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ANTIFUNGAL GLYCEROGELATIN: ATTEMPT AT FORMULATION AND EVALUATION OF A POTENTIAL TRANSUNGUAL DRUG DELIVERY SYSTEM

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ABSTRACT: Onychomycosis representing about 30% of mycotic cutaneous infections is the fungal infection that affects the nails. Although not life-threatening, it adversely affects the psychology of the patient whose nails become yellow, discolored, brittle, and unsightly. It may also pose serious problems in immunocompromised individuals. The current market of products for the treatment of onychomycosis includes topical antifungal gels, creams, medicated nail lacquers, and oral antifungals in the form of tablets. Other techniques like nail etching, use of microneedles & mesoscissioning are being studied. The authors propose the formulation and evaluation of glycerogelatin for an effective transungual delivery. Glycerogelatin are semisolid dosage forms comprising of glycerine, gelatin, water and drug which upon heating to temperatures slightly above body temperature melt and can be applied over the affected area. These upon cooling harden, cover the area and release the drug. The authors propose the use of HPMC for an effective glycerogetin formulation. This research article is an attempt to bring into the limelight the potential of glycerogelatins for transungual drug delivery.

INTRODUCTION: Onychomycosis, which is a fungal infection affecting the nail plate, was a poorly discussed topic of medical science in the 1990s. It, however, has been highlighted in recent times [1]. Onychomycosis representing 20-40% of onychopathies and 30% of mycotic cutaneous infections [2] has been said to affect approximately 5% of the world population [3]. It has been regarded as the most common disorder in adults [4]. In India, many workers have reported an incidence of onychomycosis ranging from 0.5-5% [5, 6].

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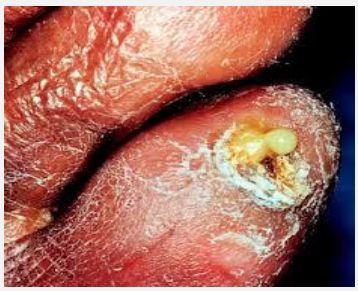
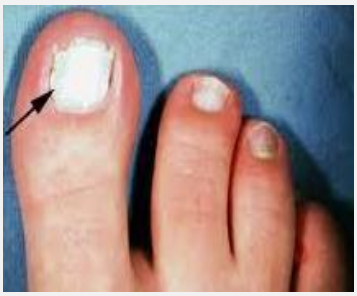
Onychomycosis, which is generally caused by dermatophytes like *trichophytons*, a few non dermatophytes & yeasts [1] requires the use of antifungal agents for treatment. Topical antifungal agents have been preferred due to their localized effects and improved adherence [7].

Topical treatments display improved patient compliance by reducing the adverse effects associated with systemic delivery and reduced cost [8]. The recent trends in transungual delivery include exploring the vistas of techniques like mesoscissioning [9], iontophoresis [10,] and also the use of penetration enhancers. The polyethylene glycols have been studied for their penetration enhancement ability in transungual drug delivery and displayed positive results while using iontophoresis [11]. Penetration enhancers can play a promising role also in topical drug delivery.

A high throughput method for screening efficient penetration enhancers has been proposed and named TranScreen-N [12].

Clinical Categorization of Onychomycosis: Onychomycosis has been clinically classified [13] as demonstrated in **Table 1**.

TABLE 1: CLINICAL CATEGORIZATION OF ONYCHOMYCOSIS

S. no.	Clinical Category	Depiction
1.	Distal and Lateral Subungual Onychomycosis a) Onychomycosis at the distal and lateral areas of the nail plate b) Superficial Onychomycosis c) Total Dystrophic Onychomycosis	 Fig. 1: a) Distal & Lateral Onychomycosis  c) Total Dystrophic Onychomycosis
2.	Superficial White Onychomycosis	 Fig. 2
3.	Proximal Subungual Onychomycosis	 Fig. 3

Glycerogelatin: Glycerogelatin are masses usually containing 15% gelatin, 40% glycerin, 35% water, and 10% medicinal substance. These are suggested to be formulated by heating gelatin and water until the gelatin dissolves, then adding to it the medicinal agent mixed in glycerin and allowing the mixture to cool until it is congealed. Zinc gelatin is an official glycerogelatin used for treating varicose ulcers [14].

Objective of the Research: The present research attempts to formulate and evaluate a glycerogelatin modified by the addition of HPMC for transungual drug delivery. The authors intend to draw the attention of researchers towards the formulation of glycerogelatin for effective management and treatment of onychomycosis.

MATERIAL AND METHOD:

Materials Used: The materials used in the formulation of antifungal glycerogelatin are listed below in **Table 2**.

TABLE 2: MATERIALS USED FOR FORMULATION OF TRANSUNGUAL GLYCEROGELATIN

S. no.	Material	Source
1.	Fluconazole	Bal Pharma Ltd.
2.	Gelatin	Finar Chemicals Ltd.
3.	Glycerine	Finar Chemicals
4.	HPMC	Arora & Co (Chemical division)
5.	Methanol	Finar Chemicals Ltd.
6.	Distilled Water	From laboratory

Method: The work was carried out in 2013 at Devsthali Vidyapeeth College of Pharmacy, Rudrapur.

Different formulations using different concentrations (2 mg, 4 mg & 6 mg) of HPMC were first prepared and inspected for physical appearance. The glycerogelatin formed using 4mg concentration was found to be best in terms of appearance and application on melting. Thus, this formulation was prepared and subjected to evaluation.

The materials and method used in preparing the glycerogelatin, along with its evaluation parameters, are further discussed.

Procedure for Preparation of Antifungal Glycerogelatin:

1. Gelatin 5 mg was first heated with water until it dissolved.
2. HPMC in the required amount was added in the above solution followed by 2 ml of water. Glycerine was then added when the temperature had decreased to some extent.
3. Fluconazole was separately dissolved in a minimum quantity of methanol for forming a solution.
4. The above solutions were then mixed.
5. The final mixture formed in step 4, was stirred until congealed to form the desired glycerogelatin.

The Formula for Preparation of Glycerogelatin: Fluconazole glycerogelatin was prepared using HPMC and the method prescribed above. The formulation chart is shown below in **Table 3**.

TABLE 3: FORMULATION CHART OF TRANS-UNGUAL GLYCEROGELATIN

S. no.	Material	Quantity
1	Fluconazole	500 mg
2	Gelatin	5 mg
3	Glycerine	5 ml
4	HPMC	4 mg
5	Methanol	q.s
6	Distilled Water	5 ml

Evaluation Parameters for Prepared Fluconazole Glycerogelatin:

1. **Physical Characterization:** The formulated glycerogelatin was visually inspected for overall appearance.
2. **Detection of Melting Point:** This was performed with the aid of a capillary tube and regular laboratory melting point detector.
3. ***In-vitro* Diffusion Studies:**

The Use of Animal Hoof: The animal hooves have already been used as alternatives to human nail plate as in the case of a study performed using porcine hoof [15]. The transungual drug delivery of an antifungal microsponge has also been performed using goat hooves [16]. A Franz diffusion cell was used to perform the present study. The regular method was used [17] except for the use of goat hooves in place of animal skin. The goat hoof was first soaked overnight in phosphate buffer 6.8 for softening it to ease section cutting. Thin sections of the softened hoof were then cut, dried slightly and then mounted in between the compartments of the Franz Diffusion cell of 25 ml capacity. A Franz Dissolution Apparatus has been depicted in **Fig. 4**.

FIG. 4: FRANZ DIFFUSION APPARATUS

500 mg of glycerogelatin sample was taken and applied on the section of the goat hoof. The reservoir compartment was filled with phosphate buffer of pH 6.8.

The study was carried out at 37 ± 1 ºC, and speed was adjusted such that the vortex touched the nail plate. The study was carried out for 2 h. 1 ml of sample was withdrawn from the reservoir compartment at 30 min interval, and each withdrawn ml was replaced with fresh phosphate buffer pH 6.8. The samples were analyzed Spectrophotometrically at 260 nm.

Preparation of Standard Curve of Fluconazole: 100 mg of fluconazole was dissolved in 100 ml of methanol in a volumetric flask to form a solution of 1mg/1ml.

This standard solution was then used to prepare solutions containing 10, 20, 30, 40 and 50 micrograms per ml of drug in methanol. The absorbance of the samples against methanol as blank was taken spectrophotometrically at 260 nm.

RESULT AND DISCUSSION:

1. **Physical Characterization:** The glycerogelatin formed was slightly hazy in appearance and was smooth.

2. **Melting Point:** The melting point ranged between 41-43 ºC.

3. **The Standard Curve of Fluconazole:** The calibration curve of fluconazole, along with the UV spectroscopy data, has been represented in **Table 4** and **Fig. 5**.

TABLE 4: UV SPECTROSCOPY ANALYSIS OF FLUCONAZOLE

S. no.	Concentration (in µg/ml)	Absorbance
1	10	0.231
2	20	0.446
3	30	0.619
4	40	0.802
5	50	0.807

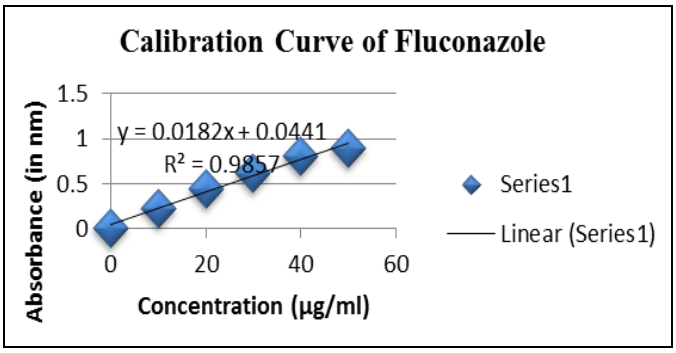


FIG. 5: GRAPH DEMONSTRATING CALIBRATION CURVE OF FLUCONAZOLE

4. **The *in-vitro* Study:** The results of the *in-vitro* study are listed below in **Table 5** and **Fig. 6**.

TABLE 5: *IN-VITRO* ANALYSIS USING UV SPECTROSCOPY

S. no.	Time (in min)	Absorbance	Drug concentration (in µg/ml)	Drug concentration in 25 ml of phosphate buffer (in mg)	% CDR
1	30	0.232	10.44	2.60	13.52
2	60	0.301	14.27	3.56	32.03
3	90	0.414	20.55	5.13	58.71
4	120	0.463	23.27	5.81	88.9

The prepared Fluconazole glycerogelatin showed a drug release of 88.9% in 2 h.

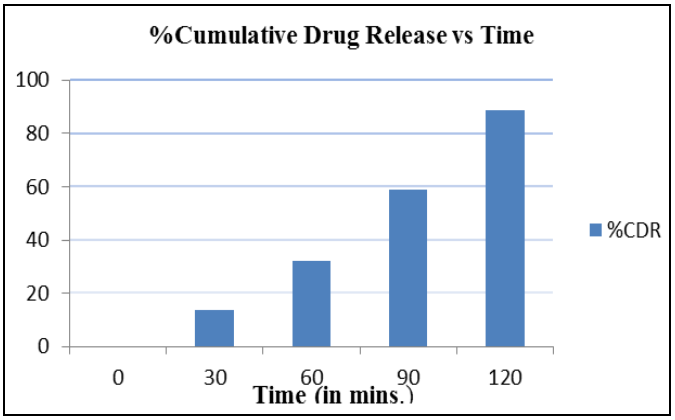


FIG. 6: GRAPH DEPICTING % CDR WITH TIME

CONCLUSION: Topical transungual formulations are effective in the management and treatment of onychomycosis. These, however, have shown to perform better with the use of appropriate penetration enhancers.

Topical glycerogelatin thus can emerge as potential transungual drug delivery systems if carefully worked upon and formulated as effective, sustained release formulations for better patient compliance. These are easy to apply and can remain adhered to the nail plate for a long period. Glycerogelatin are also not very expensive. These in the future can be modified using the novel drug delivery techniques to control the rate of drug release as desired and help combat onychomycosis.

The authors want to draw the attention of researchers towards transungual drug delivery and the potential that lies in glycerogelatin.

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CONFLICT OF INTEREST: Nil

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