Original article

Formulation and Evaluation of Herbal nail lacquer for treatment of Onychomycosis

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ABSTRACT

A fungal infection of the fingernails or toenails called onychomycosis results in thickening, detachment from the nail bed, and discoloration of the nails. Although it affects everyone, older people, kids, and patients with compromised immune systems are more likely to contract it. The goal of the current study was to create and formulate a therapeutic nail lacquer using the Neem oil to treat the condition of onychomycosis. Neem oil, an antifungal agent, was combined with castor oil, an established anti-inflammatory drug, in this study. Nail lacquer was made using a simple mixing process. Application frequency was decreased to twice a week by using polymers such ethyl cellulose to sustain medication release for up to 20 hours. Alongwith a bad odour, the infection is accompanied by pain and swelling around the nail. Ethyl acetate will therefore aid in masking the unpleasant aroma while also having an anti-inflammatory impact to increase patient compliance and acceptability. Additionally, it will function as a permeation enhancer, increasing the drug’s ability to permeate the nail bed. Drying time, non-volatile content, viscosity, water resistance test, and research were taken into consideration when optimizing the formulation. The ideal drug viscosity for the optimized formulation was around 131 cp, and the drying period was 3 min. As a result, neem oil’s nail lacquer was effectively created.

1. 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]. The elderly and people with impaired immune systems are particularly susceptible to these nail conditions. Due to its non-invasiveness, medication targeting to the site of action, reduction of side effects associated with systemic therapy, increased patient compliance, and reduced treatment costs, topical therapy is a desirable choice [2].

The poor permeability of the nail plates to the topically administered drugs was the main reason why topical therapy had little success. Enhancing ungual drug penetration is necessary for topical therapy across the nail plate to be successful [3]. However, gel, cream, or liquid formulations are not adequate for the transungual delivery since they are easily removed by washing or rubbing. This phenomenon at the site of application accounts for their inefficacy. Few days lasting drug delivery is considered as a necessary requirement for pharmaceutical formulations applied topically on the nail. Film-forming systems for transungual drug delivery are used in clinical practice, but their ability to deliver therapeutic doses of active substances remains critical for efficient onychomycosis treatment. Mechanical characteristics and water resistance make nail lacquers a promising alternative for onychomycosis topical treatment. Lacquer film is formed during solvent evaporation after lacquer application. Films formed by nail lacquers must establish attachment to the nail surface which is an necessary prerequisite of efficient drug delivery [4].

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 ungual space [5].

Currently available nail lacquer reported in literature include ciclopirox, Naftifine hydrochloride, terbinafine, ketoconazole, luliconazole [6]. Apart from above antifungal agents, castor oil and neem oil has promising anti fungal activity [7, 8, 9]. It functions as an anti-fungal agent in nail lacquer. Neem oil softens cuticles while penetrating the nail to strengthen and torment it. It serves as a repellant and lessens insect feeding. Castor oil works as an anti-inflammatory in nail lacquer. Benefits comprise strengthening, moisturizing, nurturing brittle nails, relieving nail grooves, and healing leukonychia punctate.

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It is reported, when castor oil is applied once or twice a week, there is significant reduction in fungal infection [10]. Topical application of oils on nails is troublesome leading to poor patient compliance. The goal of this work is to improve the permeation of castor oil and neem oil along with prolonging the release.

Materials and Methods:

Materials

Ethyl cellulose, ethyl acetate, propylene glycol, salicylic acid, polyvinylpyrrolidone (PVP) and glycerin were purchased from research lab, India. Neem oil and castor oil was procured from market. The solvents ethanol, ethyl acetate was of analytical grade.

Methods:

Preparation of nail lacquer

The medicated nail lacquer was prepared by simple mixing method, Table 1. The film forming polymer ethyl cellulose was dissolved in ethyl acetate using stirring. The polymer was allowed to dissolve completely, then plasticizer (propylene glycol) and PVP was added to the solution while stirring [11]. Castor oil and neem oil were added into the polymer solution. Further, salicylic acid and glycerin 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.

Formulation development

Initially, a solvent system was screened for the polymer (ethyl cellulose). Various solvent system such as ethanol, acetone and ethyl acetate were studied. After selection of solvent, the polymer concentration was optimized. Nail lacquer formulation was developed by considering different concentration of ethyl cellulose, salicylic acid, propylene glycol, PVP and glycerin. Optimization of formulation was done by preparing six different batches. As, shown in Table 2, formulation F1 to F6 were formulated. The aim was to achieve desired level of film forming ability by the nail lacquer.

Characterization and evaluation of developed formulation:

Drying time:

The drying time is the primary test used for the nail lacquer. Briefly a brush applicator was used to spread the lacquer on a 2 cm² area on a glass slide at room temperature and let to dry. After every 15 sec, a gloved finger was used to touch the film. The time required to obtain dry to touch condition was recorded [12].

Smoothness to flow:

The sample was spread on the glass slide. The glass slide was then raised vertically [13].

Gloss:

The sample covered the nail in an even layer. The gloss and the marketed cosmetic nail lacquer were visually compared.

Non-volatile content:

A glass petri plate was used for the sample measurement, and the weight was recorded. The plate was then heated for one hour at 105°C. After an hour, the plate’s weight was recorded. The difference between initial and final weight was calculated. The percentage non-volatile content was determined by formula:

\[
\% \text{ Non-volatile content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]

Viscosity:

Viscosity of formulation was determined using Brookfield Viscometer, model DV-E-5, at room temperature with spindle No. 61 running at 10 rpm.

Water resistance test:

A glass plate was used to apply the sample. After being weighed, the glass plate containing the fully dried sample was submerged in water. The sample was examined visually for discoloration, turbidity, blistering, and weight change.

Drug Content Estimation:

About 200 mg of nail lacquer was dissolved in 50 ml phosphate buffer of pH 7.4. The solution was ultrasonicated for 15 minutes. The resulting solution was filtered and volume was made up to 100 ml with phosphate buffer solution of pH 7.4. The diluted solution was estimated spectrophotometrically at wavelength of 223 nm and determined the drug content.

In-vitro release studies through artificial membrane:

The in-vitro release from medicated nail lacquer was conducted using Franz diffusion cell at 37°C. Cellophane membrane was used as artificial membrane for diffusion studies. The membrane was soaked in phosphate buffer of pH 7.4 containing ethanol 30% for 24 hrs. The formulation was applied on the cellophane membrane and was allowed to dry. The prepared membrane was placed on the cell, between donor and receptor chamber of Franz diffusion cell. 20 ml of phosphate buffer pH 7.4 was taken in receptor compartment. Entire setup was kept under stirring at 37°C. Aliquots measuring 1 ml was withdrawn through sampling arm of the Franz diffusion cell followed by immediate replenishment with the same volume of fresh receptor media. UV spectrophotometric method was used to determine the drug content in each sample, and cumulative drug contents were plotted against the time to obtain the release profile.
Stability Studies:

Stability studies of nail lacquers were carried out as per ICH guidelines. The optimized 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.

Result and Discussion:

The objective of the present study was to formulate a nail lacquer for preventing fungal growth on toe nails or finger nails so that the appearance of the nails is improved. Hence utilizing neem oil and castor oil as anti-inflammatory and anti-fungal a medicated nail lacquer is formulated to provide the requisite sustained medication release, better drug permeation, and desirable anti-fungal effectiveness.

The prepared formulation included salicylic acid as keratolytic agent and permeation enhancer, propylene as plasticizer, PVP as film former, glycerin as humectant, release modifying polymers (Ethyl cellulose), and ethyl acetate as a solvent system. Initially, a solvent system was selected for optimization of formulation.

Selection of Solvent

Film formation is influenced by solvent system used which should efficiently dissolve the film-forming components and drug substance. The trial experiments were performed to screen solvent system. It is essential that the resultant lacquer has capacity to hydrate the nail with the hydrophobic component while achieving desirable physical characteristics of the lacquer such as resistance and adhesion with the hydrophobic component. Solvent system consisting of ethanol, acetone and ethyl acetate were used for formulation of nail lacquer, as shown in Table 2.

From the trials, it was observed that the polymer aggregates in the nail lacquer containing ethanol. Further, when acetone was used as solvent, it produce clear solution with the polymer. However, it cannot be used as it rapidly evaporates leaving behind the polymer. The solvent system ethanol and acetone was not suitable for this formulation. Therefore, ethyl acetate was used as the solvent to formulate the nail lacquer. A linear increase in viscosity was observed when ethyl acetate was used as the solvent for dissolving the polymer (ethyl cellulose).

Evaluation of Nail lacquer:

Formulated nail lacquers were subjected to preliminary evaluation tests.

a) Drying Time

Drying time for formulations F1 to F4 was found between 30 seconds to 80 seconds. It was found that as the polymer concentration increases from 0.5 % w/v to 2 % w/v the drying time increases respectively. The time required for the solvent to evaporate from the more viscous solution is more than the less viscous solution. Formulation F5 showed optimum drying time of about 100 sec. Formulation F6 showed maximum drying time as it contained higher amount of polymer.

Table 3: Drying time of various batches

<table>
<thead>
<tr>
<th>Batch</th>
<th>Ethyl cellulose (gm)</th>
<th>Drying time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.5</td>
<td>30 sec</td>
</tr>
<tr>
<td>F2</td>
<td>1</td>
<td>50 sec</td>
</tr>
<tr>
<td>F3</td>
<td>1.5</td>
<td>60 sec</td>
</tr>
<tr>
<td>F4</td>
<td>2</td>
<td>80 sec</td>
</tr>
<tr>
<td>F5</td>
<td>2.5</td>
<td>100 sec</td>
</tr>
<tr>
<td>F6</td>
<td>3</td>
<td>120 sec</td>
</tr>
</tbody>
</table>

Smoothness to flow and gloss

Optimized formulation F5 when poured onto the glass plate was found to have satisfactory flow property and result in a uniform smooth film, as compared to other formulation batches.

Non-Volatile Content of Nail Lacquer

The increase in polymer concentration from 0.5 % to 3 % causes increase in non-volatile content of nail lacquer. Non-Volatile Content depends on polymer content. Thus, higher the polymer concentration higher is the non-volatile content of nail Lacquer.

Viscosity

The viscosity of the sample varied from 114 to 131 centipoise (cp). This viscosity range provided good adherence and flow property. The viscosity of various formulation batches is given in Table 4.

Table 4: Viscosity of formulated batches

<table>
<thead>
<tr>
<th>Formulation Batch</th>
<th>Viscosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>114</td>
</tr>
<tr>
<td>F2</td>
<td>112</td>
</tr>
<tr>
<td>F3</td>
<td>117</td>
</tr>
<tr>
<td>F4</td>
<td>122</td>
</tr>
<tr>
<td>F5</td>
<td>126</td>
</tr>
<tr>
<td>F6</td>
<td>131</td>
</tr>
</tbody>
</table>

Water Resistance Test

As shown in, Table 5 increase in polymer concentration increases the water resistance. Formulation F1, F2, F3 and F4 shows lower water resistance than F5 and F6.
Table 5: Water resistance test formulated batches

<table>
<thead>
<tr>
<th>Formulation Batch</th>
<th>W1 (gm)</th>
<th>W2 (gm)</th>
<th>Difference in weight (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>5.28</td>
<td>5.38</td>
<td>0.10</td>
</tr>
<tr>
<td>F2</td>
<td>5.28</td>
<td>5.43</td>
<td>0.15</td>
</tr>
<tr>
<td>F3</td>
<td>5.28</td>
<td>5.48</td>
<td>0.20</td>
</tr>
<tr>
<td>F4</td>
<td>5.28</td>
<td>5.51</td>
<td>0.23</td>
</tr>
<tr>
<td>F5</td>
<td>5.28</td>
<td>5.38</td>
<td>0.25</td>
</tr>
<tr>
<td>F6</td>
<td>5.28</td>
<td>5.54</td>
<td>0.26</td>
</tr>
</tbody>
</table>

aW1 and bW2 - Weight of glass slide along with nail lacquer before and after dipping in water.

Drug Content Estimation

Percentage drug content for all the formulation batches were found to be satisfactory and in between 80.0 % - 96.0 % which is reported in Table 6. Highest % of drug content was found to be 96% (F5) and the lowest 80% of drug content (F1). If the drug content is more than 90 % the formulation shows high amount of drug present in it. This ensure better therapeutic response.

Table 6: Drug content estimation of formulated batches

<table>
<thead>
<tr>
<th>Formulation Batch</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>80.0±0.02</td>
</tr>
<tr>
<td>F2</td>
<td>83.4±0.17</td>
</tr>
<tr>
<td>F3</td>
<td>85.0±0.22</td>
</tr>
<tr>
<td>F4</td>
<td>86.4±0.20</td>
</tr>
<tr>
<td>F5</td>
<td>96.0±0.03</td>
</tr>
<tr>
<td>F6</td>
<td>96.8±0.14</td>
</tr>
</tbody>
</table>

In vitro diffusion study

Franz diffusion cell was used to conduct diffusion experiments with a artificial membrane (cellophane). On the membrane’s surface, an optimised nail lacquer formulation (F5) was evenly applied. Similar study was performed using castor oil and neem oil only. The diffusion study was continued up to 20 hours, as shown in Fig.1. Nail lacquer formulation (F5) showed the highest release of 94.48 %. It was found that due to presence of permeation enhancer (salicylic acid), the release of drug increases. Moreover, ethyl cellulose sustains the release of castor oil and neem oil up to 20 hours. The expected mechanism of permeation of nail lacquer is shown in Fig.2.

Stability Study

The results of the stability analysis showed that when the medicated nail lacquer was kept at a temperature of 37°C for a month, it exhibited good stability. Colour, non-volatile content, viscosity, drying time, and smoothness have not changed significantly.

References


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