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# Formulation and Evaluation of Ketoconazole Nail Lacquer

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**ABSTRACT:** The present study was aimed towards the formulation and evaluation of medicated nail lacquer. The present work investigated the amount of Ketoconazole released fromdifferent formulations containing different concentrations of salicylic acid. These lacquers were compared for non-volatile content, drying time, glossiness, viscosity and in-vitro permeation study. The results obtained from in-vitrodiffusion studies showed that F3 have drug release of 98.56%. From diffusion studies, it was concluded that F3 has better permeation enhancement than F1 & F2.

**Keywords:** Medicated nail lacquer, permeation enhancers, Ketoconazole.

## I. INTRODUCTION

Fungal nail infection is commonly found in the world. Many antifungal drugs are given orally to treat the fungal infections. Azole derivatives are mostly preferred drug for the treatment. Topical therapy is highly desirable in treating nail disorders due to the localized effects, which results in minimal adverse systemic events & possibly improved adherence. The absorption of drug into nail unit, to the nail plate, is highly desirable to treat nail disorder; however, the effectiveness of topical therapies is limited by minimal drug permeability through the nail plate. Nail permeability quite lows & limits topical therapy to the fungal diseases like onchomycosis. In present investigation, nail permeation that focuses on altering the nail plate barrier by means of chemical treatment using Salicylic acid as a permeation enhancer for azole derivative is studied. Ketoconazole antifungal drug is used in the nail lacquer formulation. To avoid the side effects of the ketoconazole oral therapy, it can be derived through topical drug delivery systems. Nail lacquer will deliver the drug for a prolong time by forming a film on the affected part. Incorporation of permeation enhancers & polymer could increase the absorption of drugs through this hard-to-reach area. Nail lacquer containing ketoconazole drug could be a promising drug delivery system for treating fungal nail infection.

The purpose of the present investigation is to formulate and evaluate an ketoconazole nail lacquer for treatment of onchomycosis. A nail lacquer will be formulated, consisting of antifungal drug ketoconazole, film forming polymers like ethylcellulose, plasticizer like propylene glycol and other required additives. An attempt will be done to enhance the transungual drug permeation of Keoconazole using various concentrations of permeation enhancer.

## II. MATERIALS AND METHODS

**a) Materials**:

Ketoconazole was bought from Yarrow chemicals, Mumbai. Nitro cellulose and Ethyl cellulose, Ethanol were purchased from Kemphasol, Mumbai. Propylene glycol was bought from Otto kemi, Mumbai. Salicylic acid was bought from Nice chemicals Pvt. Ltd, Cochin.

**B)Methods:**

**Preformulation studies[1]**

**a) Soluboility studies:**

Saturated solubility of Ketoconazole was studied using 10ml of distilled water/acetone/chloroform/methanol.

**b) Melting point determination:**

Melting point of drug was determined by taking a small quantity of drug in a capillary tube sealed at one end and placed in melting point apparatus and temperature range at which the drug melted was noted.

**c) Determination of $\lambda_{max}$:**

100mg of pure ketoconazole was taken in a volumetric flask and dissolve in a little of phosphate buffer pH of 7.4 and madeupto 100ml (1

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mg/ml) concentrations was obtained. 10ml of the above solution was taken and further diluted to 100ml, the concentration of (10µg/ml) was obtained. 1ml of the above solution was taken and further diluted 10ml (10µg/ml) concentration was obtained. 1ml of the above solution was taken and further diluted 10ml, the concentration of (1µg/ml) was obtained. The final solution scanned for maximum absorption in double beam UV-Visible spectrophotometer in between the range of 400-200nm against phosphate buffer pH 7.4 as the blank.

**Analytical methods:**

**a) Preparation of standard stock solution & Calibration curve of Ketoconazole**

100mg of Ketoconazole pure drug was weighed and transferred into a volumetric flask. Then the volume was made upto 100ml with PBS of pH 7.4 to obtain standard stock solution of ketoconazole, having concentration 1000µg/ml.

Pipette out 10ml from the above solution and make up to 100ml with PBS and then it gives concentration 100µg/ml. Then pipette out 1ml from the above solution and make upto 10ml with PBS, it gives concentration of 10µg/ml. From the above aliquots of 1ml, 2ml, 3ml, 4ml, 5ml, was pipette out into another 10ml volumetric flask and made uupto 10ml with PBS of pH 7.4 to obtain a concentration range of 1µg/ml, 2µg/ml, 3µg/ml, 4µg/ml, 5µg/ml solution. This solution was analysed at 206nm by using UV- Visible spectrophotometer. A graph of concentration Vs absorbance was plotted. Drug content estimation and diffusion studies were based on this calibration curve.

**B) Determination of drug-polymer compatibility**

The FT-IR spectrum of pure Ketoconazole, Ethyl cellulose, and other polymers, Physical mixture of ketoconazole and polymers were analysed for their incompatability. The IR spectrum of drug and excipients were analysed in the range of 4000- 400 $cm^{-1}$. The values obtained in the spectra was compared with standard values.

**Formulation of nail lacquer of ketoconazole:**

The mixture of ethyl cellulose was dissolved in small amount of ethanol in the required quantity using a magnetic stirrer at a constant speed. To above clear solution required quantity of Salicylic acid and propylene glycol were mixed thoroughly and finally ketoconazole was added & this mixture was made upto 25ml with ethanol. The prepared nail lacquer was transferred to a narrow mouthed, plastic screw capped glass bottle.

Table 1: Formulation of nail lacquer

| Ingredients | F1 | F2 | F3 |
|---|---|---|---|
| Ketoconazole | 0.25g | 0.25g | 0.25g |
| Salicylic acid | 0.3mg | 0.5mg | 1g |
| Ethyl cellulose | 5g | 5g | 5g |
| Propylene glycol | 5ml | 5ml | 5ml |

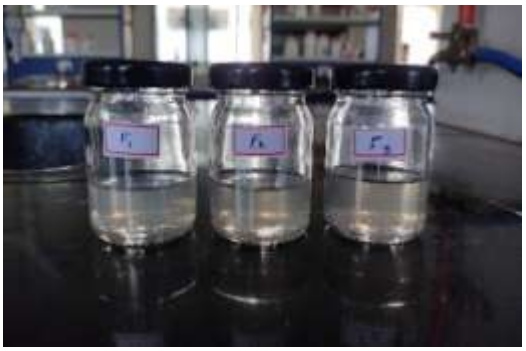

Fig 1: Formulated nail lacquer

**Evaluation of nail lacquer:**

**a) Non-volatile content[2]**

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

**b) Drying time[3]**

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.

**c) Smoothness to flow[4]**

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.

**d) Glossiness[5]**

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

**e) Viscosity[5]**

Viscosity was determined using Brookfield Viscometer; at room temperature using spindle no.3 at 20 rpm.

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**f) Water resistance[6]**

This is the measure of the resistance towards water permeability of the film. This was done by applying a continuous film on a surface and immersing it in water. The weight before and after immersion was noted and increase in weight was calculated. Higher the increase in weight lowers the water resistance.

**g) Drug content estimation[5]**

Nail lacquer equivalent to 200mg was dissolved in 50 ml phosphate buffer solution of pH 7.4. Then the solution was ultra-sonicated for 15mins. The resulting solution was filtered, made upto 100 ml with PBS of pH 7.4. Then the diluted solution was estimated spectrophotometrically at wavelength of 206nm and determined the drug content.

**h) Diffusion across artificial membrane[5]**

Diffusion studies were performed by Franz diffusion cell using artificial membrane. The membrane was soaked for 24hrs in solvent system and the receptor compartment was filled with solvent. Nail lacquer equivalent to 10mg 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℃ and the speed of stirring was kept constant 60rpm. The 5ml aliquot of drug sample was taken at specific time intervals of 30min, 1hr, 1.5hr, 2hr, 2.5hr, 3hr, 3.5hr, 4hr, 5hr, 5.30hr, and it was replaced by the fresh solvent to maintain sink conditions. Samples were analysed by double-beam UV spectrophotometer at 206nm wavelength.

Fig 2: Franz diffusion cell with magnetic stirrer

## III. RESULTS AND DISCUSSION

**Preformulation studies**

**a) Solubility studies**

The result of solubility characteristic of pure Ketoconazole is given below

| Solvents | Solubility |
|---|---|
| Dichloromethane | Freely soluble |
| Chloroform and methanol | Soluble |
| Ethanol | Sparingly soluble |
| Water and ether | Practically insoluble |

Table 2: Solubility studies of Ketoconazole

**b) Melting point determination**

The melting point was found to be 149℃ and as per the IP 2007 melting point of Ketoconazole was within the range of 148-152℃

**c) Determination of $\lambda_{max}$**

Pure Ketoconazole sample was scanned using phosphate buffer solution (PBS) of pH 7.4 between 200nm and 400nm using UV-visible spectrophotometer. The highestpeak of ketoconazole was obtained at 206nm and thus the $\lambda_{max}$ of Ketoconazole was fixed at 206nm and was used further spectrophotometric evaluations during the investigation.

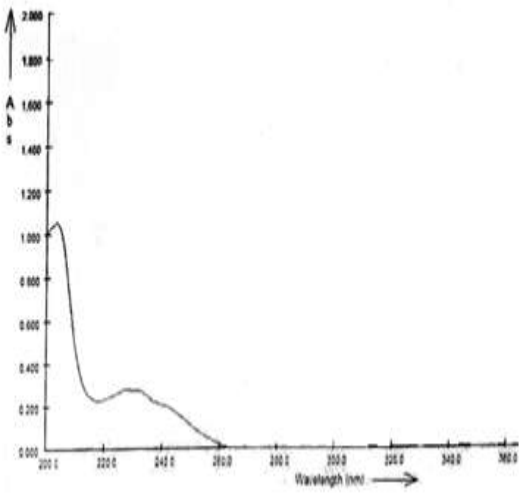

Fig 3: UV spectrum of Ketoconazole in phosphate buffer solution of pH 7.4

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**Analytical methods:**

**a) Preparation of standard stock solution & Calibration curve of Ketoconazole**

Standard solutions of Ketoconazole in different concentrations were prepared using phosphate buffer of pH 7.4 and their absorbance was measured at 206nm. Standard curve for Ketoconazole was plotted with drug concentrations vs. Absorbance.

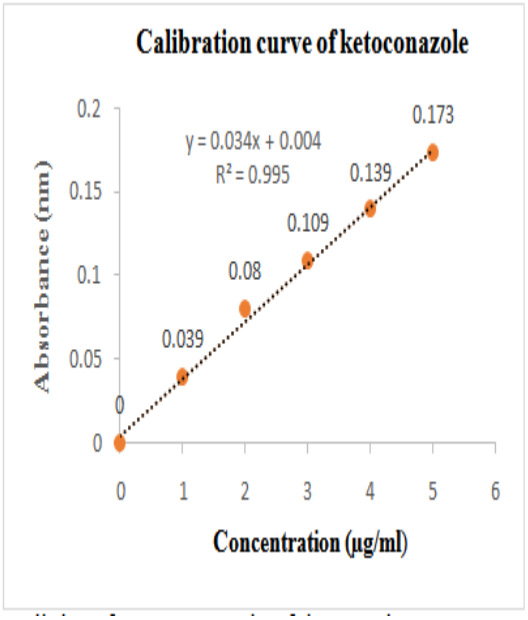


Fig 4: Calibration curve of Ketoconazole in phosphate buffer solution of pH 7.4

**b) Drug excipient compatibility study**

All the references IR peaks of the pure drug Ketoconazole were also present in the spectra of mixture of drug-polymer and drug-permeation enhancer-excipients. After spectral comparison it was confirmed that no incompatibility reaction took place between drug and excipients, as all major characteristic IR peaks of Ketoconazole are present in the physical mixture with individual excipients.

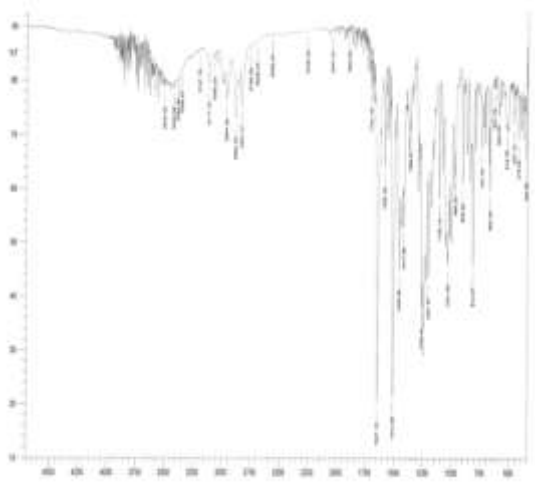

Fig 5:IR spectra of Ketoconazole

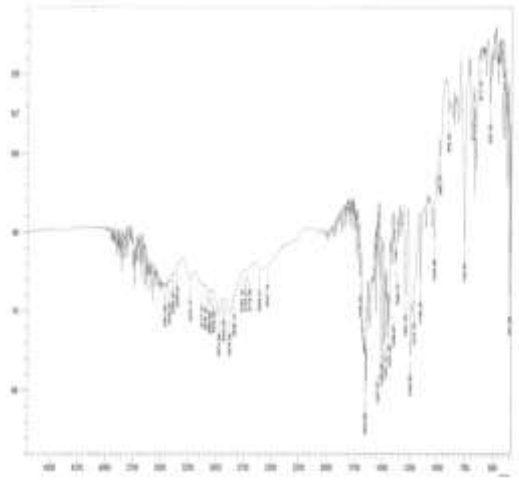

Fig 6: IR spectra of Ketoconazole + Ethyl cellulose + Salicylic acid

| Transition with IR Range ($cm^{-1}$) | Absorption wave number ($cm^{-1}$) | |
|---|---|---|
| | Ketoconazole | Ketoconazole +Ethyl cellulose+ Salicylic acid (Physical mixtures) |
| N-H stretch (3400 – 3250) | 3420.52 | 3384.84 |
| C-H stretch (3100 – 3000) | 3068.53 | 3078.18 |
| C=O stretch (1665 – 1760) | 1710.10 | 1696.28 |

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| | | |
|---|---|---|
| **C-C stretch(1600 – 1585)** | 1512.09 | 1600 |
| **C-N stretch (1335 – 1250)** | 1259.43 | 1291.25 |
| **C-O stretch (1320 – 1000)** | 1201.57 | 1212.8 |
| **C-Cl stretch (850 – 550)** | 814.87 | 759.90 |

Table 5: FTIR compatibility study interpretation

**EVALUATION OF NAIL LACQUER**

All formulations showed desired film formation, smoothness of flow was good. Desired amount of non-volatile matter (52.6 – 56.3) was seen with complete evaporation of volatile matter leaving a film. Drying time was found to be within 55-57 sec. All formulations showed rapid drying rate.

a) **Non-volatile content**

The non-volatile content of all formulations is gven below

| Formulation code | Non-volatile content (%) |
|---|---|
| F1 | 52.6 |
| F2 | 55.4 |
| F3 | 56.3 |

Table 6: Non-volatile content of nail lacquer

**b) Drying time**

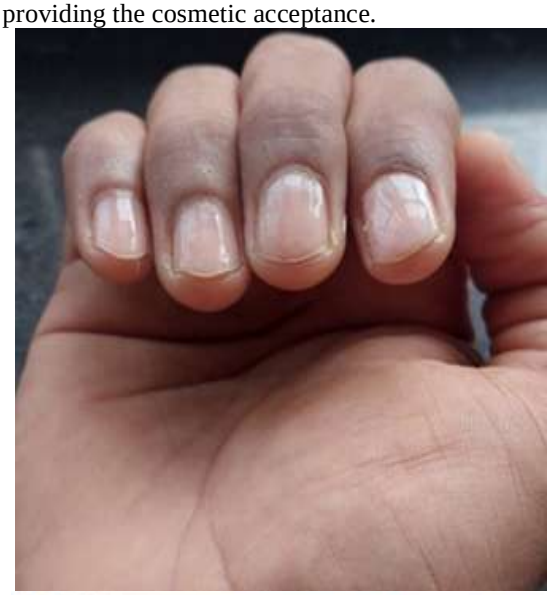
The drying time of all formulations is given below.

| Formulation code | Drying time (sec) |
|---|---|
| F1 | 55 |
| F2 | 57 |
| F3 | 56 |

Table 7: Drying time of nail lacquers

c) **Smoothness to flow and Glossiness**

Both these parameters were found to be satisfctory. The nail lacquer poured onto a glass plate was found to be spread and result in a uniform smooth film. The gloss of the applied lacquer was comparable with marketed cosmetic sample providing the cosmetic acceptance.



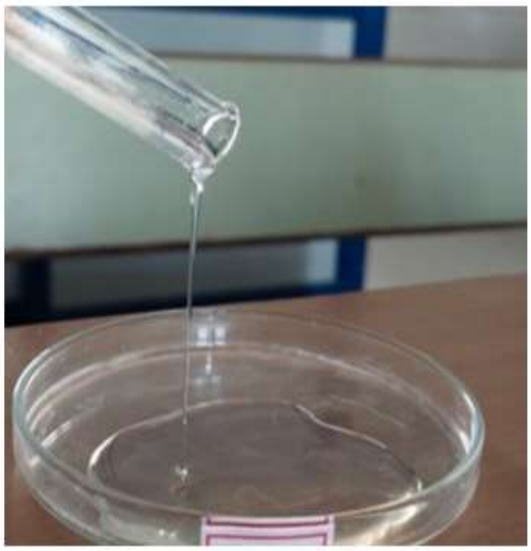


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Fig 7: Smoothness to flow and Glossiness of film

**d) Viscosity**

The viscosity of the sample ranged from 100 to 130 centipoises & it was observed that the product was clear and glossy. More over this viscosity range provided good adherence and flow property. Viscosity outside this range produces clouding and decreases gloss which will not be cosmetically acceptable.

| Formulation code | Viscosity (Cp) |
|---|---|
| F1 | 127 |
| F2 | 113 |
| F3 | 105 |

Table 8: Viscosity of nail lacquers

**e) Water resistance**

The weight before and after immersion was noted and increase in weight was calculated. Higher the increase in weight lowers the water resistance. F3 has comparatively low weight and has the better water resistance.

| Formulation code | $W_1$(g) | $W_2$(g) |
|---|---|---|
| F1 | 6.83 | 6.97 |
| F2 | 6.84 | 6.95 |
| F3 | 6.86 | 6.90 |

Table 9: Water resistance of nail lacquers

**f) Percentage drug content determination**

Percentage drug content for all the lacquers was found to be in between 95.37 – 98.56%. highest % of drug content was found to be 98.56% (F3) and the lowest % of drug content was 95.37% (F1). Drug content more than 90% in the formulation shows the high amount of drug present in the formulation, ensuring that the methods of formulation and the ingredients selected are not affecting the stability of drug. High drug content gives the assurance that, a good therapeutic outcome can be expected.

| Formulation code | Drud content (%) |
|---|---|
| F1 | 95.37 |
| F2 | 96.24 |
| F3 | 98.56 |

Table 9: Percentage drug content

**g) Diffusion studies across artificial membrane**

Diffusion studies of all the formulations were carried out using artificial membrane for 5.5 hrs. The diffusion studies were conducted on all formulation

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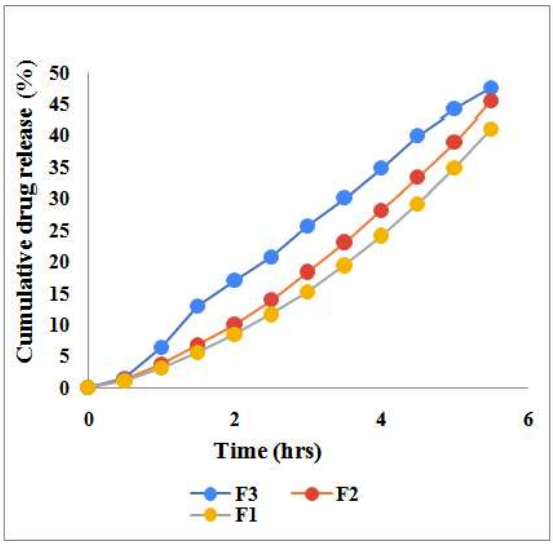

Fig 8:Percentage cumulative drug release

## IV. SUMMARY AND CONCLUSION

The nail lacquer formulation was prepared using Ketaconazole using simple mixing method for the treatment of Onchomycosis.

The permeability of drug enhanced by using the permeation enhancer (salicylic acid). The prepared medicated nail lacquer evaluated for Various parameters such as non-volatile content, drying time, smoothness of flow, gloss diffusion studies that show satisfactory results. From the FTIR studies, it was concluded that the drug and the excipients used in the formulations were compatible with the drug.

Optimised batch of nail lacquer F3 showed high permeability 47.57808% in 5.30hr, this formulation had salicylic acid at concentration of 1g as permeation enhancer. In-vitro drug diffusion of nail lacquer formulation showed required release in desired period of time. The F3 optimised batch has a Non-volatile content 52-57%, Drug content 98.56%, Drying time 52-60 secs.

It can be concluded that, the nail lacquer formulation containing ketoconazole is patient friendly and it is effective dosage form for treating fungal nail infection. Apart from treating the nail infections, the medicated nail lacquers can be also used for beautification of nails with ease of application. This improves patient compliance and acceptability.

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