INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

FORMULATION AND EVALUATION OF MEDICATED NAIL LACQUER OF ITRACONAZOLE

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ABSTRACT

Onychomycosis is a fungal infection of the nail bed or nail plate that accounts for approximately 50% of all nail diseases and is the most common disorder in adults. Onychomycosis though rarely life threatening, they can be very painful, discomfortable and disfiguring for the sufferer and may produce serious physical and occupational limitations, psychological and emotional effects, and affect quality of life. Deformed nails can lead to surrounding tissue damage and may promote secondary bacterial infection. The objective of the present work was to formulate a medicated antifungal nail lacquer containing itraconazole for the treatment of Onychomycosis. In the present study, nail lacquer containing a permeation enhancer salicylic acid and release extender ethyl cellulose in different concentration are tried out and comparison of extent of drug permeation has been done among the same. Then, the formulated nail lacquers were compared for physical appearance, drying time, nonvolatile content, gloss, water resistance, drug content, drug diffusion and anti -microbial studies.

Key words: Onychomycosis, Itraconazole, nail lacquer

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INTRODUCTION

Onychomycosis is a fungal infection of the nail bed or nail plate that accounts for approximately 50% of all nail diseases and is the most common disorder in adults. Onychomycosis though rarely life threatening, they can be very painful, discomfortable and disfiguring for the sufferer and may produce serious physical and occupational limitations, psychological and emotional effects, and affect quality of life. Deformed nails can lead to surrounding tissue damage and may promote secondary bacterial infection. Diseases. The treatment of onychomycosis is a challenging task because of unique barrier properties of the nail plate which hampers the passage of antifungal drugs in a concentration required to eradicate the deeply seated causative fungi in the nail bed (1, 2).

MATERIALS AND METHODS

Itraconazole was purchased from Yarrow Chemicals Mumbai, and other excipients were purchased from Medwin Chemicals Malapuram, Kerala.

Solubility study

Saturated solubility of Itraconazole was prepared using 10 ml of distilled water/ ethanol/ methanol in 25 ml volumetric flasks in triplicate. The sample withdrawn (1 ml after filtration) was diluted with appropriate medium and analyzed by using UV spectrophotometer at 261 nm.

Determination of drug- polymer compatibility

FT-IR spectral analysis of pure drug and polymer were carried out individually and as mixtures. The compatibility between Itraconazole, ethyl cellulose, propylene glycol, salicylic acid and prepared formulation were carried out in the ratio 1:1.

Formulation of nail lacquer

The formulation trials were done as per formula given in Table-1. Itraconazole nitrate was dissolved in Ethyl alcohol in the required quantity using a magnetic stirrer at a constant speed. To above clear solution required quantity of ethyl cellulose, Salicylic acid, and propylene glycol were mixed thoroughly and made up to the volume to 100ml. The prepared nail lacquer was transferred to a narrow mouthed, plastic screw capped glass bottle.

Table-1 Formulation of Itraconazole nail lacquer

INGREDIENTS (%)	F1	F2	F3	F4	F5	F6
Itraconazole	2	2	2	2	2	2
Salicylic acid	10	15	20	15	15	15
Ethyl cellulose	-	-	-	0.25	0.5	0.75
Propylene glycol	10	10	10	10	10	10
Ethanol (q.s.)	100	100	100	100	100	100

EVALUATION OF NAIL LACQUER

Physical appearance

The nail lacquers were visually observed for their appearance such as colour, application properties and transparency.

Non-volatile content

10 ml of sample was taken in a petri dish and initial weights were recorded. The dish was placed in the oven at 105ºC for 1 hour; the petri dish was removed, cooled and weighed. The difference in weights was recorded. Average of triplicate readings was noted.

Gloss

Sample of nail lacquer was applied over the nail and gloss was visually seen, compared with marketed cosmetic nail lacquer.

Drying time

A film of sample was applied on a petri dish with the help of a brush. The time to form a dry-to- touch film was noted with the help of stop watch.

Smoothness to flow

The sample was poured from a height of 1.5 inches into a glass plate and spread on a glass plate and made to rise vertically and visually observed for smoothness of film.

Water resistance

This is done by applying a continuous film on a surface and immersing it in water. The weights before and after immersion are noted and increase in weight, is calculated.

Drug content estimation

Nail lacquer equivalent to 200mg was dissolved in 50 ml alcohol. Then the solution was sonicated for 15 mints. The resulting solution was filtered, made up to 100 ml with alcohol. From the above solution take 10ml and made up to 100ml with alcohol. Then the diluted solution was estimated spectrophotometrically at wavelength of 261 nm and determined the drug content.

Diffusion studies across artificial membrane

Diffusion studies were performed by Franz diffusion cell using artificial membrane (cellophane) of 0.8µm. The membrane was soaked for 24hrs in solvent system and the receptor compartment was filled with solvent. Nail lacquer equivalent to 200mg was applied evenly on the surface of the membrane. The prepared membrane was mounted on the cell carefully to avoid entrapment of air bubbles under the membrane. The whole assembly was maintained at 37°C, and the speed of stirring was kept constant for 24hrs. The 5ml aliquot of drug sample was taken at time intervals of 2hr, 4hr, 6hr, 8hr, 10hr, 12hr, 16hr, 20 hr and 24hrs and was replaced by the fresh solvent. Samples were analyzed by double-beam UV spectrophotometer as per method mentioned in drug content estimation. Each experiment was repeated thrice.

***In vitro* ungual permeation studies**

Hooves from freshly slaughtered cattle, free of adhering connective and cartilaginous tissue, were soaked in distilled water for 24hrs. Membranes of about 1mm thickness were cut from the distal part of hooves. In vitro permeation studies were carried out by using Franz diffusion cell, the hoof membrane was placed carefully on the cell.

Then the nail lacquer equivalent to 200mg was applied evenly on the surface of the nail membrane. The receptor compartment was filled with solvent phosphate buffer solution of pH 7.4, and the whole assembly was maintained at 37°C with constant stirring for 48hrs. The 5ml aliquot of drug sample was taken after a time intervals of 2hr, 4hr, 6hr, 8hr, 10hr, 12hr, 16hr, 20 hr and 24hrs and was replaced by the fresh solvent. The drug analysis was done by using double-beam UV spectrophotometer at 261nm.

Determination of antimicrobial activity

Candida albicans were employed for testing antifungal activity using the cup-plate method. The culture was maintained on Sabouraud's agar slants. 20 ml of melted Sabouraud's agar medium was inoculated with 72 hrs old 0.2 ml suspension of Candida albicans in the Petri dish and allowed to set by keeping undisturbed for 15 mints. The cups (10mm diameter) were punched in the Petri dish and filled with 0.05 ml of a solution of the sample. The plates were kept for diffusion at 40ºC for 1hr, and followed by incubation at 30ºC for 48 hrs. After the completion of incubation period the zone of inhibition in millimeter were measured. Along with the test solution in each petri dish one cup was filled up with solvent, which act as control. The zone of inhibition was recorded and compared with control.

Stability study

Stability studies of nail lacquers were carried out as per ICH guidelines. 40 ± 2ºC/75 ± 5% RH for 1 month. Then the samples were analyzed for non-volatile content, drying time, gloss, and smoothness of flow, drug content, diffusion and anti-microbial studies.

RESULTS AND DISCUSSIONS

Solubility study

From the study, the solubility profile of Itraconazole was insoluble in water, soluble in ethanol and methanol.

Determination of drug- polymer compatibility

The IR Spectra of Itraconazole, the mixture of drug with polymer are given in the figure. All the samples were scanned over the wave number region 4000-400 cm-1 using KBr disk method. The selected formulation shows the characteristics peak similar to that obtained in the pure Itraconazole indicating that there were no incompatibility between the drug and the excipient used (Fig-1 and 2).

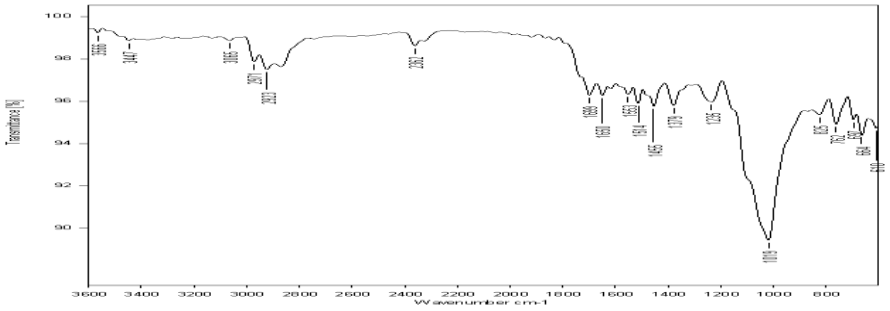

Fig-1 IR spectra of Itraconazole

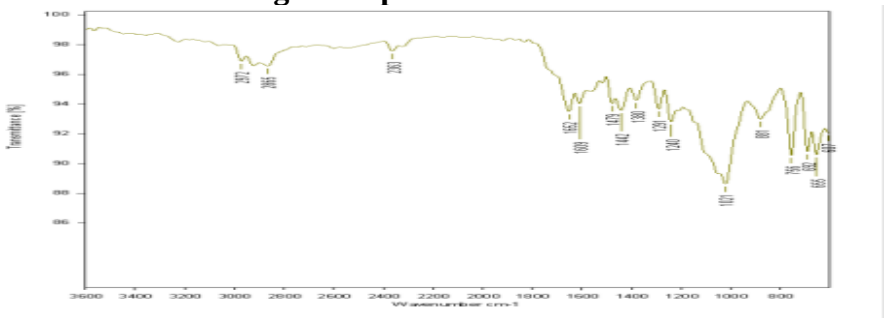

Fig-2 IR spectra of Physical mixture

EVALUATION OF NAIL LACQUER (3-8)

Physical appearance

The physical appearance of F1-F6 was carried out for their clarity, gloss and smoothness to flow. All the preparations were clear, smooth and evenly dispersed. F1-F3 showed good gloss and F4-F6 showed very good gloss. The results were compared with that of marketed product (Table-2).

Table-2 Physical appearance of nail lacquer

FORMULATION CODE	CLARITY	GLOSS	SMOOTHNESS TO FLOW
F1	Clear	++	Smooth, evenly dispersed
F2	Clear	++	Smooth, evenly dispersed
F3	Clear	++	Smooth , evenly dispersed
F4	Clear	+++	Smooth, evenly dispersed
F5	Clear	+++	Smooth ,evenly dispersed
F6	Clear	+++	Smooth ,evenly dispersed
Marketed product	Clear	++++	Smooth ,evenly dispersed

(++) GOOD, (+++) VERY GOOD, (++++) EXCELLENT

Non Volatile Content

The non-volatile content was found to be in the range of 20-21% for F1-F6. Non – volatile content increases with increase in polymer concentration (Table-3).

Drying Time

Drying time of the lacquers was found in range of 62-64sec. Drying time increased with increase in polymer concentration (Table-3).

Water Resistance

Formulations F1-F6 showed water resistance in the range of 5.11 g - 5.40 g. Higher the increases in weight lower the water resistance (Table-3).

Percentage Drug Content

The drug content was found to be in acceptable range for all the formulations indicating uniform distribution of drug. The percentage drug content of formulations varies from 96-98% (Table-3).

Table-3 Non Volatile Content, Drying Time, Water Resistance, % Drug Content

FORMULATION CODE	NON VOLATILE CONTENT (%)	DRYING TIME(sec)	WATER RESISTANCE(g)	% DRUG CONTENT
F1	20±0.25	62±0.45	5.11	96.18±0.15
F2	20±0.36	62±0.67	5.14	96.35±0.35
F3	20±0.48	62±0.89	5.18	96.56±0.56
F4	21±0.09	64±0.13	5.32	98.25±0.25
F5	21±0.22	64±0.24	5.36	98.45±0.55
F6	21±0.34	64±0.36	5.40	98.74±0.65

DRUG RELEASE

Diffusion studies of all the formulations were carried out using artificial membrane (cellophane membrane -0.8µm) for 24 hrs. Salicylic acid at concentrations of 10% (F1), 15% (F2) and 20% (F3) was tried out. The diffusion studies revealed that only 52.62%, 64.52%, and 65.18% respectively was released in 24 hours. It was clear that salicylic acid has improved the drug permeation due to its keratolytic activity. But it was also found that the drug permeation was not still complete and further increase in salicylic acid concentration is not expected to improve permeation. Hence it was decided to select 15% w/v of salicylic acid as the optimum concentration.

To sustain the drug release over an extended period it was decided to include a rate controlling polymer ethyl cellulose at concentrations of 0.25% (F4), 0.5% (F5) and 0.75% (F6) into formulations. The result showed an extended and complete drug release of 95.56% at 24th hr in F4, 98.36 % in F5 and 98.96% in F6. It was observed that further increase in the concentration of ethyl cellulose do not have much effect in the drug release. The formulation F5 was selected as the optimized nail lacquer formulation based on drug diffusion studies.

In vitro ungual permeation studies were carried out using bovine hoof membrane for F5 formulations (Fig-3-5).

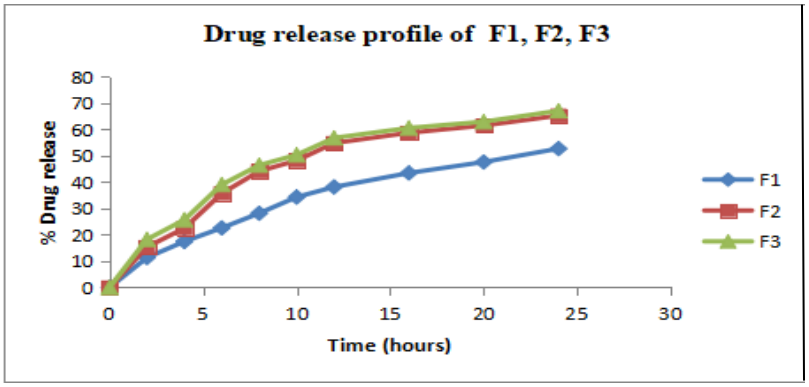

Fig-3 Drug release profile of F1, F2, F3

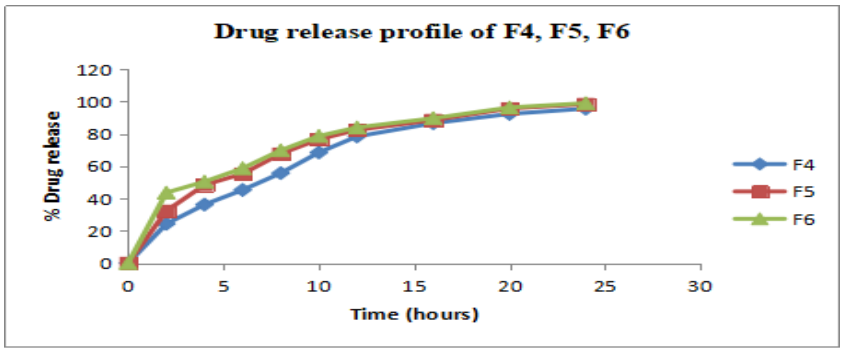

Fig-4 Drug release profile of F4, F5, F6

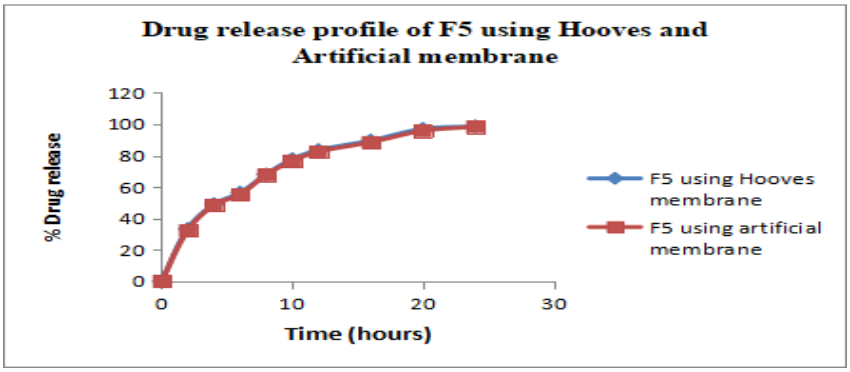

Fig-5 Drug release profile of F5 using Hooves and Artificial membrane

Zone of Inhibition

The zone of inhibition for the various formulations was determined, and it was found to range from 14-22mm, which is comparable with that of standard with 15mm. This indicates that all the formulations were sensitive to the microorganism Candida albicans.

Stability studies

The evaluation of formulations after stability charging showed there was no significant change with respect Physical appearance, Non -volatile content, Drying time, Water resistance, % drug content, drug diffusion and antimicrobial study with respect to results obtained before stability charging. Thus it was concluded that the formulations were found to possess stability compliance requirements as per ICH guidelines.

CONCLUSION

The objective of the present work was to formulate a medicated antifungal nail lacquer containing Itraconazole for the treatment of Onychomycosis. From the above studies, it can be concluded that medicated nail lacquers proved to be a better tool as a drug delivery system for the ungual drug delivery of an antifungal in the treatment of onychomycosis.

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