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## FORMULATION AND EVALUATION OF PREUNGUAL DELIVERY SYSTEM CONTAINING EUGENOL FOR THE TREATMENT OF ONYCHOMYCOSIS

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### Abstract

The purpose of the study was to formulate a Preungual delivery system containing Eugenol for the treatment of Onychomycosis. And to find out the best polymer concentration, concentration of penetration enhancers and to carry out the anti-fungal testing on the best formulation obtained. The in vitro diffusion studies were carried out in Franz diffusion cell using phosphate buffer pH 7.4 and methanol as medium, whereas the permeation studies were carried out using hooves membrane. The percentage of cumulative drug released was determined by a UV spectrophotometer. The formulation containing 10% w/v of ethyl cellulose along with 2.5%w/v thioglycolic acid and 2.5 %v/v of dimethyl sulfoxide showed a good release. Eugenol nail lacquer's sensitivity against *Candida albicans* was determined by measuring the zone of inhibition by comparing it with a standard drug. The formulation showed a zero-order release pattern and the Higuchi model for the mechanism of release.




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### Introduction

The nail is a horny structure. Nail plate is responsible for penetration of drug across it. As it is hard enough, the penetration becomes difficult, only a fraction of topical drug penetrates across it. Hence the effective therapeutic concentration is not achieved. Topical nail preparation like lacquers, varnish, enamel etc. are generally used to impart colour and luster to nail [1]. Hence nail plate is thicker and harder because of the stable disulphide bonds which restrict drug penetration. Potential penetration enhancers can be used permeate formulations inside nail barrier [2]. For the enhancement of the nail penetration physical, chemical, and mechanical method are available. Mechanical methods like nail avulsion, nail abrasion [3] are invasive and potentially painful, while chemical methods are carried by keratolytic enhancers, keratinolytic enzymes and physical methods include carbon dioxide laser [4], electroporation, microneedle [5] etc. Apart

from the traditional formulation recent technologies like electro chemotherapy, mesoscissioning technology, Nano patch nail fungus are introduced in the development of more sufficient drug delivery. "Trans" means "through" and "Unguis" means "Nail", so transungual or preungual drug delivery system is nothing but a system associated with drug delivery through the nail to achieve a targeted drug delivery system of the nail to treat diseases of nail itself. The advantages of delivering the drug as preungual delivery as it avoids hepatotoxicity, high tissue concentration, high efficacy, sustained and optimised release of drug, better adherence of the formulation to nail. The preungual delivery system is used to treat the fungal infection of nail plate, Onychomycosis [6]. Onychomycosis is a fungal nail infection of the nail bed, this chronic infection caused by dermatophytes, yeast, mould. Those individuals with age older than 60, poor circulation, diabetes, repeated nail trauma and immunosuppressant bare more susceptible to onychomycosis [7]. A dermatophyte represents a group of three types of fungi that commonly cause skin disease in animals and human beings. This group consists of Epidermophyton and Trichophyton, Microsporum. However, Trichophyton rubrum is the number one responsible to cause fungal nail infection [8-9].



**Figure 1: Onychomycosis of fingers**

Both topical and oral agents are available for the treatment. Oral therapy for onychomycosis includes griseofulvin, terbinafine, itraconazole, and ketoconazole. But the disadvantages of the oral therapy include headache, gastrointestinal disturbance, rashes. Topical therapy are not usually effective against nail fungus hence nails are hard for external application to penetrate. The nail lacquers which are currently available are ciclopirox and amorolfine nail lacquers. when nail lacquers are applied to the nail provides a hard, clear, water resistant film containing the anti-fungal agent. The film is resistant to multiple washings and is effective in the treatment of onychomycosis [10]. Eugenol is lipophilic drug used to cure dentinal hypersensitivity a condition characterized by occurrence of pain. Disclosed dental composition comprising of eugenol and an effective amount of anionic liposomes [11].

**Materials and methods**

The studies were carried out by use of diverse range of chemicals. These chemicals from Research lab chem. industries, Mumbai, Ethyl cellulose was provided by HI media laboratories, Eudragit RL 100, Glycerine, Propylene glycol, Thioglycolic acid, DMSO, Ethyl alcohol, came from nice chemicals, cochin.

**Pre formulation Studies**

**Determination of solubility**

The Eugenol was dissolved in various solvents like water, methanol, ethanol to in excess quantity and analysed spectrophotometrically.

**Analytical Method [12]**

The UV spectrophotometry method was developed for the analysis of drug using double beam Shimadzu 1700 spectrophotometer.

**Determination of lambda max**

Eugenol dissolved in methanol and diluted with water, scanned for maximum absorbance in UV double beam spectrophotometer (12) (Shimadzu- 1700) in the range from 200 to 400 nm, using methanol-water mixture as blank.

**Standard Curve for Eugenol**

A series of solutions with different concentration range was prepared from stock solution and make up to 10ml with buffer solution. Linearity was observed in the concentration range of 5-50 µg/ml. calibration curve was prepared using absorption maxima method. By appropriate dilution of stock solution and scanned in the spectrum mode from 400 nm to 200 nm the max 280 nm was selected for the analysis.

**Drug excipients compatibility studies**

FTIR can be used to investigate and predict any physiochemical interaction between different excipients. A physical mixture of drug, polymer and other excipients were prepared and mixed with suitable quantity of potassium bromide. It was scanned from 4000 to 400 cm<sup>-1</sup> in a FTIR spectrophotometer (FT IR. Shimadzu). The IR spectrum of the physical mixture was compared with those of pure drug and polymer and peak matching was done to detect any appearance or disappearance of peaks.

Table 1: Formulae used for the development of Nail lacquer

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Eugenol (mg)	100	100	100	100	100	100	100	100	100	100
Polymer (mg)	100	100	100	100	100	100	110	100	100	100
Propylene glycol (ml)	10	10	10	10	10	10	10	10	10	10
Glycerine (ml)	10	10	10	10	10	10	10	10	10	10
DMSO (ml)	1.75	1.75	2.5	1.75	2.5	1.75	1.75	2.5	1.75	2.5
Thioglycolic acid (ml)	1.75	1.75	1	2.5	2.5	1	1.75	1	2.5	2.5
Ethanol (ml)	100	100	100	100	100	100	100	100	100	100

**Method of preparation**

Eugenol nail lacquer was prepared by simple mixing method and concentration (100mg) was kept constant. The formulations F0a and F0b contain the polymer ethyl cellulose and car RL 100 respectively. Among these two polymers the ethyl cellulose shows better film formation. So, the ethyl cellulose was selected for further studies. Formulations F1 F2, F3, F4 and F5 contained 10%w/v of ethyl cellulose along with the different concentrations of thioglycolic acid and dimethyl sulfoxide (1% to 25% v/v) whereas formulations F6, F7, F8, F9 and F10 contained 11%w/v of ethyl cellulose with different concentrations of thioglycolic acid and dimethyl sulfoxide (17 to 2.5%w/v).

The mixture of Eugenol and ethyl cellulose was dissolved in ethanol and mixed using magnetic stirrer. To this solution added glycerine, propylene glycol and required amount of penetration enhancer.

**Evaluation of prepared nail lacquer**

**Gloss**

Gloss of film was seen and compared to the marketed nail lacquer

### Water resistance

It is the measure of the resistance towards water permeability of the film, it was done by applying film on surface and drying the immersing in water

### Non-volatile content

Sample was taken in a glass Petri dish and it is spread equally. The dish was placed in the oven at 105° C for 1hr the Petri dish was removed, cooled, and weighed. The difference in weight of sample after drying was determined that gives the volatile content present.

### Drying time

A film of sample was applied on a glass Petri dish with the help of brush. The time to form a dry to touch film was noted using a stopwatch.

### Drug content

It was determined by dissolving accurately nail lacquer in ethanol. After suitable dilution absorbance was recorded by using UV-visible spectrophotometer (UV-1700, Shimadzu, Japan) at 280 nm.

Drug Content = (Concentration Dilution Factor Volume taken) Conversion Factor

### Diffusion studies across artificial membrane

Diffusion studies were performed using artificial membrane (cellophane). The membrane soaked in solvent was mounted on cell and whole assembly maintained at constant conditions for 12 hours. The drug analysis was done by using double – beam UV spectrophotometer.

### In-vitro transungual permeation studies

These studies were carried out by hooves membrane by using Franz diffusion cell. The prepared nail lacquer was applied on hooves membrane. Later drug analysis was done by using double beam UV spectrophotometer

### Determination of zone of inhibition

This was done by cup plate method. In this method a previously liquefied molten sabouraud dextrose agar media was inoculated with fungal suspension of *Candida albicans*. After complete solidification of liquefied inoculated medium, the wells were made aseptically with corn borer having 6mm diameter. In one plate formulation (nail lacquer) and in another plate pure drug solution was placed carefully. Plates were kept for pre diffusion for 30 minutes. After it was normalized to room temperature; the plates were incubated at 22-27°C for 72hrs.

### Stability studies

According to ICH guidelines at 40 ± 2°C/75+ 5% RH sample was stored in stability chamber for one month. The sample was evaluated for non-volatile content, drying time, gloss, and smoothness of flow, water resistance and diffusion across artificial membrane.

### Kinetic release studies [13-14]

For determination of drug release kinetics, the in- vitro permeation data were analysed by zero order, first order, Higuchi and Kosmeyer and Peppas's equations.

### Mathematical methods:

- **Zero order release kinetics**

Zero order release kinetics refers to the process of constant drug release from a drug delivery device such as oral osmotic tablets, transdermal systems, etc. zero order release can be represented as

$$Q=Q_0+K_0 t$$

- **First order release kinetics**

The rate laws predicted by the different mechanisms of dissolution both alone and in combination, have been discussed by Higuchi.

$$\text{Log } C=\text{Log } C_0-kt/2.303$$

- **Higuchi Model**

Higuchi tried to relate the drug release rate to the physical constants based on simple laws of diffusion. Release rate from both a planar surface and a sphere was considered. Higuchi was the first to derive an equation to describe the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion.

$$Q_t = kH (t)^{0.5}$$

## Results and discussion

Twelve formulations of antifungal nail lacquer using different concentration of ethyl cellulose and different concentrations of DMSO and thioglycolic acid was successfully prepared

### Solubility of Eugenol

From the solubility studies it was found that Eugenol is insoluble in water and soluble in organic solvents.

### Analytical Method Used in the Determination of Eugenol:

#### Determination of Lambda max

The max of the drug was found to be 280 nm.

#### Standard graph for Eugenol

#### Preparation of standard stock solution

100 mg of pure drug was dissolved in little volume of methanol and make up the volume to 100 ml with phosphate buffer of pH 7.4 to obtain concentration of 1 mg/ml.

#### Preparation of sample solutions

Series of solutions with concentration range of 5,10,15,20,25,30,35,40,45,50 ug/ml were prepared by pipetting 5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5,5 ml from stock solution and make up to 100ml with buffer. Linearity for detector response was observed in the concentration range of 5-50 µg/ml. calibration curve was prepared using absorption maxima method.

#### Absorption Maxima Method

By appropriate dilution of stock solution and scanned in the spectrum mode, the lambda max 280 nm was selected for the analysis. The calibration curve was prepared and the concentration of the sample solution can be determined

#### Linearity

It was evaluated by analysing different concentration of standard solution of Eugenol. The Beer Lambert's law was obeyed in the concentration range of 5-50 µg/ml with regression coefficient of 0.998.

#### Pre-formulation studies

##### FTIR Studies

The Fourier Transform Infrared spectroscopy studies were carried out for pure drug (Eugenol) and for the Eugenol-Polymer physical mixture. There were no changes in the major peaks of Eugenol in the presence of Ethyl cellulose and Eudragit RL 100. This revealed that the drug and the polymer are compactable with each other.

##### Evaluation of nail lacquer

##### Preliminary studies

The overall evaluation of the initially prepared formulation was carried out like colour, odour, overall appearance

**Gloss and Smoothness of flow**

The gloss of nail lacquer was satisfactory, smoothness of F1, F2, F3, F4, F5 was found to be good, whereas for formulation F6, F7, F8, F9, F10 were satisfactory.

**Water resistance [15]**

Formulations F1, F2, F3, F4 and F5 showed lower water resistance as compared to F6, F7, F8, F9 and F10.

**Non-volatile content [15]**

Non-volatile content depends and varies up on the concentration of polymer used.

**Drying time [15]**

The drug content of the formulated nail lacquer was estimated by Spectrophotometrically

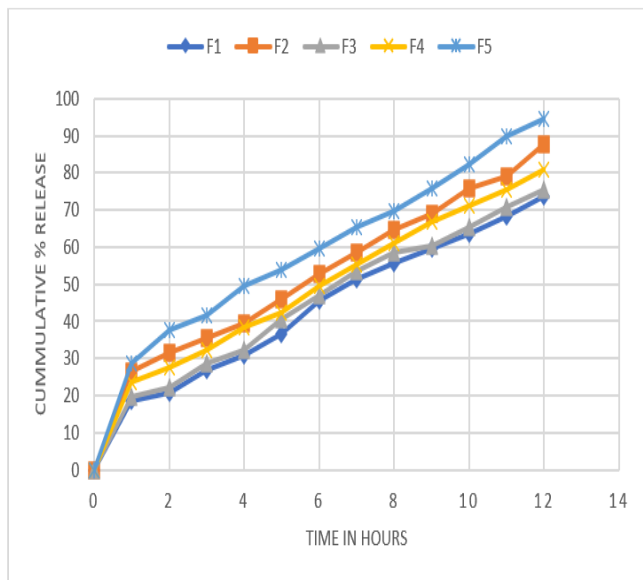
**In vitro drug release**

For in-vitro diffusion studies for formulation F1 to F10 formulation F4 containing lowest concentration of polymer. Whereas the formulation F6 containing the highest concentration of polymer. The percentage cumulative drug released for all 10 formulations ranged between 62.54 %-94.59 %. It was found that as the polymer concentration decreases and penetration enhancer concentration increases the release of the drug increases.

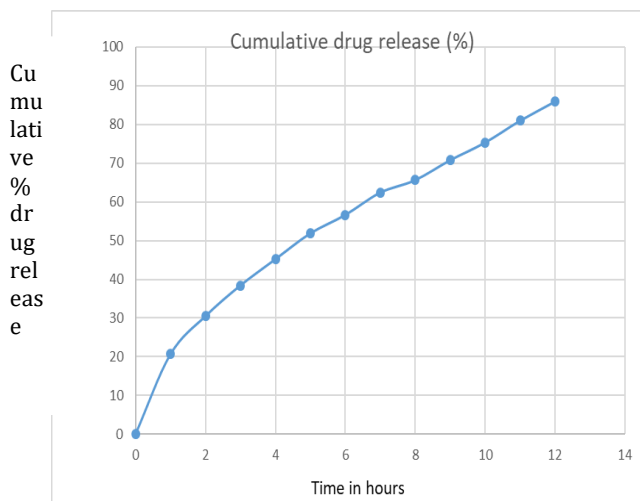
**In -vitro permeation studies**

From in-vitro permeation studies it was found that formulation F5 showed release of 85.90% at the end of 12 hours. From in-vitro diffusion studies and in-vitro permeation studies it was found that thioglycolic acid was proved to a better penetration enhancer as compared to dimethyl sulfoxide.

Time in hours	Cumulative drug release (%)
0	0
1	20.67
2	30.54
3	38.45
4	45.23
5	51.90
6	56.66
7	62.43
8	65.65
9	70.79
10	75.34
11	80.96
12	85.90



**Figure 2: comparison of in vitro %cumulative release profile of formula of F1-F5**



**Kinetics of drug release**

The results obtained from in vitro release studies were plotted in different kinetic models. The release kinetics data indicates that the release of drug from nail lacquer F5 best fits to zero order release model because the correlation-coefficient values are higher in case of zero order equation and the release from lacquer fits to Higuchi model.

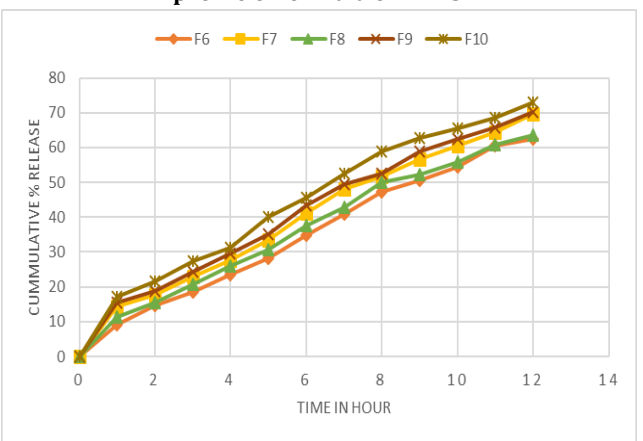
**Determination of zone of inhibition**

It was found that best formulation F5 was effective as pure drug as the zone of inhibition of best formulation was closer to that of zone of inhibition for pure drug.

**Conclusion**

The present investigation deals with the design and development of eugenol nail lacquer for the treatment of onychomycosis. Formulations were subjected to pre-formulation studies. Ethyl cellulose nail lacquer was chosen as the best from nail lacquer prepared from Eudragit RL 100 and ethyl cellulose.

Nail lacquers was formulated and subjected to physiochemical studies, in vitro studies, and permeation studies. The pH of the



**Figure3: Comparison of in- vitro % cumulative release profile formulation F6-F10**



formulation was found to be in range of 6.8 -7.4 which would not produce skin irritation.

The best formulation was found to be F5 which shows best release as it contains low concentration of polymer and high concentration of the permeation enhancers and it showed a release of 94.59% at the end of the in- vitro permeation studies. This result shows that polymer concentration decreases and penetration enhancer's concentration increases the release of the drug increase, also found that thioglycolic acid have better penetration enhancing effect comparing to the DMSO. The studies like determination of the zone of inhibition, kinetic data analysis, stability studies concluded that the nail lacquer are safe for topical delivery system for onychomycosis treatment.

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### Conflict of interest

Authors are declared that no conflict of interest.

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### Ethical consideration and inform consent

Not applicable

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