IJPSR (2025), Volume 16, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 November 2024; received in revised form, 19 November 2024; accepted, 21 November 2024; published 01 April 2025

DEVELOPMENT AND EVALUATION OF TEA TREE OIL INFUSED ANTIFUNGAL NAIL LACQUER: A PROMISING ALTERNATIVE FOR TREATING ONYCHOMYCOSIS

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Keywords:

Onychomycosis, Nail Lacquer, Tea tree oil, Transungual permeation

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ABSTRACT: Onychomycosis is a fungal infection of fingernails and toenails which accounts for majority of all nail disorders caused by Dermatophytes, Candida and Nondermatophytic Molds. Numerous Antifungal formulations are available in the market in the form of cream, ointment, lotion, powder, and solutions which require high concentration of active agents to be incorporated and have short residence time on the nail bed leading to inadequate penetration and lower efficacy. In the current study an effort is given to develop a superior alternative dosage form using essential oil as an antifungal agent. A medicated antifungal nail lacquer containing Tea Tree oil was developed using different penetration enhancers followed by evaluation of critical quality attributes. The formulation containing both Thioglycolic acid and salicylic acid at the concentration of 15% w/v exhibited favorable characteristics including non-volatile content, drug release, drug content, antimicrobial efficacy and permeability. The formulation containing both thioglycolic acid and salicylic acid exhibited prolonged release for around 12 hours with good permeability. Moreover, the nail lacquer forms a stable film immediately after application which ensures proper residence time for the drug at site. The developed tea tree oil based antifungal nail lacquer containing a combination of both salicylic acid and thioglycolic acid can be considered as a promising alternative to available marketed formulations owing to its superior penetrability and enhanced antifungal activity.

INTRODUCTION: Development of transungual drug delivery systems intended for administration through the nail bed has become the most challenging task to the pharmaceutical researchers because of the architecture and composition of the nail plate which severely limits the penetration of topically applied drugs [1]. Additionally, reduction of blood supply and the physical or chemical features of the nail bed further restricts the penetration of the topically applied drug via the nail bed [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(4).1087-92

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(4).1087-92

On the other hand, oral therapies are accompanied by severe systemic side effects and notable drug interactions [3]. Hence, the effective therapeutic concentration is not achieved and as a consequence the accurate treatment of variety of diseases associated with the nail bed including onychomycosis (OM), a fungal infection of fingernails and toenails which accounts for approximately 50% of all nail disorders serves as a potential challenge to the formulation development scientists [4].

The major causative pathogens for OM in tropical and subtropical countries includes Dermatophytes, Candida and Non-Dermatophyticmolds. In recent times much efforts have been devoted in the development of transungual delivery systems which have paved way for the formulation of

antifungal nail lacquers which can deliver drugs Exhibiting poor oral bioavailability [5]. Conventionally used topical formulations including creams, lotions and powders are not suitable for transungual delivery owing to their ready removability and limited permeability *via* the nail bed [6].

Research works in the field of drug delivery *via* the nail plate have led to the development of antifungal nail lacquers which serves as a drug depot upon application to the nail surface permitting sustained drug diffusion across the nail leading to continuous penetration of the active drug moiety [7]. In addition, effective therapeutic concentration in the nail bed is achieved which is the primary requirement for the proper treatment of OM. Thus, Medicated nail lacquers can be an effective strategy for achieving maximal transungual antifungal efficacy.

Tea Tree Oil (TTO), an essential oil obtained from the leaves of *Melaleuca alternifolia* (Myrtaceae) Is proven to be a natural alternative for the traditional antifungal drugs due to its antifungal and anti-inflammatory properties, reduced side effects and better penetration abilities [8]. TTO contains terprenoids or isoprenoids (terpinen-4-ol), which are extensively utilized for their potential antifungal activity and thus can be a suitable alternative for synthetic antifungal compounds owing to its nontoxic nature [9].

Recent research works supports the broad spectrum antimicrobial activity of TTO against multiple dermatophytes affecting the nail plate and its enhanced usage in comparison to conventional medications owing to its better penetrability [10]. Existing marketed formulations of medicated nail lacquers include Penlac® Nail Lacquer (ciclopirox) Topical Solution, 8% which comes with the inherent disadvantage of enhanced side effects as well as local reactions such as pruritus and burning sensations [11]. Thus, the objective of the present work focuses on developing a topical antifungal nail lacquer containing Tea Tree Oil (TTO) for the treatment of OM, aiming to enhance clinical effectiveness and improve patient compliance [12].

MATERIALS AND METHODS:

Materials: All the required chemicals and reagents involved in the research were obtained commercially and were used as received. TTO was obtained from Yarrow Chemicals (Mumbai, India). The different Keratolyctic agents including Salicylic acid, Thioglycolic acid and Urea (99% extra pure) were purchased commercially from Himedia Labortaries. Pvt. Ltd (Mumbai, India). Hydroxy Propyl Methyl Cellulose (HPMC K15 m), Menthol, Propylene glycol (PEG 400) and Ethanol (99.9% purity) were obtained from SD-Fine Chem Ltd (Mumbai, India).

Preparation of Nail Lacquer: Nail lacquers containing Tea Tree oil were prepared by a simple mixing process. Initially, the film forming agent HPMC K 15 m was dissolved in ethanol and TTO was added gradually under continuous stirring [13]. To the above mixture, PEG and keratolytic agents including Salicylic acid/Thioglycolic acid and/Urea were added one by one under stirring and the stirring was continued for another 30 min until clear solution was obtained [14]. Menthol was included in the preparation containing thioglycolic acid to mask any unpleasant odor. A total of six different compositions were prepared and stored in glass bottles with screw caps which were fitted with brushes for further evaluation and stored at room temperature. The composition of the prepared nail lacquers is shown in **Table 1**.

TABLE 1: FORMULATION OF NAIL LACQUER

Sr. no.	Formulations	F1	F2	F3	F4	F5	F6
	Material name	Quantity					
1	Tea Tree Oil	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
2	HPMC K15M	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg
3	Salicylic Acid	-	5 mg	10 mg	15 mg	20 mg	15 mg
4	Thioglycolic acid	-	-	-	5 mg	10 mg	15 mg
5	Menthol	-	-	-	5 mg	10 mg	15 mg
6	Urea (99% extra pure)	-	-	-	-	5 mg	-
7	Propylene Glycol 400	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
8	Ethanol	qs	qs	qs	qs	qs	qs
Total		100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

Evaluation of Prepared Nail Lacquers:

Determination of Smoothness to Flow: 1 ml sample of the developed nail lacquer was poured on a glass slide on an area of approximately 1.5 square inches and the sample was made to spread within that area by tilting the glass slide. Smoothness of flow was observed visually and was scored as follows: poor, satisfactory and excellent [15].

Determination of Gloss: The developed nail lacquer (equivalent to 1 ml) was applied on fingernail. After drying the gloss was visually observed and was scored as: poor, satisfactory and excellent.

Determination of Non-volatile Content: Approximately 10 ml of the prepared sample was applied on a previously cleaned petridish and the weight was noted as W1. The petridish was placed in a hot air oven and was kept at 105 ± 2 °C temperature for a duration of 1 hour. The Petridish was removed after one hour and allowed to cool down. The weight of petridish after drying was measured and the same was noted as W2. The difference in the weight was calculated and the non-volatile content was expressed in percentage.

Determination of Drying Time: A thin film of the sample (1 ml) of the Nail lacquer was applied on a petridish with the help of a brush and the time taken for the formed film to dry completely was noted down using a stopwatch. The uniform and complete drying of the applied film was confirmed by pressing the same with a finger, until no mark remains on surface [16].

Determination of Water Resistance: A thin film of the developed nail lacquer (1 ml) was spread evenly on a clean glass plate and dried at 25 ± 2 °C temperature in a hot air oven for 1 hour. The glass plate was weighed and immersed in water bath maintained at 37 °C temperature. The glass plate was removed after 24 hours, wiped properly with tissue paper and reweighed. Difference in the weights were calculated for determination of water resistance [17].

Drug content Estimation: 1 ml of developed Nail Lacquer was dissolved in 50 ml phosphate buffer solution (PBS) of pH 7.4 and the resulting solution was ultra-sonicated for 15 min. The sonicated solution was filtered with Whatman filter paper, and the volume was made up to 100 ml with PBS pH 7.4. The diluted solution was measured for absorbance spectrophotometrically at 265 nm and estimated for drug content.

***In-vitro* Transungual Permeation Studies:** *In-vitro* drug permeation study of the developed nail lacquers was conducted in Franz diffusion cell using goat hoof membrane. Hooves of freshly slaughtered goat were collected, and the membrane of 1 mm thickness was separated from the hooves. The separated membrane was soaked in water for 24 hrs prior to permeation studies. The membrane was placed carefully between donor and receptor compartment of the diffusion cell and 1 ml of nail lacquer was applied on the hoof membrane. The receptor compartment was filled with phosphate buffer pH 7.4 and ethanol in the ratio of 4:1. The whole assembly was set up on magnetic stirrer with thermostat maintained at 37±2 °C temperature. 5 ml aliquot of samples were withdrawn from sampling port at regular intervals (every 30 minutes) and were analyzed spectrophotometrically at 265 nm. Sink conditions were maintained during the entire permeation study by replacing equal amount of fresh media.

***In-vitro* Antifungal Activity Study:** *In-vitro* antifungal activity against *Candida albicans* was determined using Agar cup-plate method [18]. Nutrient agar plates were prepared and sterilized by autoclaving at 120 ºC temperature and 15 pounds' pressure for 15 min. The developed Nutrient agar media was then inoculated with fungal strains of *C. albicans*. The mixture was poured in sterilized petridishes containing previously prepared wells of 5 mm diameters. 0.2 ml sample from each of formulations were transferred to the cups aseptically and the prepared petridishes were maintained at room temperature for 2 h to allow the diffusion of the solutions into the medium. The petridishes were then incubated at 28 °C for 48 hrs. Finally, the diameter of zone of inhibition surrounding each of the well was measured visually using scale and recorded.

RESULTS:

Smoothness to flow: Uniform film was formed for all the nail lacquers prepared. Smoothness to flow was measured by visual inspection and was scored as: poor, satisfactory and excellent. The

smoothness of all the developed formulations was found to be satisfactory and the results are summarized in **Table 2**. However, excellent smoothness to flow was observed in the case of Formulation F6.

Determination of Gloss: The glossiness of the prepared nail lacquers was measured by visual inspection and was scored as: poor, satisfactory and excellent and the results are given in **Table 2.** The prepared nail lacquers specially formulation F6 exhibited excellent glossiness.

TABLE 2: PHYSICAL APPEARANCE OF TTO NAIL LACQUER

Formulation Code	Smoothness to flow	Gloss
F1	Satisfactory	Satisfactory
F2	Satisfactory	Satisfactory
F3	Satisfactory	Satisfactory
F4	Satisfactory	Satisfactory
F5	Satisfactory	Satisfactory
F6	Excellent	Excellent

Non-volatile Content: The Indian standards prescribe a minimum limit of 20% by mass for non-volatile content in case of an ideal nail lacquer which ensures the formation of a stable film which can offer maximum adherence as well as protection to the nails [19]. Non-volatile content for all the formulations were found to be in range of 25 to 36% and the results are summarized in **Table 3.**

Drying Time: Drying time of all the nail lacquers were found to be in the range from 60 to 80 sec and the drying time data of all the formulations summarized in **Table 3** indicated that optimum drying time of nail lacquer lied within the range of 1-2 min.

Determination of Water Resistance: The developed nail lacquers were subjected to water resistance test. The amount of water absorbed by the nail lacquer after keeping in water for 24 hours was found to be negligible. The results are of water resistance test for all the formulations are given in **Table 3**.

Drug content Estimation: Drug content for all the nail lacquers were found to be satisfactory and the values were found to be in the range 90 to 95%. The highest % of drug content was found to be 95.63% and the lowest % of drug content was found to be 90.65%. The results are summarized in **Table 3**.

TABLE 3: CHARACTERIZATION PARAMETERS OF TTO NAIL LACQUER

Formulation Code	Non-volatile content (%)	Drying time (Sec)	Water Resistance (%)	Drug content (%)	Percentage Cumulative Drug Permeation (%)	Zone of inhibition (mm)
F1	23±0.33	72±0.23	95.32±0.13	90.65±0.29	26.23±0.22	15±0.21
F2	26±0.34	67±0.43	96.45±0.25	91.23±0.19	33.39±0.34	18±0.17
F3	28±0.45	65±0.55	97.22±0.44	93.44±0.87	45.45±0.56	20±0.34
F4	31±0.53	64±0.45	98.23±0.15	93.78±0.23	52.67±0.23	21±0.45
F5	39±0.53	80±0.33	98.67±0.54	94.21±0.19	66.65±0.43	25±0.33
F6	37±0.53	60±0.44	99.22±0.39	95.63±0.22	88.23±0.66	28±0.19

The results are the mean ± SD of three experiments.

***In-vitro* Transungual Permeation Studies:** Permeation studies of all the formulations were carried out using goat hoof membrane.

Highest amount of drug diffused through the membrane was observed in case of formulation F6 and lowest permeation was seen in case of formulation F1 for 24 hours (summarized in **Table 3** and **Fig. 1**).

***In-vitro* Antifungal Activity Study:** The *in-vitro* antifungal activity of nail lacquer containing TTO was studied using nutrient agar medium.

On comparing the zone of inhibitions, it was observed that the highest antifungal activity was seen in case of formulation F6 (28 mm) and the lowest was observed in case of formulation F1 **Table 3**.

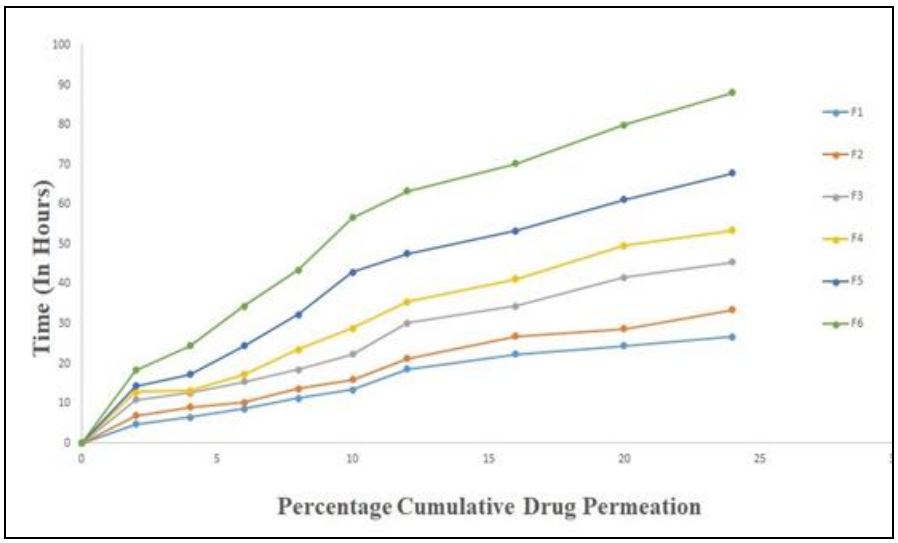

FIG. 1: PERCENTAGE CUMULATIVE PERMEATION PROFILES OF FORMULATIONS F1 ( ), F2 ( ), F3 ( ), F4 ( ), F5 ( ) AND F6 ( )

DISCUSSION: Table 2 summarizes physical parameters related to the appearance of TTO nail lacquer. All the formulations were tested and visually observed for smoothness to flow and gloss where amongst all the developed formulations, F6 exhibited excellent smoothness to flow as well as gloss. **Table 3** summarizes the results of different evaluation parameters related to the quality and efficacy of the developed nail lacquer. Non-volatile content ensures the formation of a stable film to offer maximum adherence and protection to the nails and from **Table 3** it is evident that all the formulations (F1 to F6) exhibited desired amount of nonvolatile matter with complete evaporation of volatile matter.

The result indicates complete evaporation of volatile matter leaving a thin film which can be considered ideal in terms of stability and adherence. The smooth application and uniformity of coating of an ideal nail lacquer mostly depends on the volatility characteristics of its solvent system which in turn is dependent on the drying time of the applied lacquer film. The result shows that drying time observed in case of all the developed formulations were comparable and within the desired range. However, minimum drying time was observed in the formula containing both salicylic acid and thioglycolic acid and maximum drying time was observed in formula containing urea. Therefore, drying time of the developed nail lacquers is independent of their composition within the studied range. The result of the water resistance test indicates that the formulation prepared with both salicylic acid and thioglycolic acid exhibited excellent water resistance whereas formulation prepared with salicylic acid alone showed comparatively less water resistance. The result of *in-vitro* permeation study indicates that thioglycolic acid along with salicylic acid emerged as a better penetration enhancer when compared to salicylic acid alone. The better penetrating effect of thioglycolic acid was attributed to its small molecular weight and its ability to mobilize the dense keratin network present in the dorsal nail layer. Thus, formulations containing 15% w/v thioglycolic acid allowed the drug to penetrate more easily via the hoof membrane by loosening the nail structure arising from the reduction of lipid content of dorsal nail layer [20]. The findings of the *in-vitro* antifungal activity indicate that highest zone of inhibition was observed in case of Formulation F6 possibly due to the inherent antifungal activity of thioglycolic acid combined with that of TTO [20].

CONCLUSION: The study was aimed to develop and evaluate a nail lacquer dosage form containing Tea Tree Oil as a potential treatment for Onychomycosis which will exhibit good permeability across the nail bed and improved residence time in comparison to conventionally used formulations. Different compositions were prepared using the same quantity of TTO but different concentrations of keratolyctic agents including salicylic acid, thioglycolic acid and urea.

Various quality attributes such as nonvolatile content, drying rate, nail gloss, smoothness, water resistance, drug content, *in-vitro* drug permeation, and *in-vitro* antifungal activity were determined for the developed nail lacquer. The outcome was found encouraging as all the compositions quite satisfactorily performed in the quality tests. However, the formulation containing both thioglycolic acid and salicylic acid emerged as the optimal choice across all evaluated criteria's. Therefore, the optimum formula was found to be capable of providing effective antifungal activity with good permeability and prolonged residence time on nail bed. Thus the developed formulation can eliminate the adverse effects associated with oral administration of synthetic antifungal drugs. Moreover, the controlled permeation rate of TTO from the nail lacquer holds promise for shortening the treatment duration. In summary, the developed formulation containing natural antifungal agent could be a promising alternative of existing Remedies for onychomycosis subjected to further clinical evaluations**.**

ACKNOWLEDGEMENTS: The authors extend their gratitude to NSHM College of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata, India for providing all the necessary facilities to carry out the research work.

CONFLICT OF INTEREST: No potential conflict of interest was reported by the authors.

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How to cite this article:
Chakrabarty US, Chakraborty A, Roy S, Halder P, Sinha D, Bandyopadhyay SN and Laishram D: Development and evaluation of tea tree oil infused antifungal nail lacquer: a promising alternative for treating onychomycosis. Int J Pharm Sci & Res 2025; 16(4): 1087-92. doi: 10.13040/IJPSR.0975-8232.16(4).1087-92.