

The adhesive strength of the nail lacquer was assessed in a laboratory setting utilizing a film peel-off test. Between 2.53 and 8.24% of the nail polish coating might be eliminated. Formulations containing salicylic acid had the poorest film tear-off but the highest adherence, whereas formulations incorporating thioglycolic acid achieved the best combination of both properties.

Hydration enhancement factor

The hydration enhancement factors of the selected keratolytic medicines were established. An effective method for assessing the ability of keratolytic medicines to enter the nail is by the evaluation of their hygroscopic effect factor (HEF). Urea, thioglycolic acid, and salicylic acid are keratolytic agents that cause harm and erosion to the outer layer of the nail plate. The nail pieces immersed in a solution of thioglycolic acid yielded the most precise measurements of hydrogen evolution factor. Thioglycolic acid was more suitable for manicures due to the abundant presence of disulfide linkages in nail keratin. "Among the harmful environmental factors, the nail clippings that underwent a salicylic acid soak exhibited the lowest level. The Characterization of Efinaconazole niosomal nail lacquer shown in Table 5.

Percentage drug content

The analysis results showed that each nail lacquer contained an adequate amount of medicine, with concentrations ranging from 85 to 98%. F5 displayed the greatest proportion of drug material, whereas F1 showed the lowest proportion.

Table 7: Stability study

Time interval (days)	*0*	*30*	*60*	*90*
Gloss	Pass	Pass	Pass	Pass
Blush test	Pass	Pass	Pass	Pass
Smoothness to flow	Pass	Pass	Pass	Pass
Water resistance test	Excellent	Excellent	Excellent	Excellent
Drying time (sec)	67	66	65	65
Drug content uniformity (%)	98.00	98.00	97.76	96.89

Antifungal Activity Niosomal Nail Lacquer

Agar diffusion methods

Following is a Table 6 and Figure 7 that shows how effective efinaconazole niosomal nail lacquer is against fungal infections caused by various types of dermatophytes (ENNL).

Histopathology of the skin of animal post-treatment

The histological assessment of the efficacy of efinaconazole niosomal nail lacquer (ENNL-5) as a treatment was conducted using periodic acid Schiff staining to identify fungal hyphae (PAS)". "The hair follicle, shaft, and epidermis were all undergoing regrowth, as indicated by the PAS results, and there were no fungal hyphae present. However, there were no signs of a fungal infection seen on the AD plates as shown in Figure 8.

Stability study

The stability experiments in Table 7 revealed that EFNL-5 exhibited desirable physical properties, as there were no substantial alterations in drug quality, drug release kinetics, viscosity, or pH seen after a storage period of six months at a temperature of 25 ± 10°C with a relative humidity of 60 ± 5%.

SUMMARY AND CONCLUSION

The primary objective of this study was to develop and evaluate efinaconazole, a medication specifically designed to treat onychomycosis". The nail lacquer underwent testing to evaluate several physical and chemical characteristics, such as its antifungal qualities, adhesion %, drying speed, shine, flow ability, resistance to water, ability to promote hydration, and content and permeability of drugs". All the parameters that were taken into account yielded satisfactory outcomes while remaining within the set limits. After considering all relevant aspects, it was determined that formulation F5 is the optimal choice. By substituting oral medications with efinaconazole nail lacquer, you can effectively alleviate the accompanying symptoms of onychomycosis. An explanation for the shorter treatment duration could be attributed to the exceptional rate at which the nail lacquer is able to penetrate.[28]

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