RESEARCH ARTICLE

Preungual drug delivery systems of Terbinafine Hydrochloride Nail Lacquer

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The purpose of the present investigation was to formulate and evaluate the terbinafine hydrochloride nail lacquer as preungual drug delivery system for the treatment of onychomycosis. Terbinafine hydrochloride was chosen as the model drug, and the formulations were prepared with and without polymer Eudargit RL 100 (Eu) within the concentration range of 1% to 5% (w/v) in the polymeric system. Then, these lacquers were compared for glossiness, film formation, drying rate, smoothness of flow, and nonvolatile content, The *in vitro* studies were preformed on the artificial membrane and bovine hooves in solvent A (phosphate buffer, pH 7.4; and methanol, AR grade, in the ratio of 4:1). The result obtained indicated that the nail lacquer formulation F2 (1.3% of the drug and 1.3% of Eudargit RL100) showed good release of the drug. Thus nail lacquers can be used as a successful tool for targeted drug delivery for onychomycosis.

Key words: *Onchomycosis, nail lacquer, preungual drug delivery.*

INTRODUCTION

Onychomycosis (tinea unguium) is a fungal infection of the nail bed or nail plate. It accounts for approximately 50% of all nail diseases and is the most common disorder in adults.[1] Most of the infections (90% - 95%) are caused by dermatophytes, the rest being caused by yeasts and molds.[2] Infected nails appear slightly discolored, thickened, and dystrophic. Among superficial infections, onychomycosis is the most difficult to manage and eradicate and it tends to recur.[3] Surgical avulsion was the only treatment for onychomycosis; since the procedure is extremely painful and traumatic,[4] it has been replaced by systemic and topical therapy.[5] Oral antifungal drugs like itraconazole, miconazole, and ketoconazole have been used in the treatment of onychomycosis.[6] Due to severe side effects such as drug interactions and relapse, oral therapy has been less accepted.

Conventional nail lacquers have been used as cosmetics since a long time for beautification and protection of nails. Nail lacquer can be used as a drug delivery system for the drugs that exhibit poor oral bioavailability.[7] The topical formulations conventionally used in dermatology (creams, oil-based lotions, powders) are not specifically adapted to the nail since they are readily removed by rubbing, whipping, and washing; and their impermanence at the site of application readily accounts for their inefficacy.[8] Medicated nail lacquers are formulations that are used for transungual drug delivery system for maximal antifungal efficacy. It has been reported that the film on the nail surface acts as a drug depot that permits optimized and sustained diffusion across the nail and leads to continuous penetration of active principle to high tissue concentration required for the efficacy for the treatment of onychomycosis.[9] Medicated nail lacquers which have been reported for the treatment of onychomycosis contain Amorolfine (5%) and ciclopirox (8%).[10]

The present study was conducted to evaluate and formulate the terbinafine hydrochloride nail lacquer for the treatment of onychomycosis. Terbinafine was selected as a model drug. Terbinafine hydrochloride is a synthetic lipophilic antifungal agent and tends to accumulate in skin, nails, and fatty tissues. After oral administration, it is well absorbed (>70%), with a peak plasma of 1 μg/mL after 2 h with a single dose of 250 mg.[11]

MATERIALS AND METHODS

Terbinafine hydrochloride (Cipla Ltd., Pharma R and D, Vikroli (W), Mumbai, India) and Eudargit RL 100 (Degussa India Pvt. Ltd., Research Centre, Mumbai, India) were obtained as gift samples. All other chemicals used were of analytical grade.

Preparation of nail lacquer formulations

The mixture of terbinafine (1%) and Eudargit (1% to 5%) were dissolved in the solvent system containing ethyl

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acetate, ethyl alcohol, triacetin, and nitrocellulose in the ratio of 5:8:3:1. The formulations were prepared excluding Eudargit. The compositions of various formulations are given in Table 1.

Evaluation

The formulations were evaluated for the following parameters:[12]

Nonvolatile content

1 ± 0.2 g of sample was taken in a glass Petri dish of about 8 cm in diameter. Samples were spread evenly with the help of tared wire. The dish was placed in the oven at 105°C ± 2°C for 1 hr. After 1 hr 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.

In vitro studies

Diffusion studies across artificial membrane

Diffusion studies were performed using artificial membrane (Gelman Laboratory) of pore size 0.2 μm. The membrane was soaked for 1 h in solvent system A (phosphate buffer, pH 7.4; and methanol, AR grade, in the ratio of 4:1), and the receptor compartment was filled with solvent A. Test vehicle equivalent to 200 μg 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°C, and the speed of stirring was kept constant (600 rpm) for 7 h. The 2-mL aliquot of drug sample was taken after a time interval of 1 h and was replaced by the fresh solvent A. Each experiment was replicated at least thrice. The drug analysis was done using double-beam UV spectrophotometer, model V-530 (Jasco Corporation, Japan).

In vitro transungual permeation studies

Hooves from freshly slaughtered cattle, free of adhering connective and cartilaginous tissue, were soaked in distilled water for 24 h. Membranes of about 1-mm thickness were then cut from the distal part of hooves. *In vitro* permeation studies were carried out by using Franz diffusion cell (respective volume, 25 mL), the hoof membrane was placed carefully on the cell, and the surface area available for permeation was 1.23 cm^2. Then the test vehicle equivalent to 200 μg was applied evenly on the surface of the nail membrane. The receptor compartment was filled with solvent A (phosphate buffer, pH 7.4; and methanol, AR grade, in the ratio of 4:1), and the whole assembly was maintained at 37°C with constant stirring (600 rpm) for 30 h. The 2-mL aliquot of drug sample was taken after a time interval of 1 h and was replaced by the fresh solvent A. Each experiment was replicated at least thrice. The drug analysis was done by using double-beam UV spectrophotometer, model V-530 (Jasco Corporation, Japan).

Table 1: Formulations containing 1% w/v of terbinafine hydrochloride nail lacquer

Formulations	EudargitRL100 % w/v	Triacetin % w/v	Ethylalcohol % w/v	Nitrocellulose % w/v	Ethylacetate % w/v
F1	1.3	5.1	51.1	10.39	28.5
F2	1.3	6.1	51.1	10.39	28.5
F3	1.3	12	51.1	10.39	28.5
F4	1.3	6.1	31.1	12	25.5
F5	1.3	6.1	41.1	10.39	25.5
F6	1.3	6.1	51.1	12	28.6
F7	3.8	6.1	51.1	10.39	28.6
F8	3.8	6.1	51.1	10.39	25.5
F9	5.1	6.1	51.1	10.39	28.6
F10	5.1	6.1	51.1	7.9	28.6
F11	1.3	6.1	51.1	7.9	28.6
F12	1.3	6.1	31.1	12	28.6
F13	1.3	6.1	51.1	7.9	28.6
F14	-	5.1	51.1	10.39	28.6
F15	-	6.1	31.1	12	33.7
F16	-	12	41.1	7.9	25.9
F17	-	5.1	51.1	10.39	25.9
F18	-	5.1	51.1	7.9	28.5

RESULT AND DISCUSSION

Table 1 and Figures 1 and 2 demonstrate the drug release data from all the nail formulations. The nail formulation excluding polymer was omitted as the nail formulation showed tackiness; the film formation was brittle, dull, and with poor spreadability. Although the formulation containing polymer showed good results, out of 13 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. It was observed that out of the 5 nail formulations (F1, F2, F3, F4, F5), F2 showed good release of the drug. In *in vitro* transungual permeation experiments, F2 also showed good release of the drug.

The data presented indicate that the drug is influenced by factors like:

A) Formation of dry film after evaporation of volatile components
B) Drug diffusion and drug partitioning within the nail membrane

Nail membranes, although more permeable than human nails and less selective towards permeants, are the commonly accepted model for human nails and in *in vitro* testing of medicated nail lacquers.[13] When compared to human nails, they have less dense keratin network that, when incubated in water, swells to a large extent - a behavior possibly due to a significantly lower content of half-cystine and disulphide linkages with respect to human nails.[14] The nail plate behaves like a concentrated hydrogel to permeating molecules and diffusion of molecules of non-electrolyte through polymer gels. Thus for optimal ungual permeation, drug molecules must be of small in size and carry no electric charge on them.

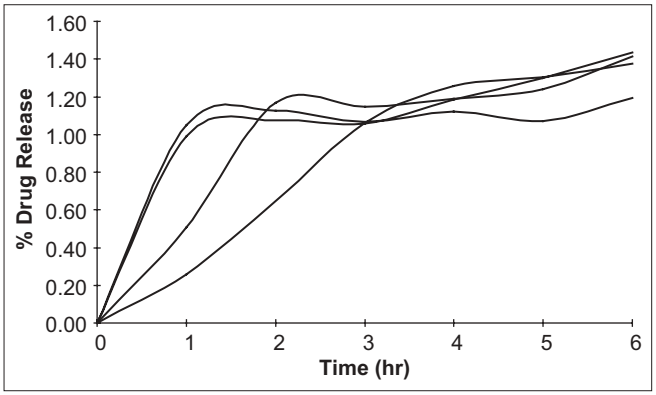

Figure 1: Drug release data of selected five nail formulations

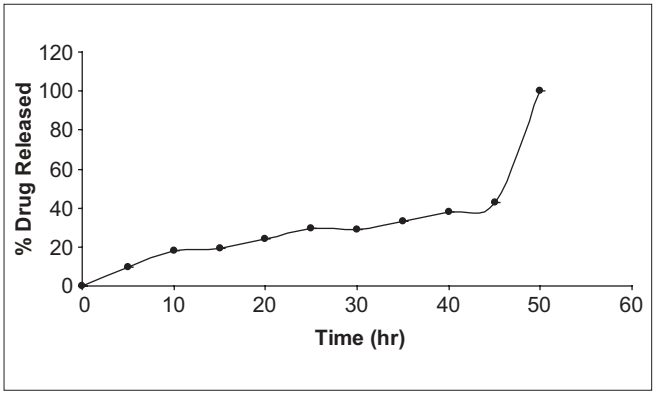

Figure 2: Permeation of optimized F2 nail formulations through hoof membrane

Nail lacquers containing drugs are an exciting new type of dosage form. Like cosmetic nail varnish, they are applied on to the nail plate using a brush. The organic solvents evaporate off, and a polymer of the film permeates into the nail plate. Drug concentration in the lacquer; nature of the lacquer components, e.g., solvents; frequency of application to the nails; and the duration of treatment have been found to influence the permeation of the drugs into the nails and the treatment outcomes.[15]

The two nail lacquers licensed for use in the treatment of onychomycosis, Loceryl® and Penlac®, are easy and convenient to use, are well tolerated, and few adverse events have been reported. Nail lacquers seem to be the vehicle of the future when topical products for the nail are desired.[16]

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 terbinafine hydrochloride lacquer as a preungual drug delivery system for the treatment of onychomycosis. Terbinafine was chosen as a model drug, the formulations were prepared with and without polymer Eudargit RL 100, within the concentration range of 1% to 5% (w/v) in the polymeric system. Then, these lacquers were compared for glossiness, film formation, drying rate, smoothness of flow, and nonvolatile content.

The *in vitro* studies were performed on the artificial membrane and bovine hoof in the solvent A (phosphate buffer, pH 7.4; and methanol, AR grade, in the ratio of 4:1).

The result obtained indicated that the nail lacquer F2 containing 1.3% of drug and 1.30% of Eudargit RL 100 showed good release of the drug. It can hence be concluded that nail lacquers can be used as a successful tool for targeted drug delivery for onychomycosis.

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