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Research Article

Effect of various penetration enhancers on permeation kinetic of itraconazole for the topical drug delivery system

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ABSTRACT

Itraconazole (ITZ) is a synthetic triazole antifungal agent having topical and systemic efficacy against familiar fungi such as *Aspergillus* and other filamentous fungi. The difficulties of ITZ with oral administration like dissolution rate limited absorption and gastric side effects can be overcome by formulating it in topical system. The aim of the this study was to evaluate the effect of various penetration enhancers on permeation kinetic of ITZ using Franz diffusion cell through pretreated cellophane membrane for topical system. Various permeability parameters like steady state flux, permeability coefficient and enhancement ratio were calculated. The permeation rate of pure ITZ was found to be 33.27 µg/cm^2/hr. All penetration enhancers (except cyclodextrin) showed 1 to 2 times enhancement ratio. The inclusion complex of the ITZ showed best drug permeation rate (452.20 µg/cm^2/hr). It was concluded that ITZ inclusion complex with HPβCD is the best way of enhancing the permeation of drug through cellophane membrane for transdermal system.

Keywords: Cyclodextrin; Inclusion complex; Itraconazole; Penetration enhancer

INTRODUCTION

Topical/transdermal drug delivery system is used to achieve both local and systemic effect by applying drug on the intact skin surface. However, the stratum corneum, the external layer of the epidermis of skin is a natural barrier and only a few drugs can penetrate the skin easily and in sufficient quantities to be effective (Saleem MA et al., 2010). Therapeutic effective concentration in body can be achieved either by increasing dose or by using penetration enhancers. However, increase in dose may lead to unnecessary side effects; hence to achieve therapeutic effective concentration of drug in body, uses of different penetration enhancers is more feasible. Therefore, in recent years, frequent studies have been performed in the area of penetration enhancement (Rathi AA et al., 2011).

Penetration enhancers improve the capability of skin to absorb drugs by varying the lipid domain of the *stratum corneum* (SC) and the protein elements of the tissue or they may increase the partitioning of a drug into the SC. The various penetration enhancers such as alcohols, tween 20, cetrimide, dimethyl sulphoxides, isopropyl myristate, dimethyl formamide have been reported to be used in many studies to increase the topical absorption of drugs (Kasliwal N et al., 2008).

Penetration enhancers may act by one or more of the following mechanisms: disruption of the highly ordered structure of stratum corneum lipid; interaction with intercellular protein; improved partition of the drug, co-enhancer, or solvent into the stratum corneum; alter the physico-chemical properties of drugs (Mathur V et al., 2010).

Itraconazole (ITZ) is a synthetic triazole antifungal agent, has a half–life of 21 hours and an absolute oral bioavailability of 55%. It is practically insoluble in water. It undergoes extensive first pass metabolism (Peeters J et al., 2002). Commercially, it is available in capsule, oral solution and parentral dosage form. Hence, obstacles with oral administration of ITZ like gastrointestinal side effect, extensive hepatic metabolism, and low bioavailability can be resolved by using topical formulation of ITZ which promises for consistent delivery of drug for longer period of time. One more advantage of topical preparations is that they act directly at the affected site.

Hence, the objective of the present study was to demonstrate *in vitro* enhancement of drug penetration through cellophane membrane using Franz diffusion cell for the development of transdermal system itraconazole. The study also involves the comparison between different penetration enhancers and the cyclodextrin complexes on penetration enhancement of itraconazole.

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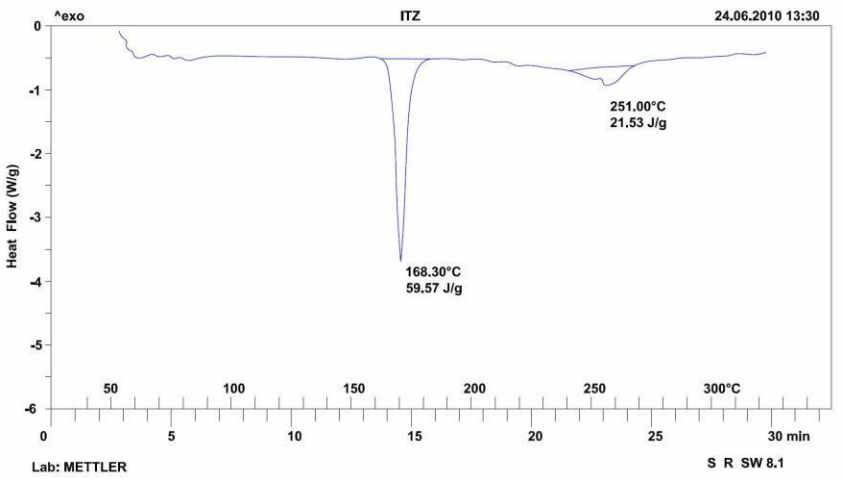

Figure 1: DSC thermogram of pure itraconazole

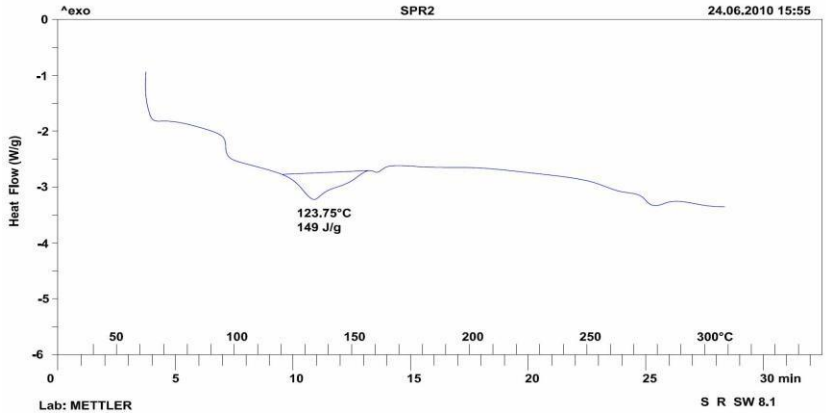

Figure 2: DSC thermogram of ITZ inclusion complex with HP-β-cyclodextrin

MATERIALS AND METHODS

Itraconazole (ITZ) and hydroxyl propyl-β-cyclodextrin (HPβCD) were kindly supplied by Vaikunth Bulk Pharmaceutical- Panoli as a gift sample. Different penetration enhancers like oleic acid, dimethyl sulfoxide (DMSO), sodium lauryl sulphate (SLS), tween 20, cetrimide and β-cyclodextrin were procured from Aatur chemicals, Vadodara. Other chemicals used were of analytical grade.

Preparation of drug inclusion complex with hydroxy propyl-β-Cyclodextrin

Spray drying method was used to prepare inclusion complex of drug with hydroxyl propyl-β-cyclodextrin (Prasad RS et al., 2010). The drug was dissolved in a mixture of methylene chloride and methanol. HPβCD was dissolved in distilled water with the help of a magnetic stirrer. Both the solutions were mixed slowly and added drop wise together on a magnetic stirrer for 30 minutes. The resulting solution was fed to mini spray dryer (Labultima-222, Mumbai, India) and sprayed in the chamber from a nozzle with diameter 0.7 mm under the atomization pressure of 2.5 kg/cm^2 with a feed rate of 3 ml/min and aspiration of 25 m^3/h. The inlet temperature was kept at 70^{o}C and out let temperature 50^o±5^{o}C. The product thus obtained was collected, packed and doubly wrapped in an aluminum foil and stored in a desiccator till further use.

Characterization of drug cyclodextrin inclusion complexes

The prepared solid inclusion complexes were characterized by differential scanning calorimetry (DSC) technique (Jagdale SC et al., 2011). DSC thermograms of the drug, HPβCD, and prepared solid inclusion complexes were recorded on the Shimadzu TGE-50 DSC instrument (Shimadzu Corporation, Japan). These thermograms represent the rates of heat uptake from sample. About 2-5 mg samples were sealed in aluminum pans and scanned at a heating rate of 10^{0}C min^{-1} over a temperature range of 30 to 300^{0}C under a nitrogen gas stream.

Partition coefficient determination

The partition coefficient of the pure drug and solid inclusion complexes between octanol/water was determined at ambient temperature (30±2^{o}C). Ten milliliters each of octanol and distilled water were taken in a glass stoppered flasks, to which 10 mg of accurately weighed drug was added and the mixture was then shaken with the help of mechanical shaker for 24 hours at room temperature. The mixture was then transferred to a separating funnel and allowed to equilibrate for 6 hours. The aqueous phase was separated,

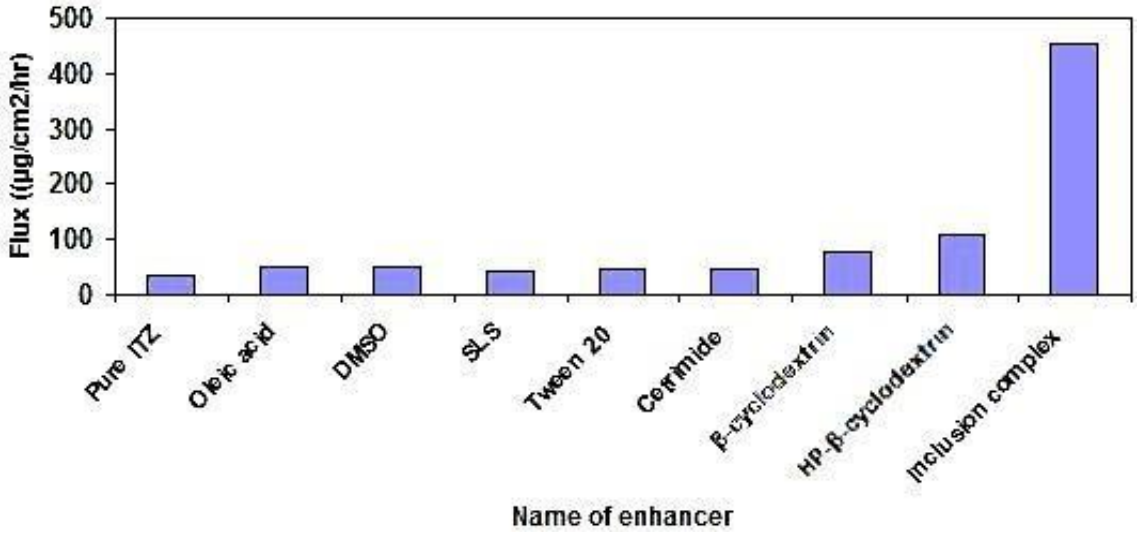

Figure 3: Comparison of effect of different permeation enhancer on permeation rate

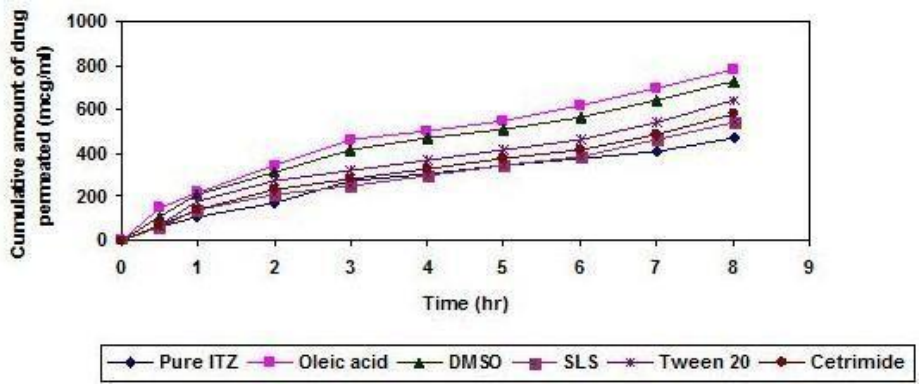

Figure 4: Comparison of in vitro drug permeation of pure ITZ with different permeation enhancer

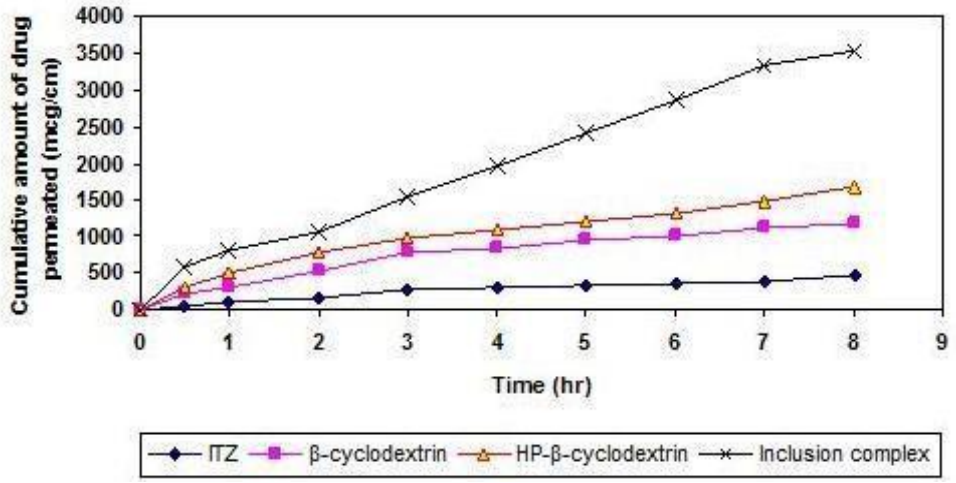

Figure 5: Comparison of in vitro drug permeation of pure ITZ with different cyclodextrin and inclusion complex

centrifuged for 10 minutes at 2000 rpm and drug content in aqueous phase was determined by UV spectrophotometer at 244 nm. Triplicate readings were taken and average was calculated. The partition coefficient was calculated by using following formula (Patel HJ et al., 2010).

$$Partition\ coefficient = \frac{Concentration\ of\ drug\ in\ organic\ phase}{Concentration\ of\ drug\ in\ aqueous\ phase}$$

Permeability study

The Franz diffusion cell was used for this study (diffusion studies were carried out using different enhancers). The cell consists of two chambers, the donor and the receptor. A pretreated cellophane membrane (effective surface area 1.77 cm^2) was placed between the two chambers. The donor compartment contained a suspension of the drug (itraconazole). The receptor

Table 1: Partition coefficients

Drug	Practical value	Therotical value
Pure ITZ	5.34 in octanol/water	5.66 in octanol /water
Inclusion complex	2.89 in octanol/water	---

Table 2: Effect of permeation enhancer on permeability coefficient and flux of ITZ

SR. No.	Enhancer	Permeability Coefficient × 10^{-2} (cm/hr)	Flux (µg/cm²/hr)	% Enhancement ratio (ER)
1	Pure ITZ	0.332	33.27	1
2	Oleic acid	0.522	52.15	1.56
3	DMSO	0.495	49.49	1.49
4	SLS	0.427	42.71	1.28
5	Tween 20	0.478	47.80	1.43
6	Cetrimide	0.454	45.42	1.36
7	β-cyclodextrin	0.793	79.27	2.38
8	HP-β-cyclodextrin	1.101	110.06	3.30
9	Inclusion complex	4.522	452.20	13.59

compartment contained phosphate buffer (12 ml) of pH 6.8. The medium was magnetically stirred at 500 rpm for uniform drug distribution and was maintained at a temperature of 37±1°C. Samples from the receptor compartment were taken at various intervals of time over a period of 8 hours and replaced by equal volume of fresh fluid. The concentration of the drug was estimated spectrophotometrically at 244 nm against their respective blank. This study was done in same manner as mentioned above by using different penetration enhancers (donor compartment contained a suspension of drug and 5% w/w concentration of different enhancer). The enhancers considered for this study were oleic acid, DMSO, SLS, tween 20, cetrimide, β-cyclodextrin and hydroxy propyl-β-cyclodextrin (Jadhav KR et al., 2010).

Calculation of permeability parameters

Parameters were calculated in this part of the study to compare the drug transfer and permeation properties amongst the tested permeation enhancers. Descriptions of these parameters are summarized below which are steady state flux, permeability coefficient, and enhancement ratio (Abdullah GZ et al., 2011).

Steady state flux

Flux is defined as the rate of diffusion or transport of a substance through a permeable membrane. After reaching the steady state of drug permeation, flux was calculated using the following equation:

$$\text{Steady state flux (Jss)} = dM/S \,.\, dt$$

Where *dM* is the amount of drug that permeates through a unit cross-section area (*S*) in a unit time (*t*). From the above equation, it is clear that the slope of the steady state portion of the permeation curve created by plotting the cumulative amount of drug permeated in micrograms versus time in hours is the flux.

Permeability coefficient

The quantity of itraconazole diffused per unit area of skin (dM/S) was calculated for each time interval, and the permeability coefficient through the membrane (Kp) was determined according to the following equation:

$$\text{Permeability coefficient (Kp)} = Jss/C_0$$

where *Jss* is the steady state flux and C_0 is the initial drug concentration.

Enhancement ratio

The enhancement ratio was calculated to find the effect of permeation enhancer on relative enhancement in the flux with respect to selected drug molecules. The enhancement ratio was estimated according to the following equation:

$$\text{Enhancement ratio (ER)} = Jss \text{ of drug with enhancer } / Jss \text{ of drug alone}$$

RESULTS AND DISCUSSION

There are numerous methods for the preparation of the cyclodextrin-guest complexes depending on the physical properties of the guest molecules, including physical mixing, kneading, coevporation, spray drying etc. Among these spray drying method was used in this study because uniform size globules were obtained by this method and also suitable for heat sensitive molecules (Patel TB and Patel LD, 2010).

Itraconazole showed a sharp characteristic endothermic peak at 168.3°C corresponding to its melting point in DSC thermograms as shown in Figure 1. In spray drying inclusion complex, peak of pure itraconazole drug was disappear as shown in Figure 2 and showed formation of true inclusion complex in solid state.

The partition coefficient of pure itraconazole was found to be 5.34±0.25 while for the spray-dried inclu-

sion complex it was estimated as 2.89±0.12 as shown in Table 1. This significant reduction in value of partition coefficient can be attributed to the enhanced aqueous solubility (hydrophilicity), which was predominantly due to amorphous nature of the formed complex (Talegaonkar S et al., 2007).

The values of steady state flux, permeability coefficient and enhancement ratio of drug alone and along with different penetration enhancers are reported in Table 2. The permeation of pure drug alone through cellophane membrane was poor and the permeation rate was found to be 33.27 µg/cm^2/hr. All penetration enhancers (except cyclodextrin) showed 1 to 2 times enhancement ratio (Figure 3, Table 2). The inclusion complex of the drug showed best drug permeation rate (452.20 µg/cm^2/hr).

The reason for differences in the permeation rate might be due to difference in drug solubility. This may possibly explained by considering that the overall permeation rate of drug from prepared systems in the donor compartment can permeate through a semipermeable membrane mainly by three consecutive sequence steps: first, dissolution of the dispersed solid particles, followed by diffusion of the drug across the dissolution media and lastly its permeation through the membrane. The improved drug solubility owing to formation of drug inclusion complex with HP-β-cyclodextrin results in increase the amount of diffusible drug molecules in the donor compartment leading to increase in the overall itraconazole diffusion (Jug M et al., 2005). However the complex could not penetrate though membrane, but it was dissociated and the free drug was available for penetration.

CONCLUSION

It was concluded that itraconazole complex with hydroxypropyl-β-cyclodextrin solubilize it in the aqueous medium and carry the drug molecules to the barrier surface where complex dissociation and drug permeation across semipermeable membrane occurred. These inclusion complexes gave highest enhancement ratio among that of all other penetration enhancers. Hence, we can conclude that the prepared itraconazole inclusion complex is suitable for topical formulation.

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