

Sustained Release Nail Lacquer Formulation Containing Combination of Luliconazole and Methyl Salicylate for the Treatment of Onychomycosis

Shidhaye Supriya Shrihari^{1*}, Tank Shivali Hargovind², Phatak Kshitija Milind³

^{1,2,3}Department of Pharmaceutics, Vivekananda Education Society's College of Pharmacy, Chembur, Mumbai, India

*Corresponding author: Shidhaye Supriya Shrihari, Department of Pharmaceutics, Vivekananda Education Society's College of Pharmacy, Chembur, Mumbai, India; E-mail: s.shidhaye@ves.ac.in

Received date: September 04, 2020; Accepted date: August 17, 2021; Published date: August 27, 2021

Citation: Shrihari S S (2021) Sustained Release Nail Lacquer Formulation Containing Combination of Luliconazole and Methyl Salicylate for the Treatment of Onychomycosis. Int J Drug Dev and Res Vol.13 No.3.

Abstract

Onychomycosis is a fungal infection of the fingernails or toenails that causes discoloration, thickening, and separation from the nail bed. It affects the general population but is more common in older adults, children and immunocompromised patients. The present study was aimed towards designing and formulating medicated nail lacquer of recently approved drug Luliconazole to control onychomycosis condition. The work involved combination of antifungal agent luliconazole with a well-established anti-inflammatory agent methyl salicylate. Simple mixing method was used for preparing nail lacquer solution. Polymers such as ethyl cellulose and Eudragit RS100 were used to sustain the drug release upto 72 hours, thereby reducing the frequency of application to twice a week. The infection is associated with pain and inflammation around the nail along with foul smell. Hence addition of methyl salicylate in the formulation will help to mask the foul odour along with anti-inflammatory effect to improve the patient compliance and acceptability. Also, it will act as a permeation enhancer there by will increase drug permeation across the nail bed. The formulation was optimized on the basis of drying time, non-volatile content, drug content, drug diffusion across artificial membrane and hooves membrane and antimicrobial studies. The optimized formulation showed a drug release of 94% in 72 hours, optimum viscosity of about 152cP and drying time of 83 seconds. Thus, the nail lacquer of luliconazole was successfully developed which can serve as a promising alternative to ameliorate patient compliance.

Keywords: Luliconazole; methyl salicylate; sustained release; nail lacquer; Onychomycosis

Introduction

Nails are the hard coverings located on the extremities of fingers and toes. They are prone to various nail infections such as Leukonychia, Onychatrophia, Onychogryposis, Onychomycosis, green nail syndrome, sub-ungual hyperkeratosis, etc [1]. Onychomycosis accounts to about 50% of all the nail disorders. It is a recurrent fungal infection of fingernails and toenails which has affected to about 19% of the world population. Its prevalence is high in case of elderly people

(above age group of 60 years) and immunocompromised people such as patients with HIV, diabetes and psoriasis [2]. Onychomycosis is majorly caused due to dermatophytes such as Trichophyton rubrum and non-dermatophytes such as Candida albicans. This infection is associated with various signs and symptoms including thickening of nail, nail discoloration, foul odour, breaking and cracking of nail and separation of nail from nail bed [3]. Onychomycosis can be diagnosed by physical observation and laboratory testing as well including electron microscopy, Raman analysis and nail penetration studies [4].

Current trends in treating Onychomycosis include oral and topical medications containing anti-fungal agents. Combination of oral and topical therapy is found to be effective against the nail infection [5]. Orally administered anti-fungal agents are highly effective. However, their utilization is limited due to safety concerns because of high systemic exposure[6]. Currently available topical therapies include use of ciclopirox, amorolfine, terbinafine, efinaconazole etc[7]. However, cure rate of the available topical therapies is very low and takes about weeks and months to cure the nail infections.

Luliconazole is a newly approved anti-fungal agent for onychomycosis[8]. It is known to be safe and effective for the treatment of onychomycosis[9,10]. It has shown potent activity against agents causing onychomycosis. It is found that Luliconazole has 4 to 1000 times lower MIC (Minimum Inhibitory Concentration) than the already available drugs for onychomycosis including terbinafine, itraconazole and amorolfine[11]. Also, the favourable drug properties of Luliconazole such as appropriate Log P value and molecular size makes it easy for the drug to cross the nail plate easily thereby making luliconazole appropriate for topical treatment[12].

The commercially available topical formulations include topical creams, lotions, solutions and powders which have shorter residence time and hence need higher application frequency. The medicated nail lacquers are modification of the cosmetic nail lacquers by addition of rate controlling polymers into it which will sustain the drug release into the nail bed [13]. The nail lacquer once applied will leave a film on the nail plate wherein the polymers will act as a depot of drug and release it slowly from the film into the unguinal space [14].

The present study makes use of methyl salicylate as a novel agent into the formulation. Incorporation of methyl salicylate

helps to serve three purposes. Firstly, it helps to enhance the permeation of the drug from the nail plate[15]. The nail plate is a hard barrier for permeation of drugs, and hence incorporation of permeation enhancers will ease the entry of drugs through the restrictive barrier[16]. Since methyl salicylate has a typical odour of its own, it helps to mask the foul odour given out by onychomycotic nails. Also, methyl salicylate inhibits the inflammatory cytokines and other inflammatory mediators thereby acting as an anti-inflammatory agent.

The currently available nail lacquers for onychomycosis have antifungal agents incorporated into polymer matrix [17-19]. However, the present study deals with formulating the nail lacquer not only with antifungal activity but with a combined antifungal and anti-inflammatory effect as highlighted in figure no. 1. Thus, it focuses on the development of a nail lacquer with increased efficacy, reduced frequency of application by using sustained release polymers and with a combined anti-fungal and anti-inflammatory effect to improve patient acceptability due to its dual activity.

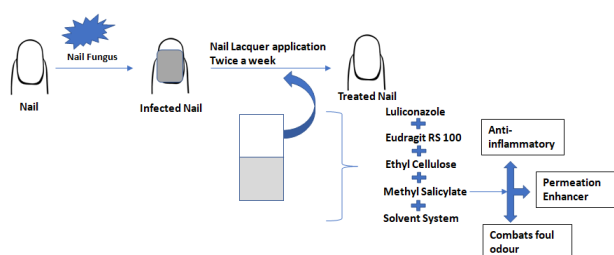


Figure 1: Overview of the research conducted

Materials and Methods

Materials

Luliconazole was procured from Cadchem Laboratories which was chosen as an antifungal agent in the formulation. Eudragit RS100 and Ethocel (Ethyl cellulose) obtained as gift sample from Evonik and Colorcon. Methyl Salicylate, butyl acetate, dibutyl phthalate were purchased from LobaChemie. The solvents including ethanol and ethyl acetate were of analytical grade.

Method of preparation

Luliconazole nail lacquer was prepared by simple mixing method. Luliconazole was dissolved in required amount of ethanol. The polymers Eudragit RS 100 and ethyl cellulose were soaked and dissolved in ethanol and ethyl acetate. The dissolved drug was added into the polymer solution. Further, dibutyl phthalate, butyl acetate and methyl salicylate were added in the desired amount and mixed properly using magnetic stirrer. The formulation was then filled in the narrow mouth containers and sealed with liner and cap.

The developed nail lacquer was further optimized to arrive at the final formulation containing desired levels of film former and release retardant, Eudragit RS 100 and Ethocel, solvent system containing ethanol and ethyl acetate and anti-inflammatory agent and penetration enhancer, methyl salicylate.

Optimization of ratio of solvent system[18]

For any topical formulation, drying time plays an important role. Drying time was optimized by selecting appropriate concentration of solvent system. The optimization of solvent system was done to achieve an optimum drying time of nail lacquer. Blank formulations were prepared in which the ratio of both the polymers (Eudragit RS 100 and Ethyl cellulose) were varied as 1:1, 2:1, 1:2 and the ratio of solvent system (ethanol and ethyl acetate) was varied from 90:10 to 60:40 (Table No. 1). The nail lacquer formulation was applied uniformly on a glass slide and was allowed to dry. The time was noted until dry to touch film was obtained. Based on the drying time, appropriate solvent system ratio was selected for further trials.

| Solvent system (Ethanol: acetate) | Eudragit RS 100: Ethyl cellulose | Drying time (seconds) |
|-----------------------------------|----------------------------------|-----------------------|
| 90:10 | 1:1 | 36 |
| | 2:1 | 43 |
| | 1:2 | 29 |
| 80:20 | 1:1 | 45 |
| | 2:1 | 49 |
| | 1:2 | 33 |
| 70:30 | 1:1 | 73 |
| | 2:1 | 81 |
| | 1:2 | 62 |
| 60:40 | 1:1 | 130 |
| | 2:1 | 150 |
| | 1:2 | 83 |

Table 1: Optimization of Solvent System for Nail Lacquer formulation

Formulation development

Nail lacquer formulation was developed by taking into account various polymers and different concentration along with different concentration of permeation enhancers. Optimization of formulation was done by preparing 8 different formulations. Amount of Luliconazole was kept constant at 5% in all formulations. Initial trials were taken with Eudragit RS 100 polymer. As seen from Table no 2 Formulation F1 to F4 were prepared containing 1% of Eudragit RS100 with increasing amount of permeation enhancer, methyl salicylate from 0 to 15%. The aim was to optimize the amount of permeation enhancers based on the drug permeability studies.

Further trials focused on combination of two polymers, namely Eudragit RS100 and Ethyl Cellulose. Formulation F5 to F8 contained various concentrations of selected polymers along with optimized amount of permeation enhancers.

| Sr. No. | Ing red | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---------|--|-----|-----|-----|-----|-----|------|-----|-----|
| | ient s | | | | | | | | |
| 1 | Luliconazole | 5% | 5% | 5% | 5% | 5% | 5% | 5% | 5% |
| 2 | Eudragit RS 100 | 1% | 1% | 1% | 1% | 2% | 3% | 3% | 3% |
| 3 | Ethyl Cellulose | - | - | - | - | - | 0.5% | 1% | 2% |
| 4 | Dibutylphthalate | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% |
| 5 | Methyl Salicylate | - | 5% | 10% | 15% | 15% | 15% | 15% | 15% |
| 6 | Butyl Acetate | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% |
| 7 | Ethanol: Ethyl Acetate (Ratio to q.s.) | 3:1 | 3:1 | 3:1 | 3:1 | 3:1 | 3:1 | 3:1 | 3:1 |

Table 2: Formulation of Nail Lacquer

All the formulations of nail lacquer were tested for various physicochemical characteristics to arrive at the optimum formulation.

Evaluation of developed formulation

Smoothness to flow: The sample was poured on a glass plate and was inclined vertically.

Gloss: The sample was uniformly applied over the nail. The gloss was visually compared with the marketed cosmetic nail lacquer.

Drying time: The optimized formulation was applied on a glass slide and was allowed to dry. The drying time was analysed until the film was dry to touch.

Non-Volatile Content: Sample measuring was poured into a glass petri plate and the weight was noted. The plate was then placed in the oven at 105 °C for 1 hour. The weight of the plate was noted after 1 hour.

$\% \text{Non-Volatile Content} = \frac{\text{Initial Weight (W1)} - \text{Final Weight (W2)}}{\text{Initial Weight (W1)}} \times 100.$

Drug Content estimation: The sample equivalent to 200mg of drug was dissolved in 50ml of acetate buffer pH 5.5: methanol (7:3). The solution was then sonicated for 15 minutes. The resulting solution was filtered and required dilutions were made to analyse drug content using UV Spectrophotometer at 299nm.

Viscosity: Viscosity of the formulations were analyzed using Brookfield Viscometer, model DV E-5 at room temperature using spindle No. 61 at 10 rpm.

Water resistance test: The sample was applied on a glass plate. The glass plate with completely dried sample was weighed and then immersed in water for seven days. After seven days the sample was visually analysed for its discoloration, turbidity, blistering and change in weight.

Determination of Anti-fungal Activity[20]: The antifungal activity was tested using *Candida albicans* by the cup-plate method. Nutrient agar plates containing Sabouraud's agar was sterilised by autoclaving. Sterilised agar measuring 20ml was poured into pre sterilised glass petri plates and was inoculated with diluted fungal strain. The plates containing the agar were allowed to solidify. Two wells of 5mm diameter were made in each plate using sterile cork borer. The formulation measuring 0.2ml was placed into the plates and allowed to diffuse. The plates were then incubated at 30°C for 48 hrs. Plates containing un-inoculated media and inoculated media without formulation were kept as negative and positive control respectively. Zone of inhibition was evaluated after 48hrs.

In-Vitro Diffusion Studies through artificial membrane: The diffusion studies were conducted using Franz diffusion cell by Teledyne Hanson. Cellophane membrane was used as artificial membrane for diffusion studies. The membrane was soaked in acetate buffer pH 5.5: methanol (7:3) for 24 hrs. The formulation was applied on the cellophane membrane and was allowed to dry. The prepared membrane was placed on the cell carefully by avoiding air entrapment and 20ml of acetate buffer pH 5.5: methanol (7:3) was taken in receptor compartment. Entire setup was kept under stirring at 37°C. Aliquots measuring 5ml was withdrawn at time intervals of 30minutes, 1 hour, 2 hour, 4 hour, 6 hour, 8 hours upto 72 hours.

In-Vitro Transungual Permeation Studies across Hooves membrane [21,22]: The hooves membrane obtained from freshly slaughtered cattle were soaked in water for 24 hours. The adhering connective and cartilaginous tissues were removed and the membrane was washed properly.

Membrane of thickness 1 mm was cut and invitro permeation studies were carried out using Franz diffusion cell apparatus by Teledyne Hanson. The membrane was placed in the donor compartment and the receptor compartment was filled with 20 ml of acetate buffer pH 5.5: methanol (7:3). The sample was applied on the membrane and the entire setup was maintained at 37°C ± 1°C under stirring. Sample aliquots were taken at pre-defined time intervals of 30minutes, 1 hour, 2 hour, 4 hour, 6 hour, 8 hours upto 72 hours.

Stability Studies

Stability studies of nail lacquers were carried out as per ICH guidelines. The formulation was stored at 25 ± 2 °C/ 60 ± 5 % RH for 3 months and 40 ± 2 °C/ 75 ± 5 % RH for 1 month. Then the samples were analyzed for non-volatile content, drying time, drug content, diffusion across artificial membrane and anti-microbial studies.

Results and Discussion

The objective of the work was to formulate Luliconazole nail lacquer containing two different polymers and permeation enhancer and to analyse the working concentration of penetration enhancers and polymer to achieve required sustained drug release with improved drug permeation along with desired anti-fungal activity. The developed formulation comprised of release modifying polymers i.e., Eudragit RS 100 and Ethylcellulose, permeation enhancer and anti-inflammatory agent, methyl salicylate, dibutyl phthalate as plasticizer and butyl acetate, ethyl acetate and ethanol as solvent system. The processing of formulation involved simple mixing technique.

Analyzing drying time of nail lacquer formulation is important. Lesser drying time will cause dripping of the formulation with uneven application. Therefore, an optimum drying time of 60 to 120 seconds was considered essential for proper application of the formulation on the nail plate. In order to get the optimum drying time, appropriate ratio of solvent system was required to be analyzed having neither too fast not too slow rate of evaporation.

As seen from table no. 1, the solvent ratio of 60:40 gave increased drying time of above 120 seconds. The minimum drying time was seen for 90:10 solvent system ratio but was not considered optimum as lower drying time leaves a non-uniform film on the nail. The optimum drying time of 60 to 90 seconds was observed with solvent system ratio of ethanol and ethyl acetate as 70:30 which was selected as the solvent system for further trials.

The prepared formulations were subjected to preliminary tests which included smoothness to flow, film formation and gloss. It was found that F1 to F7 had shown good gloss, smoothness to flow and required film forming properties. Formulation F8 having higher amount of polymer with increased viscosity showed poor flow properties with good gloss and average film forming nature. The results of evaluation are as shown in Table no.3.

Drying Time

Formulation F1 to F4 having equal amount of Eudragit RS100 polymer with slight change in methyl salicylate amount gave drying time between 40 seconds to 50 seconds. With increase in concentration of polymer from F5 to F7 the drying time was increased 70 seconds to 85 seconds. Formulation F8 showed highest drying time as it contained higher amount of polymer concentration with increase in viscosity thereby increasing drying time.

Non-Volatile Content

Non-volatile content has an impact on the amount of coverage the nail lacquer film is providing. The solid non-volatile part in the form of film covering the entire nail surface is left behind after solvent evaporation. With increase in polymer concentration the solvent system decreases where by the non-volatile content increases. Hence Non-volatile content depends on the concentration of polymer used. A minimum of 20% by mass of the nonvolatile content is required for the sufficient coverage (Bureau of Indian Standards, IS 9245:1994). For the present investigation, the non-volatile content of formulations F1 to F8 is listed in table no.3. As the solid content increased, the non-volatile content was found to be increased as expected and the content was above 20% as recommended by Indian Standards.

Drug Content Estimation

As shown in table no. 3, drug content of all 8 formulations were found to be between the range of 95% to 96% which was considered as accepted.

Viscosity

The viscosity of all the formulations ranged from 120 to 200 centipoise. Viscosity in the range of 130 to 150 centipoise resulted into clear and glossy formulations. With increase in polymer concentration, the viscosity of the formulation increased with adversely impacting the appearance of nail lacquer. The values are listed in table no.3

| Parameters | Drying time | Non volatile content (%) | %Drug Content | Viscosity (cP) | Anti-fungal activity studies (Zone of inhibition in mm) |
|------------|-------------|--------------------------|---------------|----------------|---|
| F1 | 42 | 23.22±0.22 | 96±0.167 | 122 | 21 |
| F2 | 44 | 24±0.378 | 95±0.024 | 126 | 23 |
| F3 | 45 | 24.16±0.021 | 96±0.55 | 130 | 22 |
| F4 | 47 | 24.38±0.971 | 95±0.63 | 134 | 25 |
| F5 | 71 | 25.27±0.012 | 96±0.33 | 136 | 24 |
| F6 | 78 | 27.98±0.148 | 94±0.75 | 143 | 23 |
| F7 | 83 | 28.66±0.269 | 97±0.120 | 152 | 25 |
| F8 | 120 | 30.12±0.012 | 96±0.29 | 189 | 24 |

Table 3: Evaluation of Nail lacquer formulation

Water resistance test

All the formulations were found to be water resistant. Formulations did not show any significant turbidity, blistering or change in weight in presence of water. It was observed that the water-resistant capacity of the formulations was increased with increase in concentration of polymers.

Determination of Anti-fungal Activity

As seen from table no.3, antifungal activity of luliconazole nail lacquer formulations against *Candida albicans* was similar to that by luliconazole solution. The zone of inhibition for all the formulations was obtained in the range of 20-25mm. The zone of inhibition for luliconazole solution was found to be 25 mm. Thus, the prepared formulations were found to be effective against *Candida albicans* as expected.

In vitro Diffusion Studies across Artificial Membrane

Drug release studies were carried out for all the formulations mentioned in tab no 2.

Formulation F1 gave 23% drug release in 24 hours as it did not contain any permeation enhancer. So, the addition of a permeation enhancer was felt necessary to improve permeation of drug through the artificial membrane. In further trials methyl salicylate was incorporated as permeation enhancer.

As seen from figure no 2 formulation F2 gave increased drug release of 46 % in 24 hours with 5% of permeation enhancer. Formulation F3 and F4 containing 10% and 15% permeation enhancer showed improved % drug release upto 62% and 89% respectively in 24 hours. Hence, the level of permeation enhancer, methyl salicylate, was fixed at 15%. Next aim was to extend the drug release from formulation till 72 hours as seen in figure no. 3. Formulation F5 containing 2% of Eudragit RS100 showed 92% drug release over 36 hours. With further increase in concentration of Eudragit RS100 to 3% and incorporation of 0.5% of Ethylcellulose sustained release of drug was achieved with 92% drug release at 48 hours. Further increase in concentration of Ethyl cellulose to 1% and 2% keeping concentration of Eudragit RS100 fixed at 3%, the drug release of formulation F6 and F7 was extended upto 60 hours and 72 hours respectively with %drug release of 91% and 94 % respectively. With further increase in concentration of polymers as formulation F8, % drug release of 92% was obtained at 84 hours. But the formulation was found to be highly viscous and sticky with lack of good gloss and smooth flow. Also, formulation 8 showed higher drying time of 120 seconds which was considered unacceptable. Formulation F7 was selected as optimized formulation based on in-vitro drug release studies through artificial membrane.

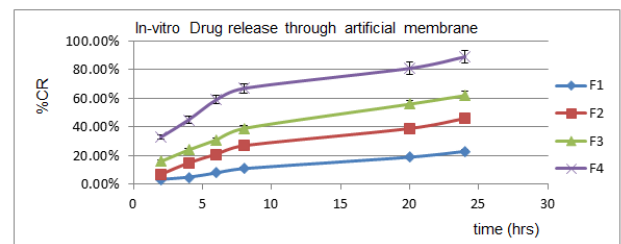


Figure 2: In-vitro drug release studies of F1 to F4 through artificial membrane

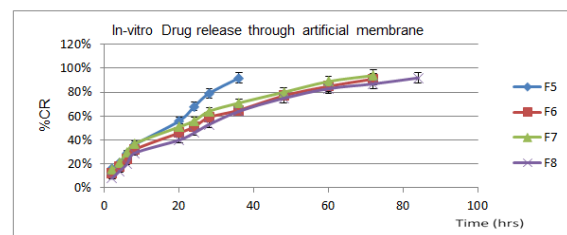


Figure 3: In-vitro drug release studies of F5 to F8 through artificial membrane

In vitro unguial permeation studies

Further diffusion study was performed using hooves obtained from freshly slaughtered cattle. Among all the formulations, formulation F7 was taken ahead for permeation studies through hooves membrane. From figure no. 4, no significant difference in drug diffusion was noticed when compared with drug release through artificial membrane. Based on the in vitro drug release studies, formulation 7 was shortlisted as the final formulation having desired characteristics.

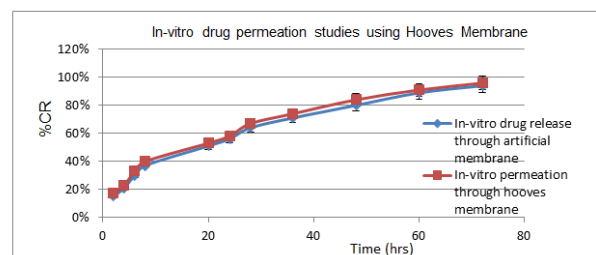


Figure 4: In-vitro drug permeation studies of F7 across artificial membrane and hooves membrane

Stability Study

Formulation 7 was further subjected to stability studies. It was found to be stable when stored at 40° C for 1 month and at 25±2°C/60 ± 5% RH for 3months. The formulation did not show any significant change in color, drying time, non-volatile content, drug content, viscosity, diffusion across artificial membrane and anti-microbial studies activity as seen from table no. 4. Thus, a stable, effective nail lacquer formulation of luliconazole was developed with good consistency, drying time and glossy appearance

Table 4: Stability data of Optimized formulation F7

| Sr. No. | Parameters | At 0th day (Initial) | At 30th Day (40° C) | At 90th Day (25±2°C/60 ± 5% RH) |
|---------|--|----------------------|---------------------|---------------------------------|
| 1. | Drying Time (seconds) | 83 | 85 | 86 |
| 2. | Non-volatile Content (%) | 28.66±0.269 | 26.33±0.11 | 27.26±0.01 |
| 3. | Drug Content (%) | 97±0.120 | 95±0.03 | 96±0.66 |
| 4. | Viscosity (cP) | 152 | 155 | 154 |
| 5. | Diffusion across artificial membrane | 94% in 72 hours | 92.26% in 72 hours | 91.44% in 72hours |
| 6. | Antifungal activity against <i>Candida albicans</i> (Zone of inhibition in mm) | 24.25 | 23.1 | 21.66 |

Conclusion

Onychomycosis being a chronic recurrent fungal nail infection requires long term treatment with regular adherence to the suggested therapy. The present study focused on the development of patient compliant nail lacquer formulation with a novel combination of recently approved drug for onychomycosis i.e., Luliconazole and Methyl salicylate as an established anti-inflammatory agent having ability to act as permeation enhancer. With incorporation of two rate modifying polymers viz., Eudragit RS 100 and Ethyl cellulose, sustained drug release upto 72 hours was achieved thus making it suitable for twice a week application. Out of all the 8 formulations, F7 was considered as an optimized formulation which gave drying time of 83 seconds with good gloss, flowability and consistency. The viscosity was found to be 152cP with drug release through artificial membrane of 94% and from hooves membrane of 96% at the end of 72 hours. The stability studies indicated that the formulation was stable at 40° C for 1 month. Thus, with reduction in frequency of application along with anti-inflammatory action and ability to mask bad odor and good efficacy, the developed formulation can serve as a promising alternative to the available formulations to treat onychomycosis.

Future Perspective

The treatment of Onychomycosis is tedious and long lasting with high chances of relapse if discontinued. Hence, it becomes difficult to completely cure the infection. There is improvement in the treatment approaches in the recent years. Various new patient friendly and sustained release formulations have been developed containing different anti-fungal agents. However, establishing in vitro-in vivo correlation is considered as a task. There are various difficulties encountered while attaining this correlation. The correlation of nail lacquer formulation can be checked to make it potential to be used for the treatment alone.

Also, the laboratory to large scale transition of the formulation is also an important factor that can hamper the formulation performance. Thus, the scaleup batches can be taken further to check its scalability as a potential commercial product. Also, the need to perform clinical trials is one of the major factors during the lab-to-patient transfer of the product. These trials can make this transfer easy and convenient thereby increasing patient compliance.

References

1. Bhowmik D (2013) Nail drug delivery system- a novel approaches for drug delivery system. *Pharma Innov* 1: 3–16.
2. Sigurgeirsson B, Baran R (2014) The prevalence of onychomycosis in the global population – A literature study. *J. Eur. Acad. Dermatology Venereol* 28: 1480–1491.
3. Elewski BE (2000) Onychomycosis: Treatment, quality of life, and economic issues. *Am. J. Clin. Dermatol* 1: 19–26.
4. Baraldi A (2015) Human Nail Plate Modifications Induced by Onychomycosis: Implications for Topical Therapy. *Pharm Res* 32: 1626–1633.
5. Khamidah N Ervianti E (2018) COMBINATION ANTIFUNGAL THERAPY FOR ONYCHOMYCOSIS Literature Review. *Indones J Trop Infect Dis* 7: 15–20.
6. Gupta AK, Ryder JE, Skinner AR (2004) Treatment of Onychomycosis: Pros and Cons of Antifungal Agents. *J Cutan Med Surg* 8: 25–30.
7. Elsayed MMA (2015) Development of topical therapeutics for management of onychomycosis and other nail disorders: A pharmaceutical perspective. *J Control Release* 199: 132–144.
8. Saunders J, Maki K, Koski R, Nybo SE (2017) Tavaborole, Efinaconazole, and Luliconazole: Three New Antimycotic Agents for the Treatment of Dermatophytic Fungi. *J Pharm Pract* 30: 621–630.
9. Jones T, Tavakkol A (2013) Safety and tolerability of luliconazole solution 10-percent in patients with moderate to severe distal subungual onychomycosis. *Antimicrob. Agents Chemother* 57: 2684–2689.
10. Watanabe S, Kishida H, Okubo A (2017) Efficacy and safety of luliconazole 5% nail solution for the treatment of onychomycosis: A multicenter, double-blind, randomized phase III study. *J Dermatol* 44: 753–759.
11. Uchida K, Nishiyama Y, Yamaguchi H (2004) In vitro antifungal activity of luliconazole (NND-502), a novel imidazole antifungal agent. *J Infect Chemother* 10: 216–219.
12. Hasuko M (2017) Affinity of luliconazole for human nail derived keratin. *Med. Mycol J* 58: 113-119.
13. Akhtar N, Sharma H, Pathak K (2016) Onychomycosis: Potential of Nail Lacquers in Transungual Delivery of Antifungals. *Scientifica (Cairo)*.
14. Bhapkar MPH (2013) Topic Name – Nail Lacquers in Nail Diseases. *IOSR J Pharm* 3: 24–48.
15. Moghadam S H (2013) Effect of Chemical Permeation Enhancers on Stratum Corneum.
16. Pati NB (2016) Nail Drug Delivery System : A Review.

17. V VK, C SC, Augusthy AR, KP, Kuriakose MR (2014) Formulation and Evaluation of an Antifungal Nail Lacquer for Onychomycosis. *Br Biomed Bull* 2: 242–248.
18. Thatai, P. & Sapra, B. Terbinafine hydrochloride nail lacquer for the management of onychomycosis: Formulation, characterization and in vitro evaluation. *Ther. Deliv.*9, 99–118 (2018).
19. Permeation, T., The, O. F., Nail, V. & Against, L. 1 , 2 , 3. 2, 25–33 (2012).
20. Alsterholm, M., Karami, N. & Faergemann, J. Antimicrobial activity of topical skin pharmaceuticals - An In vitro study. *Acta Derm. Venereol.*90, 239–245 (2010).
21. Rajendra, V. B. et al. Transungual drug delivery: An overview. *J. Appl. Pharm. Sci.*2, 203–209 (2012).
22. Mertin, D. & Lippold, B. C. In-vitro permeability of the human nail and of a keratin membrane from bovine hooves: Influence of the partition coefficient Octanol/Water and the water solubility of drugs on their permeability and maximum flux. *J. Pharm. Pharmacol.*49, 30–34 (1997).