



INSPECTION OF A NOVEL PENETRATION ENHANCER FOR TRANSUNGUAL DRUG DELIVERY SYSTEM: *PELARGONIUM HORTORUM*

Vikram Singh*, Kaushal Kishore Chandrul

School of Pharmaceutical Sciences, Shri Venkateshwara University, Gajraula, Amroha, U.P. (India)

This study was to search some natural penetration enhancer and formulate them in a transungual drug delivery formulation. This natural penetration enhancer helps to overcome the main problem in front of success of transungual drug delivery system. We selected to formulate fluconazole as a model drug for the nail fungal infection treatment with extracted penetration enhancer (PE). Model drug *i.e.* fluconazole was formulated with the natural extracted penetration enhancer with different designed formula. The solvent for PE extraction was methanol and that extracts were air dried. The cadaver human nail plates were used for penetration study, were collected from the same volunteer for negligence in the thickness and chemical composition concentration in the nail plate. The extracted PE (*pelargonium hortorum*) was selected for formulation on the basis of ethnopharmaceutical history. The human cadaver nail plates were treated with the formulation with and without the extracted PEs. *Ex - vivo* drug penetration was evaluated by Franz diffusion cells using cadaver human nail plate upto 36 hours. The drug filmability was found to be best with the polymer like 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 FT25AP4 shows total 35.67% drug penetration *i.e.* near about two times of 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.

Keywords: Penetration enhancer, transungual

INTRODUCTION

Nail is a very important part of the body and has the structure of a very effective barrier. It is made up of layers of dead, keratinized cells with high amount of water 18- 20 % and high sulphur and nitrogen content which form a 0.2 – 0.6 mm hard structure^{1,2}. Treatments of nail fungal infections usually lead to poor patient compliance. That may be due to penetration of topically applied drugs across the nails plate, systemic treatments takes a long time and resulting in side effects or painful injections in the nail folds are the usual alternatives³. Nail fungal infections are generally next to impossible if treated systemically and reoccurrence chances are very common.

The diseases like affect the nail plate: onychomycosis and psoriasis. The nail fungal infections in the nail plate are a very ignominy type of condition for a person affected with this type of infection and these infections are painful also. If nail fungal infections not treated effectively on time and completely they may cause some serious problem systemically. As untreated nail fungal infectious species are increases their population deep and deep inside the nail plate. After very big colony in nail plate they can penetrate in side the skin and cause very serious problems. 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 enhancer³.

The conception of transungual drug delivery which has the vantage of the patch system like self administration easily termination of therapy if unsuited etc. Across the nail plate is an effective route for treating these nail infections as they are site specific type of targeting. 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

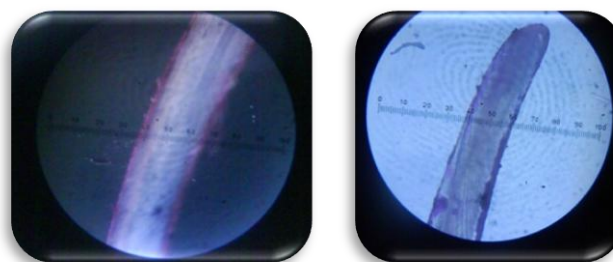


Figure no. 1: Transverse section of nail treated with *Pelargonium hortorum* extract

The nail plate is made up of “hard” hair-type (80%) and “soft” skin-type (20%) keratins^{5,6}. Sulfur and nitrogen are the most

For Correspondence

vikram.karki10@gmail.com

especial 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 ^{7,8}. 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 % RH⁹.

As this study may helps to cross big problem in the case of transungual drug delivery system *i.e.* poor penetration through nail plate. There are few methods which act as a penetration enhancers technique already used for using and formulating the transungual formulation but they are painful and sometime they leads to irreversible keratolysis. The different formulas were formulated with extracted natural penetration enhancer, film formers, plasticizers, fast evaporating solvents etc.

Material and methods

Fluconazole 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 – labtroices model No. 12, Hot air oven (Universal). Water used in studies, is of high purity demonized water (AQUOIONTM TBD50), HPMC K4M, Ethyl cellulose, Hydroxy propyl cellulose, 1- Butanol, phosphoric acid, 1-Propenol, Dibutyl phthalate.

Maceration for the extract

The sample of *pelargonium hortorum*'s flower was collected from the nearby region. We dipped the *pelargonium hortorum* flower 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^[10]

For nail plate we tried to collect from the same volunteer to subside the effect in intrasubject 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 45⁰C 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 hr¹⁰.

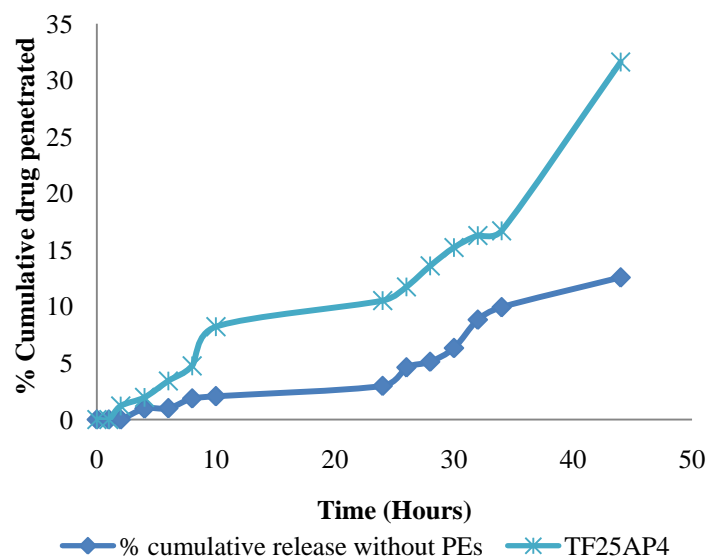


Figure 2: comparative drug penetration across the nail plate

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 *pelargonium hortorum* 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 of *pelargonium hortorum* by the transverse section of treated nail plate under the compound microscope and microscopic scale (figure no. 1). The length covered by extract of the transverse section of the nail plate indicates the penetration potential of the applied extract.

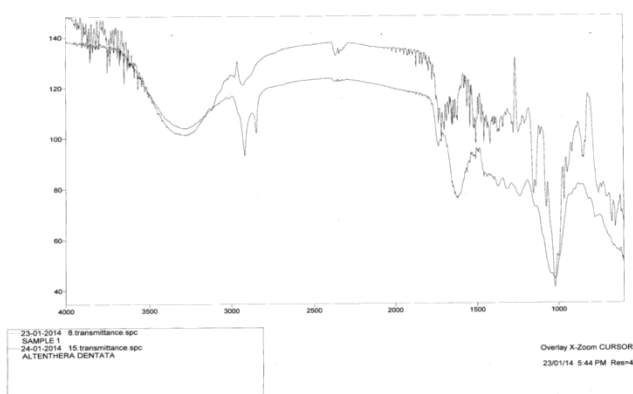


Fig. no. 3 FTIR Study for compatibility confirmation

After solving the penetration problem for transungual delivery through hard keratin the next gradation was formulate the model drug with potent natural penetration enhancer. For formulating the extracted penetration enhancer use different pharmaceutical excipients as a transungual film. Formulation were formulated with HPMC K4M, Ethyl cellulose, Hydroxy propyl cellulose, 1- Butanol, phosphoric acid, 1-Propenol, Dibutyl phthalate. The formulated transungual film were evaluated for diffusion by the help of modified franz 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.

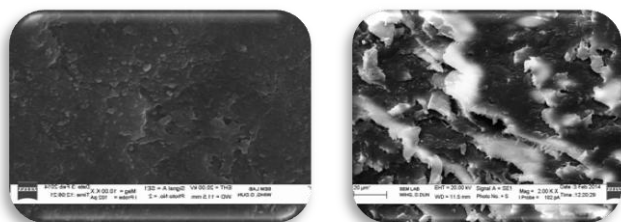


Fig. no. 4 SEM Picture of treated and untreated human cadaver nail plate.

Results & Discussion

Stability study: The *pelargonium hortorum* extracts shows a good stability profile in the respect of ionic concentration and % transmittance as it reserved its pH within the limit of 6.7 and % transmittance limit 87%.

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 *pelargonium hortorum* in the 30%w/w of the formulation was 35.67% i.e. total two folds higher then without using penetration enhancer after 44 hour of the study. (figure 2)

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.(Figure 3)

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. (Figure 4)

Conclusion

The penetration enhancer (*pelargonium hortorum*) was extracted by simple maceration process by using the methanol as a solvent. The extracted penetration enhancer *pelargonium hortorum* shows a respectable stability against the natural conditions provided by the environment from there we can state that the formulation with *pelargonium hortorum* would be a stable formula for a time being.

The drug penetration rate across the human cadaver nail plate was increased by a great extent i.e. near to two folds. It mean the total effectiveness of the formulation increase by two folds. The formulation shows a zero odors penetration pattern; 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 enhanced water caring capacity of 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.

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