

<https://doi.org/10.56770/jcp2025914>

EVALUATION OF TRANSDERMAL TARGETED NIOSOMAL DRUG DELIVERY OF TERBINAFINE HYDROCHLORIDE

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Submitted: March 13, 2024; Revised: September 20, 2024; Accepted: October 2, 2024; Published: June 30, 2025

ABSTRACT

Objective: To develop a targeted delivery to the fungal affected cells. The present study focus on developing, optimizing, and evaluating a novel Niosomal loaded nail lacquer formulation for increasing the transdermal permeation of terbinafine HCL. **Method:** Ethanol injection method was used which was followed by the incorporation of dispersion into the HPMC gel. The prepared formulations were evaluated for its vesicle size (by SEM), entrapment efficiency *in vitro* release studies, stability studies and antifungal activities as well. **Results:** Results showed the niosome gel of Terbinafine hydrochloride showed sphericity, vesicle size (20-40 nm), % Entrapment efficiency (70%) and good stability studies at 4±2°C. **Conclusion:** This formulation can be used effectively because it has increased permeability of terbinafine HCL across human nail plate. This in turn raises its therapeutic efficiency. So the formulation can successful be used for the effective treatment of onychomycosis.

Keywords: Niosomes, Transdermal, Terbinafine, Entrapped efficiency

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INTRODUCTION

Superficial fungal infections of skin, hair and nails are getting more frequent with time. Approximately 40 million people in developing and underdeveloped nations suffer from fungal infections. The progression of these infections can be rapid and severe due to their impact on immune function [1].

Topical targeted drug delivery to the site of infection has reduced systemic absorption of medications. However, ensuring the effective localization of drugs remains a critical challenge in treating dermatological issues. Efficient topical drug administration for fungal infections aims to deliver therapeutic agents directly to the target area while minimizing the risk of systemic side effects. Innovative delivery systems not only achieve this objective but also enhance drug efficacy. The landscape of drug delivery technology is becoming increasingly competitive and rapidly evolving, with ongoing developments aimed at optimizing both the efficiency and cost of therapies [2].

Terbinafine hydrochloride belongs to allylamine class of antifungals. They are preferentially used for the treatment of onychomycosis. The oral dosage forms of terbinafine was, previously, used for the treatment of fungal infection. But, there were alot of problems related to oral dosage forms of terbinafine. They cause potential unwanted side effects to the alimentary canal, liver, and also affect the immune system. So, then moved to the topical dosage form of terbinafine. The main intention was to resolve the side effects that occur due to the oral dosage form. But, there were also some problems related to the topical dosage form. The crucial problem was the less penetration rate and absorption of the drug through the stratum corneum.

The novelty of the project lies in manipulating drug formulations to enhance antifungal pharmacokinetics. Strategies include targeted delivery, sustained release, and prolonged retention of high drug concentrations at the infection site [3, 4].

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Materials Used for Terbinafine Hydrochloride Gel

Span 80 (sorbitan monostearate), ethanol, cholesterol, methyl parabens, propyl parabens and HPMC and solvent were of analytical grade were purchased from a local pharmacy and stored according to the package information leaflet.

Solubility of Drug

About 5mg Terbinafine hydrochloride was added to 10 ml of various solvent and sonicated for 10 minutes and inspected visually for solubility and found slightly soluble in water whereas freely soluble in methanol.

Preparation of Terbinafine Hydrochloride Niosomal Gel

The preparation of terbinafine HCL niosomal gel is biphasic process which involves formulation of terbinafine HCL suspension then incorporation into gel leading to formulation of final dosage form which is a gel.

Selection of Materials

Terbinafine hydrochloride was the active pharmaceutical ingredient. Ethanol was used for the formation of lipid phase Span 80 was used as

a surfactant. Hydroxypropyl methyl cellulose as a gelling agent. Cholesterol.

Method in Formation of Niosomes Suspension

Preparation of Lipid Phase

Lipid phase was prepared by adding cholesterol (50 mg) into Ethanol in small quantities and stir it vigorously to dissolve it completely into Ethanol. Then, add span 80 (200 mg) into the Ethanol solution and dissolve it. Then, add active ingredient (Terbinafine Hydrochloride) into the Ethanol solution and dissolve it completely.

Preparation of Aqueous Phase

Took 100 ml of Distilled water in a beaker and placed it in preheated water bath and maintained the temperature to 65 °C.

Dispersion of Organic Phase into Aqueous phase/ Continuous Phase

Organic phase was dispersed into preheated continuous aqueous phase by taking organic phase into 14 gauge needle at a rate of 1ml/min with continuous but, slow stirring. At the end, it was assured that Ethanol was completely evaporated from the medium and a vesicular suspension was prepared.

Table 1: Quantities of the ingredients for niosomes preparations

Sr. No.	Ingredients	Quantities
1	Terbinafine HCl	50 mg
2	Span 80	50 mg
3	Cholesterol	200 mg
4	Ethanol	40 ml
5	HPMC	4% w/w
6	Methyl paraben	0.3 mg
7	Propyl paraben	0.3 mg

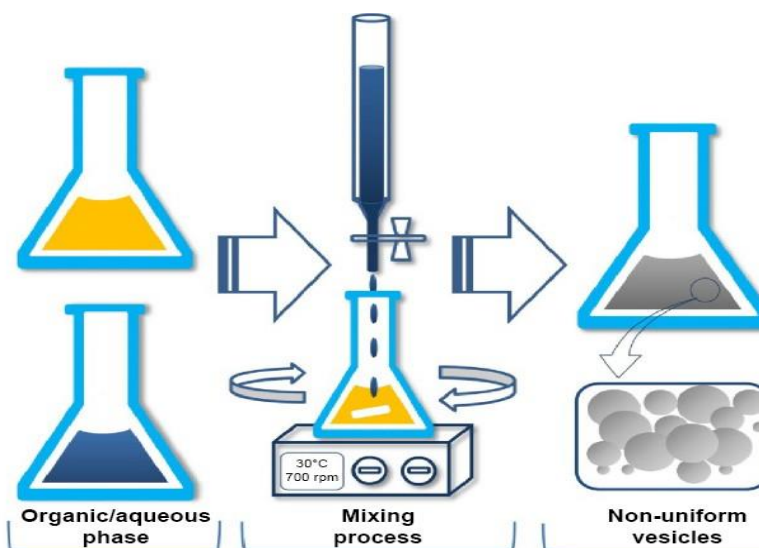


Figure 1: Preparation of niosome dispersion

Preparation of vesicular Gel

Aqueous dispersion of hydroxypropylmethyl cellulose was prepared by adding 4g of HPMC in 100 ml of water and dissolving it properly. Then, add this aqueous dispersion of HPMC in niosomal suspension by gentle shaking to prevent the breaking of vesicles. To it, add 0.3 g methyl paraben and 0.3g of propyl paraben. Finally, the niosomal gel of terbinafine HCl was successfully prepared.

Characterization of Niosomes

Various factors affecting niosomal physical chemistry as drug, amount and type of surfactant, cholesterol content and charge, temperature, microscopic characteristics, vesicle size and zeta potential. Vesicles are characterized by vesicle size, its shape, entrapment efficiency, in-vitro drug release and vesicle surface charge.

% Drug Entrapment Efficiency

It was determined by Entrapment Dialysis method [5]. The quantity of drug adsorbed onto the vesicular membrane, incorporated into the vesicle membrane bilayer, and included in the internal core phase is measured. The efficiency of drug entrapment varies based on the surfactant used in the formulation and the surfactant-to-cholesterol ratio. The percentage of Drug Entrapment Efficiency is calculated as below [6].

$$EE\% = \frac{\text{Entrapped drug}}{\text{Total drug}} \times 100$$

Particle Size Distribution

Dynamic light scattering was conducted using a Zetasizer 300HSA (Malvern Instruments, Malvern, UK). The samples were appropriately diluted, transferred to a cuvette, and placed in a temperature-controlled cell-scattering enclosure. Analysis was performed for 60 seconds at a detection scattering angle of 90°. The Polydispersity Index (PI) was measured to assess the particle size homogeneity of the prepared drug, with a small PI value (< 0.3) indicating a homogeneous vesicle population. The correlation function measurements were analyzed to obtain the diffusion coefficient [7-9].

Zeta Potential Determination (ζ)

Charge on drug loaded vesicles surface was determined using Zetasizer 300HSA (Malvern Instruments, Malvern UK). Analysis time was kept for 60 sec and average zeta potential on the niosomal dispersion was determined [10].

Drug Content Analysis

The amount of drug in the formulation was determined after lysing the niosomes using n-propanol (50%) [11].

Microbiological Studies

The antifungal assay was done using the agar well method. Sabouraud dextrose agar (SDA;

16.25 g) was weighed into a 500 ml conical flask. Purified water (250 ml) was added with some heating to dissolve it completely and allowed to solidify upon cooling. The inoculum was introduced via the streaking method to the solidified SDA at room temperature. Wells were created in a petri dish with the help of a sterile steel borer (internal diameter: 6 mm). The solvent was introduced and measured quantity of standard drug was poured in the well another technique which was used in this practice to make the solution of standard drug in solvent then introduced by the micropipette. The petri dishes were incubated for 48 hours at 37°C. The antifungal activities of the formulations were quantified in terms of the radius of the zone of inhibition.

Scanning Electron Microscope (SEM) For Morphological Studies

Photon correlation spectroscopy (PCS), was employed to determine the particle size and polydispersity of the samples [8]. This technique provides detailed information about the size of vesicles.

Niosomes were sprinkled onto double-sided tape affixed to aluminum stubs. These stubs were then placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips, Netherlands). The samples were analyzed for morphological characterization using a gaseous secondary electron detector, operating at a working pressure of 0.8 torr and an acceleration voltage of 30.00 kV (XL 30, Philips, Netherlands).

RESULTS AND DISCUSSION

They discrete in size and the size ranging from 20-40 nm. The size of the vesicles decreased with the increase in the concentration of surfactant. This is because of the decrease in the surface tension by increasing the concentration of the surfactant.

SEM was conducted at the National Textile University (NTU) Faisalabad to examine the shape and surface characteristics of niosomes. The SEM images revealed that the prepared niosomes were non-agglomerated, exhibited a smooth surface, and did not show uniform spherical formation.

%Entrapment Efficiency was 70% which was determined by centrifugation method which was low because of the use of the span 80 in 1:1 to cholesterol as compared to span 60. As the concentration of the surfactant is increased, the percentage Entrapment Efficiency is also increased which is because of the decrease in surface tension. But the % entrapment Efficiency

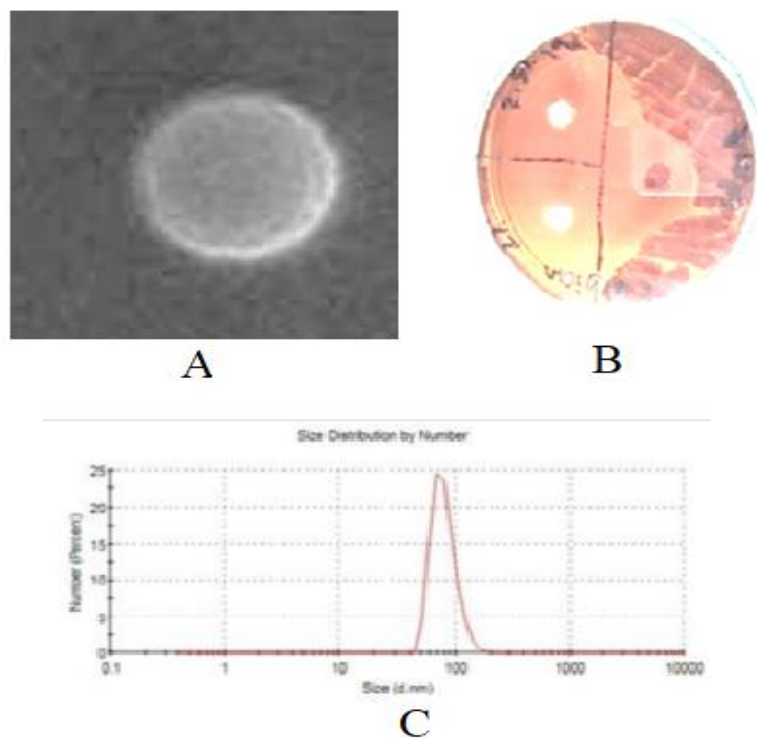


Figure 2: SEM, antifungal assay and size analysis of niosomes

is decreased with the increase in the concentration of the cholesterol. Use of HPMC (4%w/w) as gelling agent and presence of HPMC gave the formulation appropriate gel strength and gelling capacity under physiological conditions. The optimized nanoemulgels containing both APIs showed a greater zone of inhibition than that observed with the marketed cream.

There are certain Limitations of the study that is the niosomes may cause toxicity, in term of that, they may inhibit the proliferation of the human cells. It is mainly due to the presence of the surfactants in the niosomes preparation. The surfactants consist of varying lengths of hydrocarbon and polyoxyethylene chains. In contrast, the type of bond—either an ether or ester bond—linking the alkyl chain to the polyoxyethylene head group significantly impacts cell proliferation. Specifically, the concentration of ether-type surfactants required to inhibit cell proliferation by 50% is ten times lower than that of ester-type surfactants [12].

But in some cases the niosomal encapsulation of the drug may reduce the toxicity of the drug. There is another major obstacle that hinders the utility of the niosomes as targeted drug delivery system i-e Sterilization. Sterilization of lipid-based (niosomes/liposomes) products is a challenging endeavor. HPMC was used to enhance the viscosity of the gel. It has good strength as the Carbapol 940 but the limitation is related to the release rate of the drug from the niosomes that was decreased by the

use of HPMC when it was compared with the studies performed on the terbinafine niosomes where carbapol gel had been used [13].

Span 80 was used in our preparation but it is less soluble than the span 60 and its phase transition temperature is also low while span 60 has high transition temperature (50) which has a larger impact on the niosome preparation. Span 80 also gives low % Entrapment efficiency rather span 60.

CONCLUSION

The incorporation of terbinafine hydrochloride into niosomes for targeted drug delivery is a novel approach. Niosomes containing terbinafine hydrochloride were formulated using Span 80 and evaluated for various parameters. The results indicated that the optimized niosomal formulation achieved an entrapment efficiency of up to 70% and demonstrated sustained release. Additionally, gel formulations containing niosomes loaded with terbinafine hydrochloride exhibited prolonged action compared to the plain placebo gel. Therefore, niosomes represent a promising platform for transdermal drug delivery. This approach has enhanced the penetration rate, facilitating localized drug delivery and improving drug availability at the site of action, which in turn may reduce the required dosage and minimize dose-dependent side effects, such as irritation.

Author(s) Contribution: Conceptualization and supervision, A. Raza; writing-up and editing, M.Naeem.

Funding: Nill

Ethical Approval: NA

Conflict of Interest: There is no conflict of interest.

Consent for Publication: All authors approved the manuscript for publication and agreed to be responsible for all aspects of this article.

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