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# Development of Transungual Drug Delivery System for Topical Treatment of Onychomycosis By The Use of Griseofulvin a BCS Class II Drug

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**Abstract**

The main objective of this study is to develop a safer non-invasive treatment for nail infections since the current treatment regimen has drawbacks like, incidence of systemic side effects and higher cost. Proposed topical treatment on the other hand can drastically improve the situation, hence highly desirable. This work was undertaken with a hypothesis to develop a transungual microemulsion gel for topical treatment of onychomycosis.

**Keywords:** Nail; Fungal infection; Onychomycosis; Surgical

## Introduction

Nail (abnormal) infection is a common fungal infection of the nails or fingernails. It thickens, splits, breaks and breaks nails. The most unnatural infection clinically encountered is onychomycosis, mainly a chronic fungal infection of the nail bed and another nail plate. Fingernail infections can cause social, psychological or employment related problems [1]. About 50% of nail disorders are caused by onychomycosis, which is the most common nail disease in adults. The risk of nail infection is higher (4:1) [2]. The incidence of onychomycosis is increasing and diabetes, suppressed immune system and the elderly population are increasing. In fact, only 2.6% of children under the age of 18 reported having an asymptomatic infection, while 90% of the elderly were infected with onychomycosis [3-5].

Surgical removal of the fingernails is a very painful option, but systemic antifungal treatment is associated with high systemic toxicity and high cost of treatment [6]. In addition, the duration of treatment with oral antifungals can range from 3 to 12 months, depending on the progression of the disease. These limitations can be largely avoided by nail-adapting formulations and by delivering nail polish. However, there is no clinically effective delivery drug delivery system to overcome this problem, except for some limited success with nail lacquer of ciclopyrox. This is partly due to the uneven structure of the nail bed compared to the skin. While skin is primarily lipidal in nature, fingernails [7,8] have been reported to conform to hydrophilic gel layers with intermittent lipophilic channels. Therefore, an increase in normal skin penetration does not affect the nail bed. This leads to less disproportionate penetration of antifungals through the nail bed [9]. Microemulsions Promise Novel Drug Delivery Systems, Stability Profile, Drug Bioavailability, Elimination Mechanisms, Scale-Up Capacity and Focus on Pharma Pay Vision. They have been successfully recruited to provide hydrophobic and hydrophilic drugs for better pharmacodynamic use.

Therefore, the purpose of this study was to formulate a transparent microcellulation gel containing 1% grisulfulin to be applied directly through the fingernails at the site of the fungal infection, for topical bioavailability indicating appropriate drug use. Grisofulvin is insoluble in water and has intra-personal variation in large intra-personal and oral bioavailability [10,11]. This type of grisoflavin-loaded micromolecule system is expected to be clinically effective in better management of fungal nail infections with greater safety and efficacy.

## Materials and Methods

### Reagents and chemicals

Grisofulvin was supplied by yellow chem pharma productes, Mumbai. Benzyl alcohol, ethanol (absolute), isopropyl alcohol, acetone, isopropyl myristate, sesame oil, Pluronic F-68, sodium lauryl sulphate, glycerin, hydrochloric acid, dichloromethane, sodium hydroxide (pellets), disodium hydrogen orthophosphate, Tween 80, acetonitrile, methanol were supplied by Central drug house, Ltd. New Delhi, India.

### Preliminary studies

Many pre-preparation trials were performed on oils, surfactants and co-surfactants for melting test [12-15]. For the purposes of preliminary studies, various doses of oil, which deal with contact with water, were taken in the form of experiments and errors. All parts are weighted. Oil and water were mixed to form a surfactant - co-surfactant mixture to the end, e.g. after obtaining a clear clear microemulsion, 1% sonocrytallized drug was added directly to the formulation.

### Development of pseudo ternary diagram

Pseudo-ternary phase diagrams were constructed to examine the formation of microsolutions using four components: oil, surfactant, co-surfactant, and aqueous phase system (Figure 1). Benzyl alcohol and oil as IPM in precursor systems, surfactants pluronic F68, and ethanol aqueous phase and co-surfactant double-distilled water. These components were taken based on weight. A dummy ternary phase diagram was constructed to maintain the fluoronic F68 and ethanol (i.e. km-ratio) constant and the ratio of co-surfactant to the other two components separately. The kilometer ratio was determined at 1:1. Infection is detected in monophasic form. If clear and transparent microemissions were obtained after shaking, the samples were considered monophasic. The patterns are marked as points in the phase diagram. The area within these points is considered to be the microscopic field of existence. The final diagrams were drawn using the Origin 2020b software.

### Formulation

After the development of the phase diagram, six different formats were repaired by maintaining a total value of 100% structure and variability of system components. For each formulation, 1% Griseofulvin (topical dose) was added. But only four formulations took

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1% of the drug. For these four structures, experimental studies were conducted (Table 1).

### Formulation of microemulsion gel

Microemulsion obtained from the phase diagram was converted into microemulsion gel by adding 3% Carbopol 934P in the external phase. Clear transparent gel was obtained.

### Incorporation of permeation enhancers

The four stable microalgae gels formulated in this way enhance the nail permeation. Three permeation enhancers were selected, namely benzyl alcohol, urea and salicylic acid [16]. Benzyl alcohol is already in the formulations. Urea, salicylic acid and their combinations are given in Table 2.

## Evaluation of Microemulsion

### Drug content of microemulsion gel

The loading capacity of griseofulvin in a microemulsion gel was determined by spectrophotometric measurement of the wavelength of the maximum absorption (290 nm). Take one milliliter of microalvitation gel and mix 1 ml of acetonitrile, mix thoroughly and dilute 10 ml with acetonitrile. After filtration, the solution was diluted with acetonitrile, and the absorption of the final solution was checked against vacuum by means of a UV spectrophotometer (UV 1700, Shimadzu, Japan) at 290 nm. Of the loading capacity of the drug is then calculated.

### Drug entrapment efficiency

The drug entrapment efficiency (DEE) was found using the following formula (Table 3)

DEE=Amount of drug actually present / Theoretical drug load expected*100

### Drug release study

In vitro drug release studies used 900 ml cellulose acetate dialysis membrane (phosphate buffer, pH 7.4 containing 4% SLS. Dissolve medium for all layers 1 hour prior to use. The membrane was placed inside. The other side was properly bound and placed in a beaker with 900 ml of release medium. The tests were carried out for 2 h. The temperature was maintained at 32 ± $1^0$C throughout the experiment using a water bath. The alkate of one ml was withdrawn at different predetermined intervals as required. The diluents were prepared with 0.1N HCl, and the solvent was spectrophotometrically spaced at 290 nm (phosphate buffer, pH 7.4, containing 4% SLS and the 0.1N HCl mixture was analyzed in a ratio of 1:9 v). The same volume dilution medium was replaced after each extraction to maintain the sink position. According to this percentage, the release of the release drug is calculated.

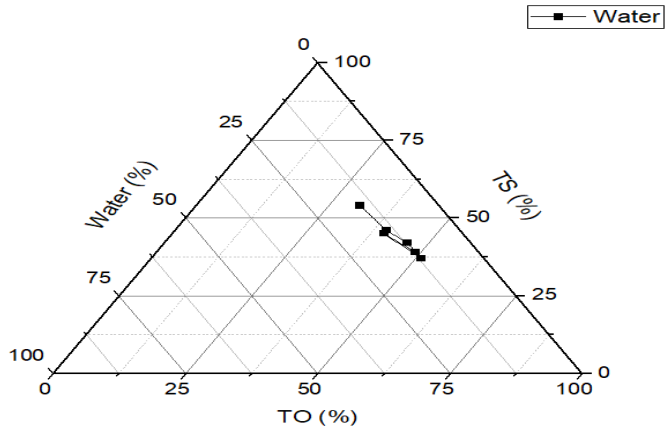


**Figure 1:** Pseudo ternary phase diagram, Km¼1:1 (clear region indicates the microemulsion.

| Formulation code | Total Oil (TO) | Total Surfactant (TS) | Water |
|---|---|---|---|
| F1 | 49 | 39 | 12 |
| F2 | 38 | 47 | 15 |
| F3 | 51 | 37 | 12 |
| F4 | 46 | 42 | 12 |
| F5 | 40 | 46 | 14 |
| F6 | 31 | 54 | 15 |

**Table 1:** Study of 1% drug uptake by micro emulsion.

| Permeation Enhancers | Code of Formulation | | | |
|---|---|---|---|---|
| Basic micro emulsion gel (MEG) | F1 | F3 | F4 | F5 |
| Basic MEG+5% urea | F1A | F3A | F4A | F5A |
| Basic MEG+5% salicylic acid (SA) | F1B | F3B | F4B | F5B |
| Basic MEG+5% urea+5% SA | F1C | F3C | F4C | F5C |

**Table 2:** Formulations after incorporation of nail permeation enhancers.

### Release kinetic study of formulations

Percentage drug release was plotted against function of time to study the pattern and kinetics of drug release. Different kinetic models namely zero order, first order, Higuchi, Hixon-Crowell and Korsmeyer–Peppas were studied.

### Drug Uptake Study By Nail Clippings

**Cleaning of nail clippings** [17]

Drug discovery research was done using healthy nail polish found in local beauty salons. The nail polish after collection is thoroughly cleaned by triple washing in successive versions of acetone and 0.6N HCl. After that they are rinsed in double tap water. Finally, it was dried at 37$^0$C for 24 hours and stored in a sturdy air container until used again.

### Drug penetration study

Wax blocks (Figure 2) were used to support the nails during the study process. The well was made on wax blocks where the measuring volume of the microalvasion gel was kept. Pre-woven nail clipping is placed on the dorsal side of the gel over this gel-well. The experimental setup was kept at 32 sets for 24 h.

### Extraction of drug from the nail clipping

After 24 hours, the nail polish was removed from the setting, and the nail surface of the nail was cleaned with tissue paper and weighed. The nails were then placed in 1ml of acetonitrile in a sealed tube and kept in RT for three days. After three days, the nail was removed and the extract was cleaned with acetonitrile as needed. The amount of drug that went into the pruning of the nails was measured with a UV spectrophotometer by 290 nm compared to blank. The location of each nail click is calculated explicitly. From this, % drug uptake/ mm$^2$ drug count is calculated.

## Results and Discussion

The goal was to develop a transgenic drug delivery system using two oils (benzyl alcohol and IPM), a surfactant (pluronic F68) and a co-surfactant (ethanol). The required dose of grisofulvin was successfully incorporated into the formulation by using fluoronic F68 as a surfactant in the ratio of 1:1 and benzoyl alcohol as the main ingredient in the complete ethanol as a co-surfactant. After developing the phase diagram, six formulations were prepared from the clear microalgae zone. Of these, only four formulations contained a complete 1% grisofulvin (topical dose). It has been found that load increases with increasing oil % in the formulation. This may be due to the increased percentage of benzyl alcohol in the highly soluble formula of the form drug. As the oil% increased and the time decreased, the resolution of the 1% drug incorporation in the empty microcalculation increased. The log separation coefficient (log p) of grisoflavin is 5.66 and the aqueous buffer solution of n-octanol at pH 8.1, which indicates the lipophilicity of the drug. Li drug can be highly trapped in the oil stage of any microorganism in view of its high lipophilicity. However, this oil is reported to be very insoluble in oils, and ri et al. In an interesting study, it was reported that the griseofulvin solubility in PEG400 was four times higher than that of castor oil 18. Therefore, it is advisable to classify grisofulvin as a hydrophobic drug rather than a lipophilic drug to emphasize its poor oil solubility. Due to this hydrophobic nature, the drug does not enter the oily phase or mix well with the aqueous phase of the microcommination and is in an intermediate position, i.e. the snake molecules of the microlemming structure. At the polyside layer inside. It has been observed that as a result of such a condition, the migration of benzyl alcohol toward the aqueous phase destroys the microgummation structure and causes the precipitation of the drug 18. But in developed formulations, the outer phase benzyl alcohol and surfactants make up a significant portion of the total microfluidic composition of the shale. Offers, and there is no possibility of immigration and therefore .drug is not even. No rain or microfluidic breakdown was observed. This may be due to the good stability of the benzyl alcohol-based micrometers we have developed, which contradicts previous reports stating instability in the presence of benzyl alcohol.

Released studies of formulations have shown that 100% of the drug is released within 60-120 minutes from all formulations tested. As the oil percentage of the micro emulsion increased, the secretion of the drug from the formulations slowed down. With 46% oil, a full release of 60 min was observed for F4 (Figure 3), and a very late F3 of 120 min showed 51% oil (data not shown). From the study of release kinetics, it was found that the aggregates did not follow a constant release sequence and obtained both zero-order and first-order dynamics for different aggregates. Korsmeyer-Peppas release exponent (N) indicates the

| Code of Formulation | Total Oil (TO) | Total Surfactant (TS) | Water | Drug Content (mg) | DEE (%) |
|---|---|---|---|---|---|
| F1 | 49 | 39 | 12 | 9.23 | 88.46 |
| F3 | 51 | 37 | 12 | 9.05 | 90.68 |
| F4 | 46 | 39 | 15 | 9.34 | 93.24 |
| F5 | 40 | 46 | 14 | 9.07 | 91.69 |

**Table 3:** Drug content and DEE of formulations.

**Figure 2:** Wax blocks used for nail uptake study.

presence of both expansion and controlled second order (zero order) to operate on different aggregates (Table 4). The nail barrier is very difficult to penetrate through the drug molecules, forming the most challenging drug molecules [16-18]. Therefore, to overcome the nail barrier, nail permeation enhancer is used to penetrate of the drug through the high keratinized nail plate [19]. In the developed formulations, benzyl alcohol was used as nail permeation enhancer, urea and salicylic acid nail softening agents. The use of nail polishing agents can help to soften the nail and increase nail permeability to work. Urea significantly increases nail hydration, and salicylic acid is a keratolytic agent that also regulates the pH of the formulation. Therefore, urea and salicylic acid alone cannot increase nail permeation but are used as adjunct to nail permeation enhancers.

Nail permeability depends on many factors, of which, nail hydration and hence inflammation is very important. In addition, water is said to be the best plasticizer for nails. As nail hydration increases, the permeation flux of molecules in the nail plate also increases. Other important factors are the molecular weight of the molecule, the pH of the formulation, and so on. In this study, it was found that micro emulsion F4 increases the nail permeation of Griseofulvin because of the highest water content of this formulation among all four microemulsions finally investigated.

Among the nail softening agents, F4 showed the highest drug penetration of 0.416%/mm2 (42 µg of drug), compared with a combination of 5% salicylic and 5% salicylic acid and 5% urea in the preparation of 5% urea. These studies lasted for 24 hours, so the result obtained was satisfactory. Therefore, the goal of developing a microevolution system of Griseofulvin for transitional deliveries was rapidly achieved. The F4 formulation was optimized because it showed the highest DDE of 93.24%, releasing 100% of the drug in 60 minutes, and the improved drug drug produced by nail clippings, similar to other formulations (Figures 4 and 5).

## Conclusion

The microemulsion gel ensures bio-adhesion on to the nail plate for enhanced residence time, thereby promoting nail permeation. The typical structure and composition of the optimum microemulsion formulation simultaneously helps in hydrating the nails and utilize

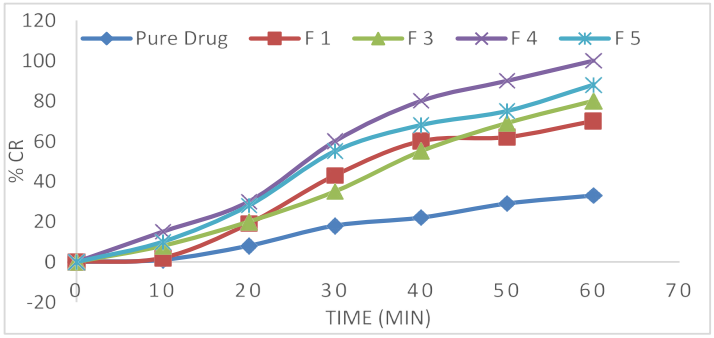


**Figure 3:** Comparison of release profile of F1, F3, F4, F5 and pure drug in 60 min.

| Code | Zero order ($R^2$) | First order ($R^2$) | Hixon-Crowell ($R^2$) | Higuchi ($R^2$) | Korsmeyer-Peppas | |
|---|---|---|---|---|---|---|
| | | | | | (N) | ($R^2$) |
| **F1** | 0.915 | 0.914 | 0.649 | 0.956 | 0.544 | 0.964 |
| **F3** | 0.934 | 0.906 | 0.633 | 0.942 | 1.545 | 0.907 |
| **F4** | 0.905 | 0.969 | 0.591 | 0.936 | 1.25 | 0.964 |
| **F5** | 0.968 | 0.928 | 0.725 | 0.937 | 0.649 | 0.937 |

**Table 4:** Coefficient of determination ($R^2$ ) of the release kinetic models.

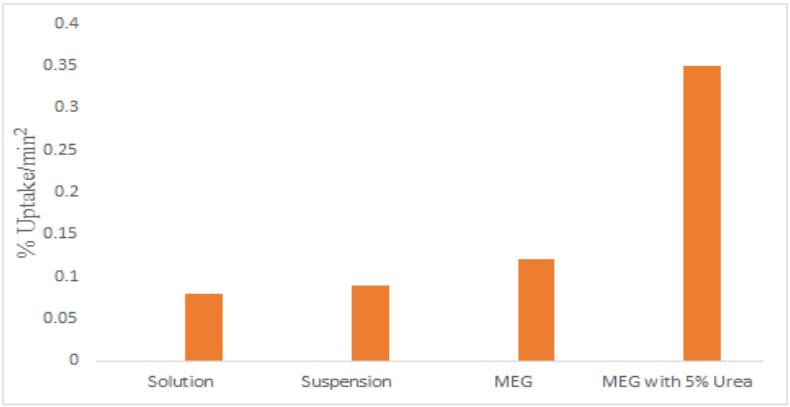


**Figure 4:** Comparison of nail uptake study of formulations showing effect of % oil and permeation enhancers.

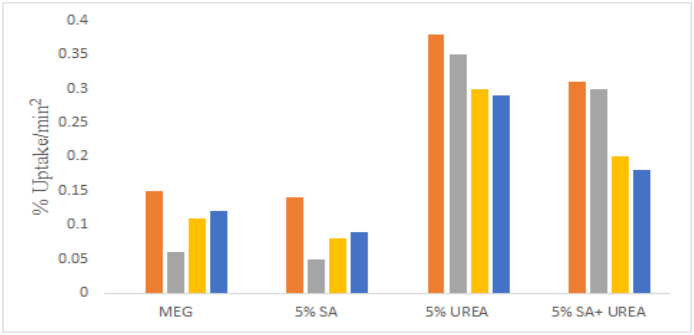


**Figure 5:** Nail uptake study with optimized formulation in comparison with drug solution and suspension.

the lipoidal channels for higher permeation through the nail plate as well as entrap and ferry larger quantity of Griseofulvin transungually. Therefore, the developed formulation offers the advantage of higher bioavailability at the site of action and optimum drug loading through transungual route, avoiding high dose systemic therapy for the treatment of onychomycosis. The microemulsion gel is expected to provide the clinicians with a new choice of an economic, safe and efficient regimen in the management of onychomycosis.

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