



UNGUAL DRUG DELIVERY SYSTEM OF KETOCONAZOLE NAIL LACQUER

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ABSTRACT

The purpose of the present investigation was to formulate and evaluate the ketoconazole nail lacquer as unguinal drug delivery system for the treatment of onychomycosis. Topical therapy of nail diseases is limited by the poor permeability of the nail plate. So far, only a few unguinal enhancers, thought to act by reducing the disulphide bonds in nail plate cystine, such as thioglycolic acid (TA) and urea hydrogen peroxide on their permeation, have been identified and thereby increase nail plate permeability to topically applied Ketoconazole drug. *In vitro* drug permeation studies were carried out across human nail plates using Franz diffusion cells. The dorsal surface of nails was pretreated with a chemical thioglycolic acid and urea H2O2 for a period of 24 hours. Concurrently, the permeation of thioglycolic acid and urea H2O2 through the nail clipping was also monitored by UV spectroscopy. Ketoconazole movement was found through nail clippings in the presence of thioglycolic acid and urea H2O2 is compared. The % of drug permeated at 24h through the nail clippings was 92.10 ±0.08 and 84±0.04 for Ketoconazole with thioglycolic acid and urea H2O2 respectively. As can be seen, significantly higher permeation was achieved in the presence of thioglycolic acid. These preliminary studies indicate that thioglycolic acid is more enhance agent compare to urea H2O2 of ketoconazole drug for the treatment of onychomycosis.

Keywords: Ketoconazole, Onychomycosis, Thioglycolic acid

INTRODUCTION

Ketoconazole is a broad spectrum synthetic antifungal agent of the imidazole class, which contains two nitrogen atoms in the five-membered azole ring. Its chemical name is *cis* -1-acetyl-4-[4-[[2-(2,4-dichloro-phenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy] phenyl] piperazine. Ketoconazole was used as a model drug, which is an anti-fungal agent with topical and systemic action that can be incorporated into several pharmaceutical forms¹. It is a recent synthetic triazole antifungal agent used in the treatment of superficial and systemic fungal infections such as, tinea corporis, tinea cruris, tinea manus and tinea pedis caused due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Microsporum canis* and for the treatment of seborrheic dermatitis².

The present invention relates to a formulation for treating fungal infections. More specifically, this formulation is a topical formulation for use on fingernails and toenails. Many people have fingernails or toenails with fungus underneath. Still others have nails that are extremely thick even approaching approximately 1 inch in thickness. Still others have yellowed or discolored nails³. Some have combinations of the above-mentioned conditions. Some medications available for treating these unsightly conditions are not able to kill fungal infections underneath the nail because they are not able to penetrate the nail⁴. Still other medications cause the nail to become brittle. In addition, other medications simply do not work. Therefore, many people are unable to remove these unsightly conditions. In order to overcome the disadvantages of medications currently available, a formulation that is able to penetrate the nail to kill fungus without permanently damaging the nail is needed⁵. This formulation should be able to be applied topically. The human nail is an excellent barrier against the ingress of foreign material, but as a consequence it also prevents effective topical treatment of unguinal disorders such as onychomycosis⁶. When infection resides in the nail plate, nail bed, or both, therapeutic antimicrobial drug concentrations must be achieved in the nail bed for treatment to be effective. However, this is difficult to achieve because the permeation of agents into the nail is low. Permeation occurs via passive diffusion with the rate determined by the physicochemical properties of the compound. Unfortunately, the most efficacious treatments for nail disorders do not penetrate the nail plate in sufficient amounts to be clinically effective.

The aim of this investigation was to further examine the physical properties of both membranes with the means of well-known unguinal

penetrates enhancers, i.e. urea H2O2 and thioglycolic acid was chosen as a model of a small and water soluble drug.

MATERIALS AND METHODS

Ketoconazole sample was purchased from m/s SMS Pharmaceuticals Ltd., Hyderabad, Polyethylene glycol 400, Thioglycolic acid, Urea and hydrogen peroxide(H2O2), was purchased from S.D. Fine Chemicals Mumbai. Glycerine and Ethanol from was purchased Merk India Ltd, Mumbai. Other chemicals used where analytical grade.

Nail lacquer is prepared in four different formulations. In all four formulations the weight of Ketoconazole (1gm) is kept constant. In formulations F1 and F2 the enhancer used is thioglycolic acid and in the formulation F3 and F4 the enhancer used is urea solution in which 1gm urea is dissolved in 1ml of hydrogen peroxide. These formulations are prepared and dissolved thoroughly. It is show in table 1

- The concentration 1% and 10% w/w UREA H2O2 or THIOGLYCOLIC ACID
- The concentration 1% and 25% w/w propylene glycol
- The concentration 1% and 15% w/w glycerin
- The concentration 1% and 25% w/w ethanol
- The concentration 1% and 80% polyethylene glycol 400 and active agent ketoconazole

Table 1: Formulation Batches for F1 to F5

Ingredients	Formulations code				
	F1	F2	F3	F4	F5
Propylene glycol	1ml	12.5ml	1ml	12.5ml	1ml
Glycerine	1ml	7.5ml	1ml	7.5ml	1ml
Ethanol	1ml	12.5ml	1ml	12.5ml	1ml
Polyethylene glycol 400	1ml	40ml	1ml	40ml	1ml
Thioglycolic acid	1ml	5ml	--	--	1ml
Urea Solution(1gm in 1ml H ₂ O ₂)	--	--	1ml	5ml	1ml

All formulation has 1 gm of ketoconazole

EVALUATIONS

Nonvolatile content⁷

1gm of sample was taken in a glass Petri dish of about 8cm in diameter. Samples were spread evenly with the help of tared wire.

The dish was placed in the oven at 105°C for 1 h. The Petri dish was removed, cooled, and weighed. The difference in weight of sample after drying was determined.

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.

Smoothness of flow

The sample was poured to approximately 1.5 inches and spread on a glass plate and made to rise vertically.

Gloss

Gloss of the film was visually seen, comparing it with a standard marketed nail lacquer.

Human Finger Nails

The whole nail tips were obtained from the fingers and toes of healthy adults using nail clippers (IRB protocol # 1001). The nail plates having a thickness of about 400 µm were used for the studies. The thickness of nail plates used for a set of test and control experiments were within 5%. The nail plates were washed, dried, and stored in desiccator until use. Prior to use, the nail plates were soaked for 6 h in the donor compartment buffer. This was done to hydrate the nail plate to impart flexibility and to avoid breaking of nails during mounting on to the diffusion cell set up.

In vitro transungual permeation studies

In vitro transport studies were carried out using Franz diffusion cells (Logan Instruments Ltd., Somerset, NJ) respective volume 25 ml, were performed by using Franz diffusion cell at $37 \pm 5^\circ\text{C}$ and phosphate buffer (pH 7.4) fitted with a custom made Teflon nail holder. Drug solution equivalent to 100 µg prepared in buffer was placed in the donor compartment. The receiver compartment was filled with phosphate buffer (pH 7.4) volume was 25 ml. The active diffusion area was 0.25 cm². The receiver compartment was stirred at 600 rpm with a 3-mm magnetic stir bar. Intermittent samples of 2 ml were drawn from the receiver compartment at 2 h intervals for 36 h and the amount of Ketoconazole transported was measured. Equal volume of fresh buffer was replaced in the receiver compartment followed by each sampling. The drug analysis was by using double-beam UV/Vis spectrophotometer, analytical model VSB-082 at 224 nm.

RESULTS AND DISCUSSION

It is an object of the present invention to provide a formulation for killing fungus on or underneath toenails or fingernails so that the appearance of the nails is improved. It is a further object of the present invention to provide a method of administering a topical nail formulation so as to rid a person of a nail fungal infection⁸. According to the present invention, the foregoing and other objects are achieved by a topical formulation for treating fungus on or beneath toenails and fingernails.

This formulation includes a penetrate enhancers of urea hydrogen peroxide, thioglycolic acid and an antifungal agent. The formulation is topically applied to a patient's fingernail or toenail to treat a fungal infection or to thin an overly thick nail. Additional objects, advantages, and novel features of the invention will be set forth in the description that follows and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

The nail formulation excluding polymer was omitted as the nail formulation showed tackiness, the film formation was brittle, dull, and with poor spread ability. Although the formulation containing polymer showed good results, out of 36 formulations, best 5 were chosen on the basis of their film formation, smoothness of flow, drying time, gloss, and nonvolatile content. The drug release was seen by using artificial membrane.

From the above studies, it can be concluded that medicated nail lacquers can be used as a tool for the transungual drug delivery system in the treatment of onychomycosis. The purpose of the present investigation was to formulate and evaluate the Ketoconazole as a perungual drug delivery system for the treatment of onychomycosis. The penetrate enhancers within the concentration range of 1% and 5% (w/v) in the nail lacquers. Then, these lacquers were compared for glossiness, film formation, drying rate, smoothness of flow, and nonvolatile content.

A topical anti-fungal agent alone is generally unable to cure nail diseases because of insufficient nail plate penetration. The understanding and knowledge of hydration effects on nail permeability may be useful clinically and cosmetically in topical treatment of nail disorders.

In the project nail lacquer is prepared in four different formulations. In all four formulations the weight of Ketoconazole (1 gm) is kept constant. In formulations F1 and F2 the enhancer used is thioglycolic acid and in the formulation F3 and F4 the enhancer used is urea solution in which 1 gm urea is dissolved in 1 ml of hydrogen peroxide.

The thioglycolic acid and urea solutions used are taken in different concentrations in the formulations. In F1 the volume of thioglycolic acid used is 1 ml and in F2 it is 5 ml. In F3 the volume of urea solution used is 1 ml and in F4 it is 5 ml. In vitro diffusion studies were conducted using diffusion cell for 36 hrs.

By the experiment we conclude that urea shows slow release than thioglycolic acid. Formulation F4 which contains urea solution as enhancer (volume 5 ml) shows very slow release of drug and formulation F1 which contains thioglycolic acid as enhancer (volume 1 ml) shows high release of drug. The percent drug releases of F1, F2, F3, F4 and F5 in 36 hrs were 90.54%, 96.37%, 81.92%, 84.04% and 93.41% respectively it show in table 2. It was observed that out of the 5 nail formulation (F1, F2, F3, F4, and F5) F4 showed good release of the drug. In *in vitro* transungual permeation experiments, F5 also showed good release of the drug the drug release study show in fig 1.

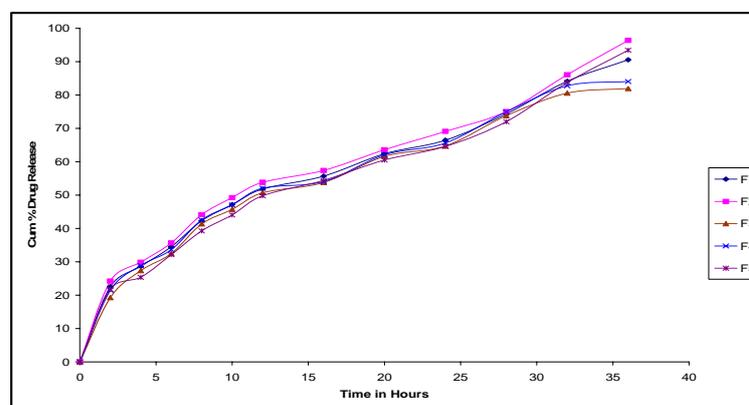


Fig. 1: Drug release data of selected five formulations

Table 2: It Shows Comparative Percentage Drug Release from Various Formulations of Ketoconazole

Formulations Code	Time in hrs											
	2	4	6	8	10	12	16	24	20	28	32	36
F1	22.53	28.61	34.5	42.3	47.14	51.8	55.66	62.38	66.43	74.35	84.11	90.54
F2	24.23	29.86	35.65	44.11	49.24	53.8	57.37	63.59	69.07	75.02	86.06	96.37
F3	19.23	27.32	32.45	41.34	45.69	50.67	53.76	61.6	64.72	73.78	80.54	81.92
F4	21.45	28.86	33.62	42.54	47.04	52.05	54.04	62.05	65.6	74.94	82.76	84.04
F5	21.73	25.34	32.15	39.27	44.03	49.8	54.39	60.5	64.57	72.00	83.72	93.41

CONCLUSIONS

The chosen penetrate enhancers have varying mechanism in enhancing the permeation of ketoconazole. Urea hydrogen peroxide enhances hydration state; Thioglycolic cleaves the disulphide bonds between keratin molecules. The release study of ketoconazole were for Urea hydrogen peroxide as can be shown from the low values of ketoconazole for compare to the thioglycolic acid and thioglycolic acid and urea peroxide both combination about 3 times more enhancement could already be observed at 5% concentration. The data presented herein demonstrates the potential use of such penetrate enhancer systems with ketoconazole in the topical treatment of onychomycosis. The pre-treatment durations reported in this study were also considerably long (36hrs) but again it is anticipated that future optimization and formulation of the penetrate enhancers.

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