FORMULATION AND EVALUATION THE TRANSUNGUAL DRUG DELIVERY SYSTEM OF FLUCONAZOLE WITH PENETRATION ENHANCER: *IRESINE HERBESTII*

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**ARTICLE INFO**

**Article history**
Received 17/12/2015
Available online 29/02/2016

**Keywords**
Penetration Enhancer, Transungual.

**ABSTRACT**

The present study was to formulate a transungual drug delivery formulation. We targeted to formulate and evaluate fluconazole film for the nail fungal infection using extracted natural and evaluated penetration enhancer (PE). Model drug fluconazole was formulated with the natural extracted penetration enhancer with different ratios. The solvent for PE extraction was methanol and that extracts were air dried. The cadaver nail plates for study were collected from the same volunteer for negligence in the thickness and chemical composition concentration in the nail plate. The extracted PE (*Iresine herbestii*) was inspected in the respect of stability before formulation. The human cadaver nail plates were treated with the formulation with and without the extracted PEs. Ex-vitro drug penetration rate was evaluated by Franz diffusion cells using cadaver human nail plate up to 36 hours. The drug filmability was best with the polymer HPMC K4M, Ethyl cellulose and hydroxyl propyle cellulose in the ratio of 1:1:1, mixture of propanol and butanol in 7:3 as solvent and 30% w/w DBP as plasticizer. The formula FT25AI4 shows 89% drug entrapment and 47% more drug penetration across the nail plate when compare to the same formulation but without any penetration enhancer. The “p” value (0.0011) of drug penetration was less than 0.05.

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INTRODUCTION

Two main diseases affect the nail unit: onychomycosis and psoriasis. Treatments of these two diseases usually lead to poor patient compliance. Indeed, due to the lack of penetration of topicaly applied drugs into the nails, long term systemic treatments resulting in side effects or painful injections in the nail folds are the usual alternatives. Fungal infections in the nail plate are a very inadequate type of condition for a person. Nail fungal infections treatment are difficult to treat effectively because of insufficient concentration reach to the site of action. For making the nail fungal infection treatment more effective we tried to make a transungual formulation for the treatment with a effective penetration enhancer.

The introducing conception which has all the vantage of the patch system, but with no weakness, nail plate is an effective route for systemic administration for a wide range of therapeutically active substance with mode of application. Nail also have the advantage that the delivery through them is not complicated by the presence of hair follicles and sweat glands, as in the skin, nor the very broad version in the permeability of stratum corneum a unlike body sites and dissimilar individuals.

The nail plate is made up of “hard” hair-type (80%) and “soft” skin-type (20%) keratins. Sulfur and nitrogen are the most special elements in nail composition. Lipids (mainly cholesterol) constitute 0.1 to 1% of the nail composition and small quantities of potassium, calcium, magnesium, sodium, copper, zinc and iron can be found. Water is the independent plasticizer in the nail and nail water content is generally 18-20% but can be as richly as 25% if cadaver nail revealed to 100% RH.

As this study may overcome the main limitation of transungual drug delivery system – insufficient penetration through nail plate. Till date only few chemical penetration enhancers are there which increases the penetration either by keratolytic action or by irreversible breakage of desmosomes bonds present in nail plate responsible for the structural integrity of nail plate. The different formulas were formulated with extracted natural penetration enhancer, film formers, plasticizers, fast evaporating solvents etc.

MATERIAL AND METHODS

Flucnazole was used as a model drug for study, Methanol [Renkem (RFCL) limited Ranbaxy], Methanol, (Changshu Yangyuan chemical, China), Chloroform (Central drug house), Centrifuge – Teknik laboratory, centrifuge machine, Colorimeter – labtoices model No. 12, Hot air oven (Universal). Water used in studies, is of high purity demonized water (AQUOHONTM TBD50), HPMC K4M, Ethyl cellulose, Hydroxy propyl cellulose, 1- Butanol, phosphoeriac acid, 1-Proopenol, Dibutyl phthalate.

Maceration for the extract

The sample of Iresine herbstii was collected from the nearby region and powdered. We dipped the Iresine herbstii powder for minimum of 8 hrs in petroleum ether for removing the fatty substances and the water insoluble dirt. For the extract, we used simple maceration for the sufficient time in the methanol with mild elevation of temperature then room temperature. After that maceration simply filter the solution (solvent with the dissolved agents). Centrifuged the sample with 4000 – 6000 rpm for 15 minutes. Tardily separate the supernatant part by pipette and used for the further part of the experiment. The separated part of the extract was drying out (air drying) for further studies and for the better stability point of view as if stored the extracts in liquid form there may be the chances of any type of instability of extracts so dried form was a better option for storage.

Collection of nail plates

For nail plate we tried to collect from the same volunteer to subside the effect in intra subiect variables like thickness, chemical concentration, age, sex etc. Before using the nail plates were kept and allowed to equilibrate with the room temperature and other conditions, cleaned with a mild liquid detergent. Thoroughly rinsed with distilled water and dried at 45°C to a constant weight. Only female fingernails (index, middle and ring finger) were use because they are already reported to be more comparable in size, weight, and thickness and more reproducible within the same donor (Lehman, personal communication). For each nail plate sample, the dry weight and thickness were measured. Thickness was measure at three points with Vernier caliper and averaged for each nail. Defatting of nail plates Cleaned nail pieces were defatted by placing them in a beaker containing chloroform: methanol (2:1) mixture (10ml) and stirred for a period of 12 hr.

Penetration study

For the penetration study firstly we defatted the nail plates with the solvent system chloroform:methanol (2:1) mixture. Dipped the human cadaver nail plates in the solvent system for whole night. The defatted nail plate treated with the extract of Iresine herbstii applied on the dorsal side of nail plate and allowed the extract to penetrate deeper in the hard compact dead keratinized nail plate, which had been considered like an impermeable structure of the human body with the normal conditions like the normal room temperature and normal atmospheric pressure. After 24 hour of applying the natural extract of plant inspect the penetration potential by observing the transverse section of treated nail plate under the compound microscope. The length covered by extract of the nail plates indicates the penetration potential of the applied extract. After beating the penetration problem through hard keratin the next step was formulate the potent natural penetration enhancer. For formulating the extracted penetration enhancer use different stabilized pharmaceutical excipients as a transungual film. Formulation were formulated with HPMC K4M, Ethyl cellulose, Hydroxy propyl cellulose, 1- Butanol, phosphoeriac acid, 1-Proopenol, Dibutyl phthalate. The formulated transungual film were evaluated for diffusion by the help of flanz diffusion cell, with a diffusion area of 0.785 cm². The acceptor chamber was filled with 5 ml PBS (phosphate buffer saline) at 37°C. The compatibility study between drug and used excipients was done by FTIR analysis and the probable mechanism of drug diffusion through nail plate concluded by scanning electronic microscopy.
RESULTS

stability study:

The *Iresine herbestii* extracts shows a good stability profile in the respect of ionic concentration and % transmittance as it reserved its pH within the limit of 6.5 to 6.8 and % transmittance limit 52% to 44%.

Penetration potential:

The total penetrated drug concentration across the defatted human cadaver nail plate was found in the performed study from the formulation without added PE was 12.56% and with the formulation with PE *Iresine herbestii* in the 30%w/w of the formulation was 86.36% i.e. total 73.80% after 44 hour of the study.
Compatibility study:
The FTIR graph shows all the peaks presented in the formulation’s fluconazole as presented in the pure Fluconazole sample, which indicate that there was no chemical or physical incompatibilities were there.

SEM study:
The SEM picture of the plane and treated defatted human cadaver nail plate. this pictures clearly indicated that there was no sign of keratolysis in the human cadaver nail plate after the treatment.

CONCLUSION
The penetration enhancer was extracted by simple maceration process by using the methanol as a solvent. The extracted penetration enhancer shows a good physical stability against the natural conditions provided by the environment. As the pH and %transmittance shows a reserved value.

The drug penetration rate across the human cadaver nail plate was increased by a great extent i.e.73.80%. In the case of both formulations the followed drug penetration pattern was of perfectly zero odors; but after 10 hour the “n” value for the formulation with Natural penetration enhancer indicated that the drug penetration was anomalous first odor. That could be due to opening of some channels in the nail plate structure. Which might be the action of used penetration enhancer which may increased the water carrying capacity of the nail plate.

The FTIR study of the formulation with penetration enhancer shows that there were no sign of any type of incompatibilities. The SEM study told that no keratolysis was there in the nail plate treated with extracted penetration enhancer.

REFERENCES