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Heighten the bioavailability of Fluconazole with Novel Penetration Enhancer *Acacia Catechu* for Drug Delivery through Nail Plate

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Abstract:
Nail fungus infections are common and very ignominy, this nail infection can seriously scathe by systemic circulation if untreated. In this study we tried for the formulation the with natural penetration enhancer (PEs) for better nail penetration of active constituents. *Acacia Catechu* extract was practiced as a novel penetration enhancer. For extract the penetration enhancer, extraction was done with methanol and dried; the *Acacia Catech's* extract present full penetrations across the nail plate. Human cadaver nail plates (dry weight 45.8 mg, thickness 220 µm approximately) defatted with chloroform: methanol (2:1) were used for penetration study. Diffusion study with the help of Franz diffusion cell with phosphate buffer (pH 7.4) saline. The transungual film F32 evaluated for the physical properties %Drug Content 96.1±0.02, Weight variation 150±0.80, Thickness 0.21±0.01, Flatness 99%, Folding endurance 210±6, WVTR 3.143±0.436, %Moisture content 2.127±0.24. The drug diffused across the nail plates closely to first order manner and affirm by the pepass "n" value *i.e.*0.92. The formulation with the *Acacia Catech's* extract penetrates the 4.80% more drug through nail plate. This study can claim that the *Acacia Catechu* as a stiff penetration enhancer for transungual delivery as the penetration is a limiting factor and it can be overcome with *Acacia Catechu*.
Key words: *Acacia Catechu,* Nail Infection, natural penetration Enhancer.

INTRODUCTION

Nowadays cases of nail fungus infections are increasing about 26% of the population infected with nail fungus infection and very common with diabetic patients and with patients of poor circulation,[1,2] although generally nail fungus infections are not causing pain but if this nail fungus infections this can lead to

many systemic problems, specially person with immune problem [3].

Nail fungus infections are very difficult to treat because of nail morphology and presence of infectious agent deep in nail plate. Oral treatment for curing the nail infections is a traditional method but that is time taking way to solve the problem with a number of unwanted effects, like hazardous effects of used drugs, total cost of the treatment, low drug concentration at the site of action for the reason a large amount of drug is needed in the formulation and retrogresses are common [4,5].

There is a significant difference between nail drug concentration and plasma drug concentration *i.e.* to maintain sufficient drug concentration [6,7,8] in infelicitous site (nail) one has to heighten the drug concentration in plasma also for a long time and that may induce grievous undesirable effects. The proficient substitute for oral drug delivery system is trans ungula drug delivery system. The absorption of therapeutic agent into the nail plate in trans ungula delivery, is highly delectable to treat the nail fungus infections. High nail permeability is highly desirable for the success of therapy which is still quite low and restrains topical therapy. Different doers suggested that the aqueous or lipophilic vehicles do not present any significant difference in the drug penetration rate [9,10].

Penetration enhancer may help in the case of penetration problem for trans-ungula therapy. But the established penetration enhancers till date are seriously damage the keratin structure of the nail plate which is irreversible mechanically. In the place of that penetration enhancer if we try for natural penetration enhancers which are traditionally used for a long time, we could get a great formula for trans ungula therapy and the long time use of that automatically understandable the inharmoniousness nature of used plant.

Material and methods

Fluconazole was used as a model drug for study, Methanol [Renkem (RFCL) limited Ranbaxy], Ethanol (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). Eudragit L-100, HPMC K4M, HPMC K14M, Ethyl cellulosse, β- cyclodextrin, cellulose acetate phthalate, 1- Butanol, phospheeric acid, 1-Propenol, 1-Dichloromethane.

Maceration for the extract

The pale bark of catechu was collect from the nearby region and powdered. We dipped the *Acacia Catechu* bark's 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 secernate 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.

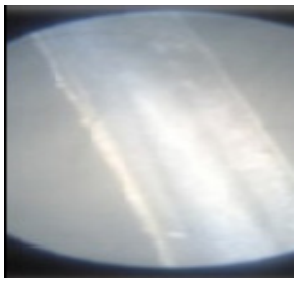
Collection of nail plates [11]

For each nail plate, clinical information (age and sex) was recorded. 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 45^0C 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 [12] 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 *Acacia Catechu* 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 transverse section of the nail plate 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 Fluconazole, Eudragit L-100, Ethyl cellulosse, cellulose acetate phthalate, 1- Butanol, phospheeric acid, 1- Propenol, 1-Dichloromethane. The formulated transungual film were evaluated for diffusion by the help of franz diffusion cell, with a diffusion area of 0.785 cm^2. The acceptor chamber was filled with 5 ml PBS (phosphate buffer saline) at 31^0C. The compatibility study between drug and used excipents was done by FTIR analysis and the probable mechanism of drug diffusion through nail plate concluded by scanning electronic microscopy**.**



Untreated human cadaver nail plate

Treated human cadaver nail plate with *Acacia Catechu*

Figure 1: Penetration through human cadaver nail plate (T.S.).

Result

Penetration study with healthy cadaver nail plate was done at room temperature and in atmospheric pressure. The penetration study's results shows that the naturally extracted biomaterial present itself a powerful penetration enhancer in the case of hard nail plate. It penetrates almost throughout the healthy cadaver nail plate. This penetration enhancer presents himself a potent candidate as a penetration enhancer for transungual delivery therapy where penetration is a limiting factor. The transungual film F32 evaluated for the physical properties and the results were –percent Drug Content 97.1±0.03, Weight variation 180±2.10, Thickness 0.21±0.01, Flatness 99%, Folding endurance 180±3, Water Vapor Transmission Rate 3.143±0.436, percent Moisture content 3.823±0.23. The drug release pattern shown in table no. I, this indicated that the percent drug release of film with extracted natural penetration enhancer was greater that is four times of the drug penetration than the film without penetration enhancer. The increase of four folds of drug diffusion through the nail plate clearly indicate that this penetration enhancer undoubtedly increase the bioavailability in the case of trans ungula drug delivery system and improve the results. This new penetration can minimizing the total therapy time for nail fungal infections. The drug moved across the nail plate in near to first order manner and support by the Pepass "n" value *i.e.* 0.87. The overlapped FTIR spectra of the formulation and drug indicate absence of any type of incompatibility in the formulation as all major peaks were matched (Figure III)

Table 1: Formula of the formulation code F32

Ingredients	**% Incorporated**
Fluconazole	1%
Eudragit L100	20%
Sod. Alginate	2%
Ethyl cellulose	3%
Cellulose acetate phthalate	2%
PEs	30%
n-butanol	30ml

Table 2: Drug penetration rate determination for the formulation

Sr. No.	**Sample withdrawn (day)**	**Drug content (%) into acceptor chamber**	
		Formulation without PEs	**Formulation with PEs**
1	1	0.00	0.00
2	2	0.00	0.078
3	3	0.00	0.27
4	4	0.00	0.56
5	5	0.12	0.65
6	6	0.23	0.89
7	7	0.37	1.33
8	8	0.62	1.89
9	9	0.93	2.43
10	10	1.2	4.81

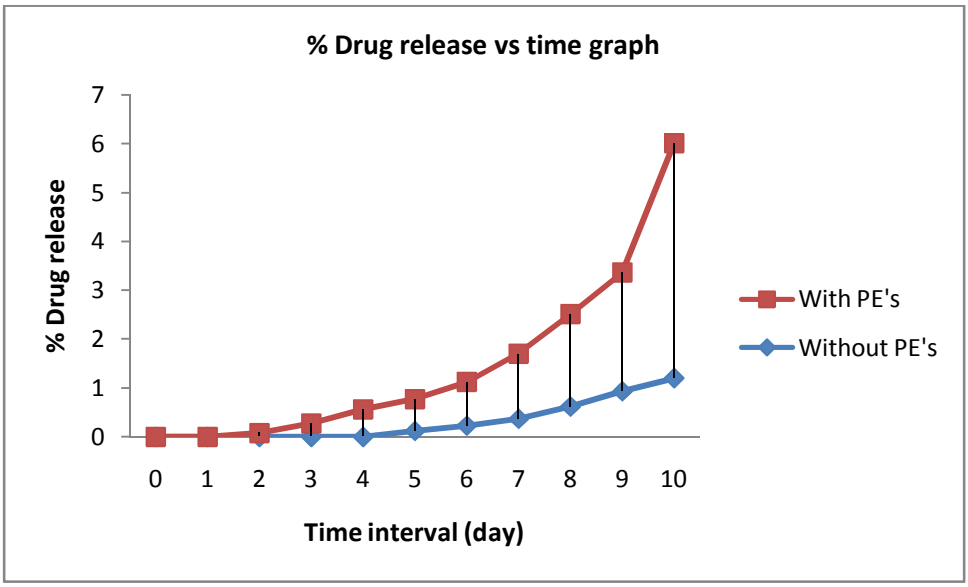


Figure II: Drug release pattern with PEs though human cadaver nail plate

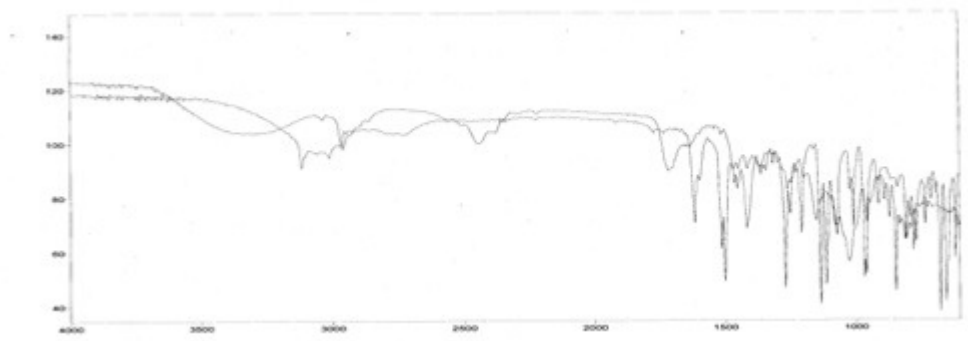
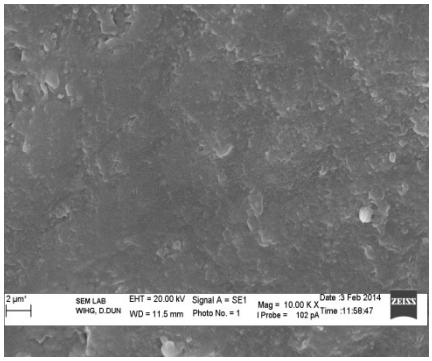
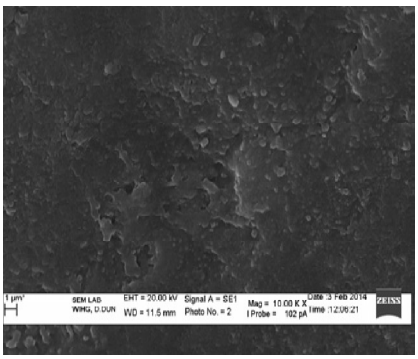


Figure III: Overlapped FTIR spectra for compatibility Study



SEM picture treated human cadaver nail plate



SEM picture human plain cadaver nail plate

Figure IV: Scanning electroscopic microscopy picture

When we noticed the SEM capture of treated nail plate with plan nail plate (figure IV) we can come with the inference that no keratolysis occurred there. Which indicate that the drug and extracted penetration enhancer cross the nail plate simply by diffusion probably or with reversible swelling of keratinized cell or relaxed the tight desmosomes junctions which allowed the higher concentration of drug to cross it.

Conclusion:

The present study can claim that the *Acacia Catechu* as a potent penetration enhancer for transungual delivery for which the penetration is a limiting factor. *Acacia Catechu* extract dose not harm the nail plate and be stable for long time with normal environmental conditions. The formulation with the extract of *Acacia Catechu* penetrates the four fold more drug in the deepest part of the human cadaver nail plate.

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