ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 18, Issue 4, 2025

Online - 2455-3891
Print - 0974-2441

Research Article

PREPARATION AND ASSESSMENT OF NAIL LACQUER INCORPORATING CICLOPIROX OLAMINE-LOADED NIOSOMES

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Received: 01 February 2025, Revised and Accepted: 14 March 2025

ABSTRACT

Objective: The emergence of transungual drug delivery systems represents a significant advancement in treating nail-related conditions, particularly fungal infections like onychomycosis. The current study aims to formulate ciclopirox olamine (CPO)-loaded niosomal nail lacquer for the treatment of onychomycosis.

Methods: CPO niosomes were synthesized using the thin-film hydration method, incorporating different proportions of cholesterol, Span 60, and Tween 40. Niosomes were assessed for their drug content, encapsulation efficiency, particle size, and zeta potential.

Results: Among various formulations of niosomes, the formulation F5 showed adequate drug loading of 94.51%, polydispersity index of 0.171, and zeta potential of −5.10 mV. Following that, the optimized formulation (F5) of the niosomal suspension was used to develop nail lacquer formulation. The optimized nail lacquer formulation (F5) showed the maximum *in vitro* drug release, achieving a rate of 92.22%. The *ex vivo* transungual study of the optimized formulation was conducted using Franz diffusion cell apparatus, resulting in a drug release rate of approximately 90.67%. The zone of inhibition obtained for niosomal nail lacquer formulation was found more than the pure drug solution.

Conclusion: The oral administration of antifungal agents, such as allylamines and azoles, is associated with numerous adverse effects resulting from the requirement for high dosages. These issues can be addressed by formulating such medications as nail lacquer, using significantly lower dosages for treatment, which consequently leads to reduced side effects.

Keywords: Transungual, Niosomes, Onychomycosis, Nail lacquer, Antifungal activity.

 DOI: http://dx.doi.org/10.22159/ajpcr.2025v18i4.53933. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

The significance of nail permeability for topical treatments has been acknowledged over the years, especially with the treatment of onychomycosis. Human nails are highly susceptible to several diseases, including leukonychia, onychatrophy, and onychauxis, as well as infections caused by bacteria, viruses, or fungus. The most common fungal infection affecting the nail and the area beneath the nail bed is onychomycosis [1,2]. Onychomycosis is a fungal illness impacting both fingernails and toenails, affecting around 19% of the worldwide population and accounting for about 50% of all nail problems [3]. Topical treatment is beneficial owing to its non-invasive characteristics, ability to provide drugs directly to the affected area, minimizing systemic adverse effects, and improving patient adherence. The human nail plate safeguards the nail matrix, which is responsible for cellular proliferation and nail development [4,5]. The structure and composition of the nail plate restrict drug penetration through the nails, hence limiting the effectiveness of treatments for nail disorders. The treatment methods for onychomycosis often encompass a range of broad-spectrum antibiotics. Prolonged oral administration of antibiotics is prevalent; however, their efficacy decreases due to the restricted bioavailability of the drugs at the site of action [6,7]. This is a major hurdle in the management of onychomycosis. To reduce the identified problems, doctors may prescribe increased doses or more frequent drug delivery. Therefore, there are several consequences, including drug interactions, a higher possibility of recurrence due to microbial resistance, and increased treatment expenses [8]. Greater potentiation in nail permeation has been shown for nanostructures compared to free drugs. Niosomes have a bilayer vesicle structure, with a hydrophilic core enveloped by one or more hydrophobic lipid bilayers. This distinctive structure allows the incorporation of both oil-soluble chemicals and the encapsulation of water-soluble drugs. Furthermore, surfactants significantly enhance the uptake of substances. They achieve this by adsorbing at interfaces, interacting with biological membranes, and altering the barrier function of the stratum corneum through reversible lipid alteration [9]. Treatment strategies for onychomycosis involve the use of topical and oral formulations. However, oral regimens generally demand extended periods (i.e., months) to be effective due to the need for a high blood drug concentration to reach therapeutic levels in affected nail sites. Therefore, topical treatment is often needed to compensate for oral inefficiency, and systemic exposure to antifungal drugs is reduced by increasing drug exposure to the affected nail region.

Ciclopirox olamine (CPO) is a hydroxypyridone derivative functioning as a broad-spectrum antifungal agent. Its method of action differentiates it from other commercial antifungal agents, such the azoles and allylamines. It shows broad efficacy against dermatophytes, yeasts, filamentous fungi, and bacteria. The biological half-life is 1.7 h, and the bioavailability is below 5% with prolonged use. Therefore, the incorporation of antifungal agents into niosomal nail lacquer delivery systems can extend the period of drug release, leading to an increased half-life and less chance of adverse reactions [10,11].

The primary objective of the present study was to develop a niosomal nail lacquer that would enhance the efficacy and permeability by combining hydrophobic polymers with surfactants and a permeation enhancer. The investigation studied the impact of various enhancers on the penetration of drugs through the nail. In addition, the drug's solvency was enhanced using methanol as a solvent.

MATERIALS

CPO was purchased from Yarrow Chem. Pvt. Ltd., Mumbai; Cholesterol was purchased from Sisco Research Laboratories Pvt. Ltd; Tween 40, Span 60, methanol, and chloroform were purchased from Central Drug House Ltd., New Delhi.

METHODS

Pre-formulation studies

The initial phase of the rational development of drug substance dosage forms is a preformulation study. It can be defined as a study of the physical and chemical properties of drugs alone and in combination with excipients. The primary goal of preformulation study is to produce data that are beneficial to the formulator in the development of bioavailable and stable dosage forms.

Organoleptic characteristics

The organoleptic studies, which included visual observations of the general appearance of the drug, such as its nature, color, and odor, were conducted in comparison to the drug standard provided in the pharmacopeia to identify the drug [12].

Melting point

For determination of melting point, USP method was followed. A small quantity of the drug was filled into a sealed capillary tube. The tube was placed in the MPA 100 melting point apparatus. The temperature within the device was progressively raised, and the temperature at which the drug began to melt was seen and recorded. In addition, the temperature at which the drug completely melted was also recorded [12].

Fourier transform infrared (FTIR) spectroscopy

Drug and drug-excipient compatibility was determined by using FTIR spectroscopy (Model Name: FT/IR-4100 type-A). The FTIR analysis was conducted by scanning the region of 4000–650 cm^{-1} to identify the characteristic peak [13].

Solubility analysis

The drug's solubility was determined using a magnetic stirrer. An extra quantity of the drug was added into a beaker containing solvent to create a saturated solution. The saturated solution was prepared by stirring for 24 h using a magnetic stirrer. The solutions were then filtered and diluted, if necessary, and then analyzed using an ultraviolet-visible (UV-visible) spectrophotometer (UV-1900i Shimadzu) at 220 nm [14].

X-ray diffraction (XRD)

The XRD patterns of the drug and the formulation loaded with the drug were obtained using X-ray diffractometer (EXPERT-PRO). The samples were examined using Cu Kα radiation at a voltage of 40 kv and a current of 40 mA, within the 5–30° range on the 2θ scale [15].

Method of preparation of CPO-loaded niosomes

CPO niosomes were developed using thin film hydration technique, using a lipid mixture consisting of drug, span 60 as a non-ionic surfactant, cholesterol, and Tween 40 in various specified ratios, as detailed in Table 1. Span 60, cholesterol, Tween 40, and CPO were solubilized in a solvent mixture containing 5 ml of chloroform and 5 ml of methanol. A rotary evaporator refer to Fig. 1 (Superfit Model no. PBU6D) was used to reduce the solvent volume by progressively lowering the pressure while maintaining temperatures between 55 and 65°C, until a thin layer of lipids was formed. A phosphate buffer with a pH of 7.4 was used to hydrate the prepared film. The round-bottom flask was subjected to continuous rotation in the rotary evaporator at a temperature maintained between 55 and 65°C for a duration of 60 min to ensure adequate hydration. Upon introducing the hydrated niosomes into a beaker, gradually agitate the mixture for a duration of 15 min using a magnetic stirrer set to a low speed. After that, subject the mixture to sonication with a probe for 2 min and transfer the formulation into a Falcon tube for centrifugation at its maximum speed [16,17].

Formulation of nail lacquer containing CPO loaded niosomes

The combination of ingredients mentioned was used to prepare nail lacquer containing niosomes loaded with CPO. Nitrocellulose was initially dispersed in 75% of the combination of solvents (ethyl acetate + butyl acetate + toluene) to form an opaque solution. After that, diphenyl phthalate, a plasticizer, was added into the combination of solvents and stirred continuously for a duration of 30 min at a speed of 100 revolutions/min using a magnetic stirrer. Finally, a concentration of 1% w/w of niosomes, loaded with the drug CPO, has been incorporated into the prepared nail lacquer [18,19].

Evaluation of CPO-loaded niosomes

Entrapment efficiency

Precisely measured niosomes, equivalent to 10 mg of the drug compound, were solubilized in 50 mL of methanol. Subsequently, the solution was subjected to filtration using Whatman filter paper, and the drug content was assessed using a UV-visible spectrophotometer at a wavelength of 220 nm. The percentage entrapment efficacy was calculated using the following formula [20].

$$\%Entrapment\ Efficiency = \frac{Weight\ of\ drug\ in niosomes}{Total weight\ of\ drug taken} \times 100$$

Drug content

The drug concentration within the formulated niosomes was determined by dissolving a accurately weighed amount, equivalent to 10 mg of the drug, in a 100 ml volumetric flask. Furthermore, the volume was calibrated to 100 ml using methanol. The content was subjected to filtration using Whatman filter paper No. 41. A 25 mL volumetric flask was initially filled with 5 mL of the solution mentioned above, and the remaining volume was subsequently filled with methanol until the flask reached its designated capacity. The concentration of the substance was quantified at a wavelength of 220 nm using the Shimadzu UV/visible spectrophotometer [21].

Particle size, polydispersity index (PDI), and zeta potential

The PDI of drug-loaded niosomes was assessed using the particle Zetasizer analyzer (Brookhaven 90 Plus, manufactured in the United States). The surface charge of the particles was quantified using the electrophoretic light scattering technique. The PDI was automatically

Table 1: Formulation table of ciclopirox olamine-loaded niosomes

Batch	Drug (mg)	Cholesterol (ml)	Span 60 (ml)	Tween40 (ml)	Methanol (ml)	Chloroform (ml)
F1	100	2ml	4 ml	2 ml	5 ml	5 ml
F2	100	2 ml	4 ml	-	5 ml	5 ml
F3	100	2 ml	3 ml	1 ml	5 ml	5 ml
F4	100	2 ml	2 ml	2 ml	5 ml	5 ml
F5	100	3 ml	4 ml	2 ml	5 ml	5 ml
F6	100	3 ml	4 ml	-	5 ml	5 ml
F7	100	3 ml	3 ml	1 ml	5 ml	5 ml
F8	100	1 ml	4 ml	2 ml	5 ml	5 ml
F9	100	1 ml	4 ml	-	5 ml	5 ml
F10	100	1 ml	3 ml	1 ml	5 ml	5 ml

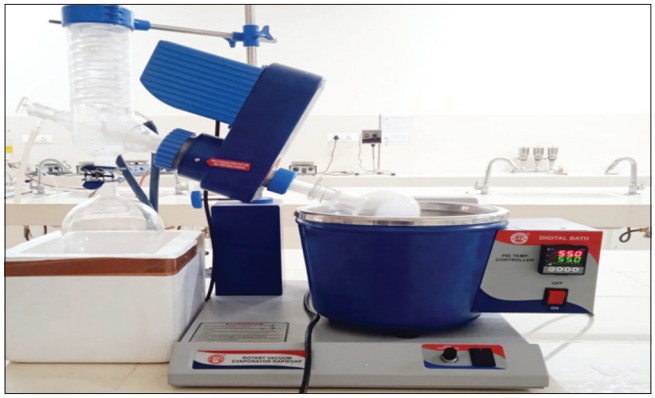

Fig. 1: Niosomes by thin film hydration method using Rotary evaporator

generated by the internal Zetasizer software for the entire spectrum of particles examined. Each experiment was conducted in triplicate. The importance of zeta potential depends upon its ability to correlate with the stability of colloidal dispersions. Zeta potential quantifies the degree of repulsion between neighboring particles possessing an identical charge within a dispersion [12].

Evaluation of CPO-loaded niosomal nail lacquer

Physical appearance, viscosity, and pH

The formulations went through visual inspection to assess their appearance in contrast to a black-and-white background. The pH of the nail lacquer was assessed using a pH meter that had been calibrated with a standard buffer before the beginning of the study. The viscosity of the nail lacquer was assessed at a temperature of 25°C using a viscometer and a spindle at different rotational speeds (rpm) [19].

Spreadability

The spreadability of the niosomal nail lacquer containing the drug was assessed using a wooden block apparatus. This apparatus includes a stationary glass slide measuring 7.5 cm in length at one end and a movable glass slide at the opposite end. The movable glass slide was attached to a weight pan that traversed along a horizontally oriented pulley system in combination with the stationary glass slide. To carry out the experiment, 1 gm of niosomal nail lacquer was installed between two glass slides. Following that, a weight of 1 kg was placed at the top of the slides for a duration of 5 min. Afterward, an additional weight of 60 gm was placed to a pan, and the two glass slides were precisely separated. The duration required to separate the glass slides was measured in seconds and duly recorded [22].

***In vitro* studies**

The *in vitro* drug release of drug-loaded niosomal nail lacquer was conducted using a Franz diffusion cell. An equivalent of 1 gram of niosomal nail lacquer was introduced into the donor compartment, while the receptor compartment was filled with phosphate buffer at a pH of 7.2, serving as the receptor medium. The dialysis membrane, possessing a molecular weight of 12,000–14,000 Da (Hi-Media, India), was first subjected to a thorough cleansing with flowing water for a duration of 10 min. Subsequently, it was immersed in a releasing medium consisting of 0.1 N hydrochloric acid for a period of 24 h. The donor and receptor compartments were separated by an active dialysis membrane. The medium in the receptor compartment was agitated using a magnetic stirrer at a speed of 50 rpm while maintaining a temperature of 37±0.5°C. Approximately 5 mL of the sample was extracted from the receiver solution at specified time intervals, and the diffusion cell was subsequently replaced with fresh buffer solution to achieve the desired volumes. The obtained solution was subjected to analysis to determine the percentage of drug release [23].

***Ex vivo* transungual studies**

Goat hooves were used to conduct permeation studies. The goat's hooves were collected from the slaughterhouse. The nail was softened by immersion in a phosphate buffer solution at a pH of 7.4 while preserving standard humidity conditions. After washing with phosphate buffer solution, the nails were dried. Franz's diffusion cell was used to experimentally assess permeability after the incision of a membrane with an outer layer of roughly 1 mm. The cell membrane was attached to the recipient compartment, while the receiver chamber contained 20 ml of phosphate buffer solution at pH 7.4. The test specimen was thereafter positioned over the barrier, and the apparatus was stirred to ensure a stable temperature of 37°C±1°C. A limited quantity of the sample was obtained at specified intervals of 1, 2, 3, up to 24 h [8,24].

Zone of Inhibition (Antifungal Activity)

The *in vitro* zone of inhibition was determined using the agar cup plate technique with *Candida albicans*. Agar plates containing Sabouraud's dextrose agar were made and sterilized applying autoclaving. 20 ml of sterilized agar were introduced into sterile glass Petri dishes, followed by the addition of a diluted antifungal culture. Subsequently, the Sabouraud dextrose agar was permitted to settle on its glass plates. Each plate exhibited a pair of 5 mm reserves, carefully formed with a suitable cork borer. With the addition of 0.2 ml of solution to each plate, the plates were let to diffuse. The plates were then incubated at 30°C for 48 h [25].

RESULT AND DISCUSSION

Pre-formulation studies

Organoleptic characteristics

The investigation of organoleptic characteristics was performed by visual observation using sensory perception. The drug is colorless to light yellow, odorless, and has an unpleasant taste. The organoleptic characteristics of the test drug correlate with the reported description.

Melting point

The study of melting point was performed using digital melting point apparatus. The experimental results indicate that the measured average melting point of the test drug was 145°C, which corresponds with the standard value reported. This may serve as a preliminary identification tool for drug.

Fourier transform infrared (FTIR) spectroscopy

The FTIR spectrum of the test substance was obtained using FTIR instrument. The FTIR spectrum obtained for the drug and the physical composition of the drug excipients, as illustrated in Fig. 2, reveals the presence of various functional groups. Upon comparison with the standard spectra, no significant differences were noted. Therefore, it was confirmed that the sample obtained is CPO. The FTIR spectrum of CPO exhibited distinctive peaks corresponding to the functional groups O-H, C=O, N-H, and C-O, which were observed at the respective wavenumbers of 1636.78, 1764.67, 3228.61, and 1063.62 cm^{-1}. The FTIR spectrum of the physical mixture of the drug and polymer confirmed no sign of interaction between the two substances.

Solubility analysis

CPO was found to be soluble in alcohol and in methylene chloride, sparingly soluble in water, slightly soluble in ethyl acetate, and practically insoluble in cyclohexane.

X-ray diffraction scan (XRD)

In XRD analysis, the results indicate that the drug in its pure form is crystalline. When the drug is converted into a formulation, the XRD graph shows a transformation to an amorphous form as shown in (Fig. 3). This change is significant because amorphous forms generally have higher solubility and bioavailability as compared to their crystalline form.

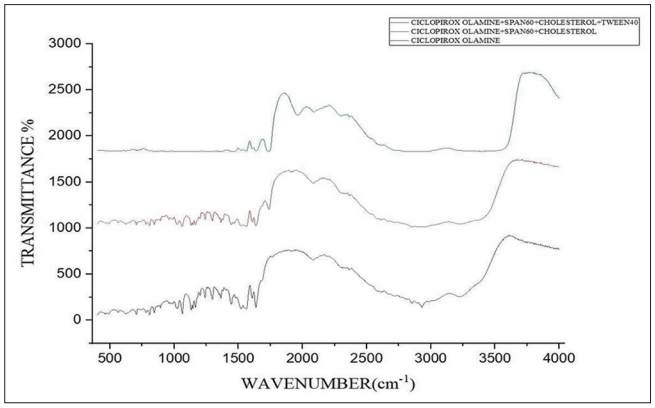

Fig. 2: FTIR scan of ciclopirox olamine (drug) and physical mixtures

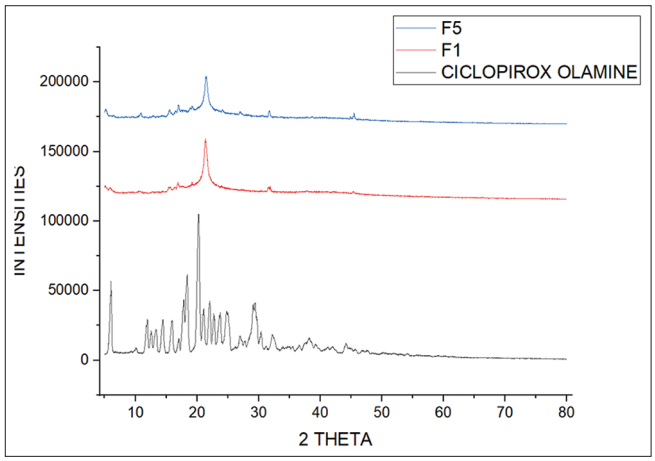

Fig. 3: XRD image of ciclopirox olamine (drug), formulation F1, and F5

EVALUATION OF CPO LOADED NIOSOMES

Drug content

The drug content of the developed formulations is shown in Table 2; the estimate of drug content was conducted by measuring absorbance using a UV spectrophotometer. The drug concentration in all formulations ranged from 58.92% to 94.51%. Experimental findings indicated that the quantities of surfactant and co-surfactant in formulations influence drug loading in niosomes. As the concentration of surfactant/cosurfactant in the formulation increases, the drug loading also increases significantly.

Entrapment efficiency

The entrapment efficiency of all formulations was assessed, and the findings are shown in Table 2. The entrapment efficiency varied from 50.94% to 90.19%. The ratio of surfactant and cholesterol improves the drug entrapment efficiency of niosomes.

Polydispersity index (PDI), and zeta potential

The PDI of the prepared formulation F5 is shown in Fig. 4. Studies indicate that a PDI score below 0.5 indicates monodispersity; hence, the formulation was found to be monodisperse. This may result from the extensive size distribution of the particles. The electric charge of the formulated product was assessed by measuring the zeta potential. The zeta potential of the formed niosomes was measured at −5.10 mV, as seen in Fig. 5.

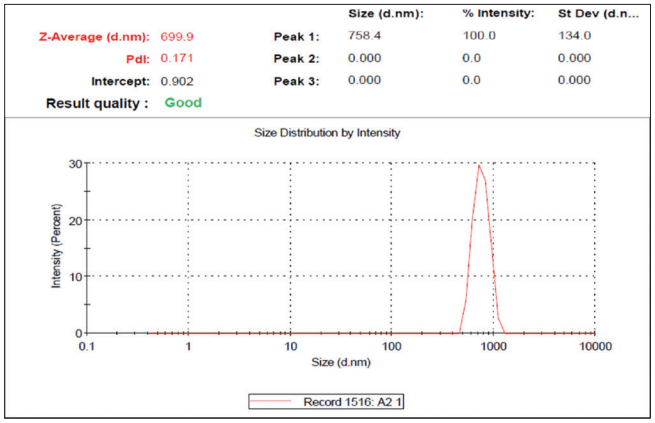

Fig. 4: PDI of formulation (F5)

Table 2: Drug content and entrapment efficiency of all formulations

Batch	Drug Content (%)	Entrapment Efficiency (%)
F1	89.54±0.23	88.62±0.21
F2	73.70±0.11	78.21±0.29
F3	79.84±0.17	77.05±0.37
F4	62.75±0.18	57.44±0.44
F5	94.51±0.35	90.19±0.35
F6	82.35±0.28	74.05±0.53
F7	64.76±0.44	79.56±0.47
F8	63.84±0.52	52.69±0.58
F9	58.92±0.38	50.94±0.21
F10	77.43±0.43	80.94±0.32

Number of experiments (n) =3

Table 3: Spreadability, pH, viscosity, and physical appearance

Batch	Spreadability (g/cm/sec)	pH	Viscosity (cps)	Physical appearance
F1	21.56±0.38	6.6±0.67	8214±0.54	Milky white
F2	19.36±0.43	6.3±0.43	8240±0.68	Milky white
F3	24.25±0.23	6.6±0.42	8239±0.33	Milky white
F4	25.94±0.27	6.6±0.86	8225±0.93	Milky white
F5	28.45±0.54	6.7±0.58	8201±0.47	Milky white
F6	27.52±0.13	6.8±0.64	8248±0.58	Milky white
F7	21.38±0.45	6.6±0.34	8251±0.62	Milky white
F8	25.12±0.65	6.7±0.23	8210±0.31	Milky white
F9	24.49±0.68	6.6±0.18	8222±0.41	Milky white
F10	24.88±0.74	6.8±0.32	8253±0.54	Milky white

Number of experiments (n) =5

Evaluation of CPO-loaded niosomal nail lacquer

Spreadability

The spreadability of all nail lacquer formulas ranged from 19.36 to 28.45 g/cm/sec, as seen in Table 3. The findings demonstrated excellent spreadability of the nail lacquer post-application.

pH

The pH of all formulations ranged from 6.3 to 6.8, as shown in Table 3, which matches with the standard pH criteria. Consequently, it is not going to cause any irritation post-application.

Physical appearance, viscosity

The prepared formulation had a milky white appearance. The viscosity of the developed formulations was assessed using a Brookfield

Table 4: *In vitro* drug release of all formulations

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	4.34±0.34	8.52±0.49	7.34±0.32	7.63±0.38	6.24±0.22	8.28±0.31	7.23±0.22	7.26±0.34	9.28±0.35	7.82±0.21
2	11.10±0.42	16.62±0.12	15.23±0.16	12.45±0.32	13.34±0.31	15.95±0.28	12.93±0.27	15.25±0.37	16.52±0.32	15.76±0.22
3	18.24±0.33	22.38±0.32	24.62±0.21	19.42±0.21	20.73±0.35	26.42±0.26	21.64±0.34	24.66±0.29	22.73±0.28	27.46±0.34
4	35.31±0.12	37.56±0.25	36.20±0.22	28.22±0.22	36.42±0.39	35.74±0.32	32.32±0.33	33.64±0.22	29.57±0.26	34.22±0.39
5	44.74±0.53	42.64±0.35	44.61±0.27	39.87±0.19	44.38±0.24	42.79±0.33	37.46±0.21	47.18±0.19	40.68±0.24	47.49±0.29
6	56.60±0.32	53.56±0.42	52.23±0.17	48.26±0.18	57.34±0.19	50.23±0.28	40.15±0.18	52.90±0.34	53.48±0.18	55.43±0.27
8	67.87±0.55	62.14±0.22	63.50±0.21	54.56±0.26	69.43±0.26	59.58±0.27	51.32±0.13	60.38±0.31	62.22±0.13	63.27±0.21
12	76.48±0.61	68.24±0.29	74.28±0.17	61.32±0.23	78.24±0.43	67.41±0.32	59.57±0.32	68.53±0.29	69.89±0.17	71.38±0.22
16	80.04±0.38	73.72±0.19	79.44±0.29	68.93±0.29	83.64±0.29	77.46±0.34	67.44±0.30	75.49±0.24	74.29±0.21	78.33±0.28
24	88.67±0.44	77.60±0.32	85.43±0.31	76.82±0.21	92.22±0.33	84.24±0.31	78.64±0.36	84.52±0.22	85.20±0.22	84.72±0.31

Number of experiments (n) =2

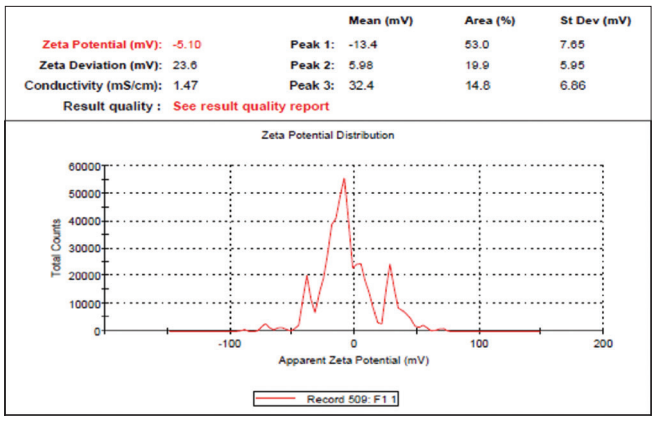

Fig. 5: Zeta potential graph of formulation F5

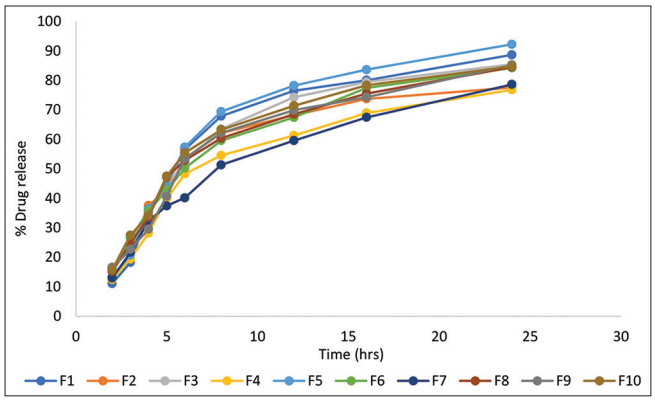

Fig. 6: *In vitro* release of niosomal nail lacquer

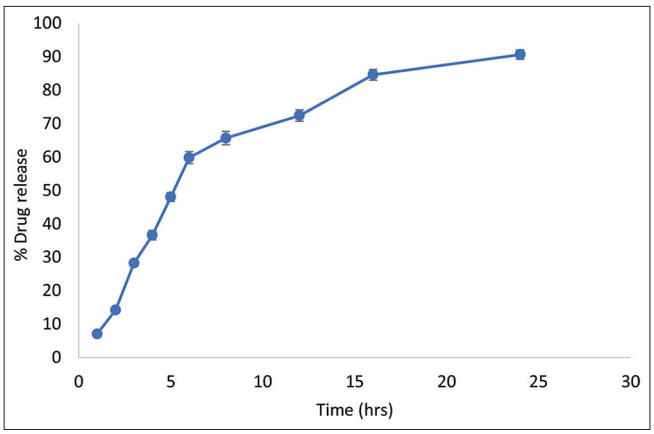

Fig. 7: *Ex vivo* transungual permeation study of formulation F5

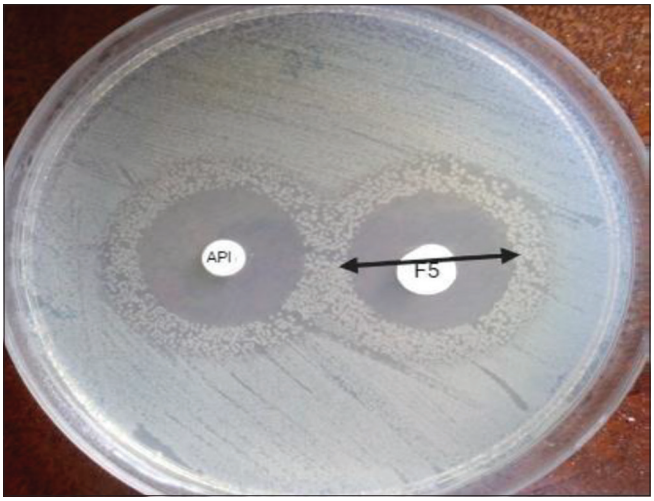

Fig. 8: Zone of inhibition (antifungal activity) of ciclopirox olamine (API) and formulation (F5)

viscometer, with values ranging from 8201 to 8253 cps, as shown in Table 3.

In vitro studies

The *in vitro* release of CPO from the formulated niosomal nail lacquer was conducted in phosphate buffer at pH 7.4 for 24 h. All formulations showed an effective rate of drug release. Formulation F5 exhibits the highest drug release of 92.22%, whereas formulation F2 demonstrates the lowest drug release of 77.60%. It was found that an increased concentration of surfactant and cholesterol in the formulation may enhance drug penetration. *In vitro*, drug release profiles are given in Table 4 and Fig. 6.

Ex vivo transungual studies

The *ex vivo* transungual study of the optimized formulation was conducted using Franz's diffusion cell apparatus, resulting in a drug permeation release of around 90.67%. The *ex vivo* permeation study indicated that the optimized formulation is most suitable for transungual administration, hence effectively reaching its target location. The drug permeation profile from the optimized formulation is shown in Table 5, and the corresponding graph is illustrated in Fig. 7.

Zone of inhibition (antifungal activity)

The zone of inhibition (antifungal activity) of niosomal nail lacquer is compared with the pure drug solution of CPO. The zone of inhibition obtained for niosomal nail lacquer formulation was found to be (18 mm) more than the pure drug solution (16 mm), and it was concluded that it has sufficient antifungal activity as shown in Fig. 8.

Table 5: *Ex vivo* transungual studies of formulation F5

Time (h)	Formulation (F5)
1	7.04±0.1
2	14.18±0.5
3	28.24±1.1
4	36.62±1.4
5	48.05±1.3
6	59.83±1.8
8	65.66±2.1
12	72.42±1.7
16	84.63±1.6
24	90.67±1.4

Number of experiments (n) =2

CONCLUSION

Medicated nail lacquer formulation showed efficient penetration through the nail plate. The evaluated combination of a lipid formulation consisting of drug, span 60 as a non-ionic surfactant, cholesterol, and Tween 40 used to prepare formulation F5 shows diverse mechanisms for enhancing permeation and penetration into the nail plate, thereby enhancing its antifungal efficacy, which correlates with a drug release rate of 92.22% at 24 h through a cellophane membrane and 90.67% through goat's hooves membrane. The formulated nail lacquer (F5) exhibits a rapid drying rate, will not be easily removed from the nails, compared to traditional antifungal creams or moisturizers. Therefore, this approach eliminates the need for the repeated application of drugs to the nail. Given that the formulated nail lacquer is transparent, it is suitable for all genders. The oral administration of antifungal agents, such as allylamines and azoles, is associated with numerous adverse effects resulting from the requirement for high dosages. These issues can be addressed by formulating such medications as nail lacquer, using significantly lower dosages for treatment, which consequently leads to reduced side effects.

ACKNOWLEDGMENT

The authors expressed their gratitude to Mr. Jitender Joshi, President, Prof. (Dr.) Dharam Buddhi, Vice Chancellor of Uttaranchal University Dehradun, and Prof. (Dr.) Vikash Jakhmola, Director, Uttaranchal Institute of Pharmaceutical Sciences, for their encouragement and guidance in publishing this review work.

FUNDING

None

CONFLICT OF INTEREST

None

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