Microemulsion-based Hydrogel Formulation of Itraconazole for Topical Delivery

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ABSTRACT − The present study was aimed at preparing microemulsion-based hydrogel (MBH) for the skin delivery of itraconazole. Microemulsion prepared with Transcutol as a surfactant, benzyl alcohol as an oil and the mixture of ethanol and phasphatidyl choline (3:2) as a cosurfactant were characterized by solubility, phase diagram, particle size. MBHs were prepared using 0.7 % of xanthan gum (F1-1) or carbopol 940 (F1-2) as gelling agents and characterized by viscosity studies. The *in vitro* permeation data obtained by using the Franz diffusion cells and hairless mouse skin showed that the optimized microemulsion (F1) consisting of itraconazole (1% *w/w*), benzyl alcohol (10% *w/w*), Transcutol (10% *w/w*) and the mixture of ethanol and phospahtidylcholine (3:2) (10% *w/w*) and water (49% *w/w*) showed significant difference in the flux (~1 μg/ cm^2/h) with their corresponding MBHs (0.25-0.64 μg/cm^2/h). However, the *in vitro* skin drug content showed no significant difference between F1 and F1-1, while F1-2 showed significantly low skin drug content. The effect of the amount of drug loading (0.02, 1 and 1.5% *w/w*) on the optimized MBH (F1-2) showed that the permeation and skin drug content increased with higher drug loading (1.5%). The *in vivo* study of the optimized MBH (F1-2 with1.5% *w/w* drug loading) showed that this formulation could be used as a potential topical formulation for itraconazole.

Key words − Itraconazole, Benzyl alcohol, Microemulsion-based gel, Topical skin delivery

Itraconazole is a therapeutically important triazole-derived antifungal agent (Grant et al., 1989) that has been widely used in clinics for a variety of serious fungal infections including Onychomycosis of the toenail and the fingernail (Lortholary et al., 1999). It is orally administered 2-3 times a day (200-400 mg/day) for 3-6 months to treat Onychomycosis. Patients are reluctant to take itraconazole due to side effects such as nausea and vomiting. In addition, oral delivery of itraconazole is plagued with other barriers that inhibit effective delivery to the affected site.

It has been reported that due to the fat soluble nature of itraconazole, significant concentrations are stored in fat cells, thereby reducing the amount available for the targeted nail bed in Onychomycosis treatment (Richardson and Warnock, 2003). Aqueous solubility of itraconazole is further decreased if the patient is taking antacids, which eliminates the acidic environment that it needs to be solubilized. Complications encountered that inhibit the oral bioavailability of poorly water soluble drugs include: slow dissolution in the gastrointestinal (GI) tract, metabolism in the liver, low membrane permeability and complex formation as a result of interactions with the sub-

stances in the GI tract (Hong et al., 2006; Balakrishnan et al., 2009a and 2009b). Even prescribed dosages can overload the metabolic capability of the liver, leading to damage of the liver and heart failure in some cases (Trey et al., 2007). Hence, the topical delivery of itraconazole is of great interest for the treatment of Onychomycosis and other skin fungal infections, but it is frequently ineffective due to poor drug penetration in the skin.

Recently, microemulsion-based hydrogel (MBH) formulations have generated considerable interest as a potential topical delivery system (Feng et al., 2009; Zhu et al., 2009; Gannu et al., 2010). The existence of microdomains of different polarity within the same single-phase solution enables both hydrophilic and lipophilic materials to be solubilised. Advantages associated with microemulsions include their thermodynamic stability, optical clarity, ease of preparation and high diffusion and absorption rates when compared to solvent without the surfactant system (Lawrence and Rees, 2000; Jadhav et al., 2006). Moreover it has been reported that the ingredients of microemulsion may reduce the diffusion barrier of stratum corneum and enhance the permeation of drug (Araújo et al., 2010). Hence, it is promising for both transdermal and dermal delivery of drugs as an efficient route of drug administration. However, the low viscosity of microemulsion restrains its application in the pharmaceutical industry (Santos et al., 2008).

To overcome this disadvantage, various gelling agents are added into the microemulsion to form microemulsion-based hydrogels (MBHs), which include polymeric materials like gelatin, carbomer 940, xanthan gum and carrageenan (Zhu et al., 2009, chen et al., 2006; Gulsen and Chauhan, 2005).

In this study, MBH formulation containing itraconazole was prepared using carbopol and xanthan gum as gelling agents, and its physicochemical properties were characterized. *In vitro* drug permeation through excised mouse skin and *in vivo* drug distribution in mice skin were evaluated. As there are no reported study on the itraconazole topical formulations, this study could give the insight for the possibility of itraconazole topical formulation.

Material and Method

Materials

Itraconazole was supplied by Chong Kun Dang Pharm. Co. Ltd (Seoul, South Korea). Benzyl alcohol was obtained from Junsei Chemical Co. Ltd (Tokyo, Japan). Castor oil, tetraglycol, tocopherol and Transcutol (diethylene glycol monoethyl ether) were purchased from Sigma-Aldrich (MO, USA). Soybean phosphatidylcholine (PC) was kindly provided as a gift by Lipoid Company (Ludwigshafen, Germany). Carbopol 980 was purchased from Noveon Inc (Cleveland, USA). Xanthan gum was purchased from Arthur Branwell Co. Ltd. (Wicklow, Ireland). All other chemicals were of reagent grade and used without further purification.

Solubility of itraconazole

Solubility studies were conducted by placing an excess amount of itraconazole (approximately 200 mg) in a 2 mL microtube containing 1 mL of each vehicle (Table I). Then, the mixture was vortexed and kept for 3 days at 37°C in a shaking water bath to facilitate the solubilization. The samples were

Table I. *Solubility of Itraconazole in Various Solvents Saturated for 72 hours at 37°C (n=3)*

|	Solvent	Solubility (mg/mL)
Water		<0.2 µg/mL
Oil	Benzyl alcohol	159.17±2.50
	Castor oil	0.64±0.00
	Tocopherol	0.30±0.00
Surfactant	Transcutol	0.46±0.02
	Ethanol	0.08±0.00
	Tween 20	0.14±0.01
	Tween 80	0.11±0.01
	Labrasol	0.26±0.01

centrifuged at 10,000 rpm for 10 min to remove the undissolved itraconazole. The supernatant was taken and diluted with methanol for quantification of itraconazole by high-performance liquid chromatography (HPLC) system equipped with a Waters 515 pump, a Waters 2487 UV detector, a Waters 717 autosampler. The column was a Capcell pack C_{18} column (4.6 × 250 mm, Shiseido) used at room temperature. The mobile phase was a mixture of acetonitrile, water and triethaylamine (70:30:0.05 *v/v,* pH 7.0), filtered through 0.45-µm membrane filter and eluted at a flow rate of 1.0 mL/min. Effluents were monitored using a fluorescence detector (2487, Waters) at 260 nm for excitation and 365 nm for emission.

Construction of pseudo-ternary phase diagrams

Based on the solubility study, benzyl alcohol and Transcutol were selected as oil and surfactant, respectively. It has been reported that the phospholipid-based formulations have a good chance of 'recognizing' membranes and adhering to them, thereby improving the permeation efficacy of the active molecules (Spernath et al., 2007). Thus, the mixture of ethanol and phospholipid (3:2 ratio) was used as a cosurfactant. The pseudo-ternary phase diagrams were constructed by instillation of homogenous liquid mixtures of oil, surfactant, and cosurfactant, with water at ambient (25°C) temperature (Yin et al., 2009). The phase diagram was prepared with the 1:1 weight ratio of surfactant to cosurfactant. The phase diagram at 1:1 surfactant/cosurfactant weight ratio, the ratios of oil to the mixture of surfactant and cosurfactant were varied from 0.5:9.5 to 9.5:0.5. Water was added drop by drop under gentle stirring to each oily mixture. The compositions of microemulsion at which phase separation from homogeneous microemulsion to heterogenous phases occurred were recorded.

Preparation of microemulsion and microemulsion-based hydrogels

Based on the phase diagram (Fig. 1), the itraconazole-loaded microemulsion formulation (F1) was selected at different component ratio (Table II). Itraconazole (0.02 or 1 or 1.5% *w/w*) loaded microemulsion system was obtained by mixing oil, surfactant and cosurfactant together, and adding water drop by drop to these oily phases with magnetic stirring at ambient temperature. The optimized formulation was selected based on the following considerations, as a high concentration of benzyl alcohol could cause skin irritation (Bagley et al., 1996), 10% (w/w) of benzyl alcohol was selected. It has been reported that the hydration of stratum corneum will affect the drug dermal permeation profile and the highest skin flux and permeability coefficient was observed for the formulation that contains 49%
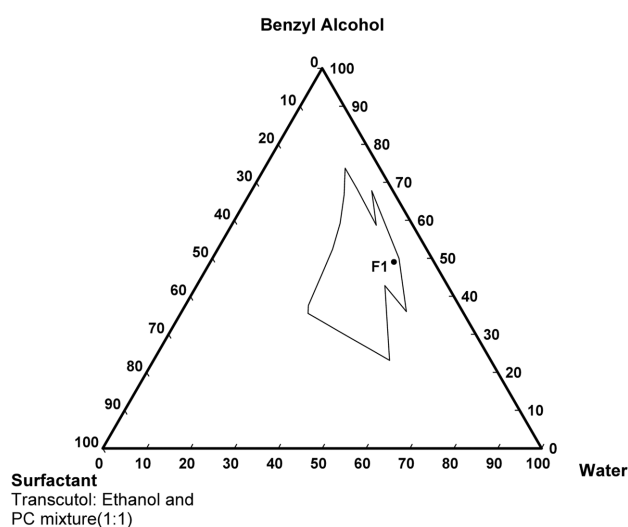
Figure 1. The pseudo-ternary phase diagrams of the oil-surfactant-water system at 1:1 weight ratio of Transcutol to cosurfactant mixture (ethanol/PC at 3:2 ratio) at 25°C.

Table II. *Composition of Microemulsion and MBH Formulations (% w/w)*

Component	F1	F1-1	F1-2
Itraconazole	0.02	0.02	0.02
Benzyl alcohol	10	10	10
Transcutol	20	20	20
Xanthan gum	-	0.7	-
Carbopol	-	-	0.7
Ethanol	12	12	12
S_{75} PC	8	8	8
Triethanolamine	-	-	0.2
water	49.98	49.28	49.02

(w/w) of water among the studied range 20, 32, 42, 49% (w/w) of water (Changez et al., 2006). Hence, the 49% (w/w) of water proportion was selected; further 10-20% (w/w) of surfactant and 20-30% (w/w) of cosurfactant were selected for stable and successful microemulsion formulation.

Carbopol 940 and xanthan gum were selected as the gel matrix to prepare the MBH formulations. MBHs were prepared by adding oil and surfactant/cosurfactant mixture into water containing carbopol 940 or xanthan gum under stirring (Chen et al., 2006). In the carbopol 940 MBH formulation, triethanolamine was used as a neutralizer (Schwarz et al., 1995). Gels were claimed for those clear and highly viscous mixtures that did not show a change in the meniscus after tilted to an angle 90°.

Characterization of microemulsion and MBH
Solubility of microemulsion
The solubility of itraconazole in the optimized microemul-

sion formulation (F1) was determined by adding an excess amount of itraconazole and mixed by vortex. The samples were then shaken in a water bath at 37°C for 72 h for solubilization. The samples were centrifuged at 10,000 rpm for 10 min and the supernatant was analyzed by HPLC after filtered through a membrane filter.

Droplet size analysis
The droplet size of the microemulsion loaded with itraconazole was measured by an electrophoretic light-scattering spectrophotometer (ELS-8000, OTSUKA Electronics Co. Ltd., Japan). The microemulsion was transferred to a standard quartz cuvette and the droplet size of the microemulsion was determined *via* dynamic He-Ne laser (10 mW) light-scattering at an angle of 90° at 25°C. Data analysis was conducted using a software package (ELS-8000 software) provided by the manufacturer.

Viscosity of MBH
The viscosity of MBH was determined using a viscometer (BROOKFIELD, USA) at 50 rpm with spindle # LV4 at room temperature.

In vitro skin permeation and skin deposition studies
In vitro skin permeation study was performed by using Franz diffusion cells with an effective diffusion area of 2 cm². The excised skin samples (dorsal side of 5~6 weeks old hairless mice, 18~20 g) were clamped between the donor and the receptor chamber of Franz diffusion cells with the stratum corneum facing the donor chamber. Then, 0.5 g of microemulsion or MBH (0.5 g) containing 0.02% (w/w) itraconazole was administrated onto the donor chamber. The receptor chamber was filled with 12 mL of the mixture of benzyl alcohol, phosphate buffer saline (PBS) and PEG400 at 3:8:4 (v/v/v). The receptor medium was maintained at 37 ± 0.5°C and stirred at 600 rpm throughout the experiment. For each experiment, 0.4 mL receptor medium was sampled at predetermined time intervals and then the same volume of pure medium was immediately added into the receptor chamber. All samples were filtered through a 0.45 μm pore size cellulose membrane filter and analyzed by HPLC.

After 8 h of the *in vitro* skin permeation experiment, the surface of skin specimens was washed with methanol. The effective surface area of the skin (2.0 cm²) was separated and minced with a surgical sterile scalpel then finally homogenized in a vial filled with methanol (1 mL/cm²) by using ultra turrax homogenizer at 16,000 rpm for 5 min (T25 Basic, Germany) on ice bath (4°C). The tissue suspension was centrifuged for

5 min at 3,000 × *g*, and then the supernatants were filtered and assayed for their itraconazole content by HPLC.

In vivo skin deposition study

Male hairless mice (5-6 weeks old, 18~20 g) were anaesthetized with ether and fixed on the abdominals. Aliquot of optimized MBH F1-2 (0.3 g) containing 1.5% (*w/w*) itraconazole was applied on the dorsal surface (3 cm^2). At 2, 4 and 8 h after dorsal application, about 300 µL of blood was collected through the eyes and centrifuged at 12,000 rpm for 10 min to separate 100 µL of plasma. The mice were put to death by cervical dislocation after blood collection, and then the administrated skins were stripped. The skins were thoroughly washed with methanol, after which the surface was dried with a cotton swab and itraconazole content in the dermis skin layer was determined as described above. The experimental protocols involving animal study were approved by the Animal Care and Use Committee of the College of Pharmacy, Seoul National University.

Data analysis

All the experiments in this study were repeated at least three times and the data was expressed in terms of mean ± standard deviation (SD). The statistical analysis was assessed using two-tailed Student's t-test and a value of *p*<0.05 was considered statistically significant.

Results and Discussion

Solubility of itraconazole

Itraconazole is a hydrophobic (Log P=5.66) triazole antifungal agent and practically insoluble in water (<0.2 µg/mL), thus it is quite challenging to formulate it into solution. The solubility of itraconazole in various pharmaceutically acceptable vehicles was determined in order to choose the oil and surfactants for the microemulsion formulation (Table I). Despite its hydrophobic nature, it showed poor solubility in castor oil. The solubility of itraconazole was the highest in benzyl alcohol among the vehicles tested, thus it was selected as an oil phase. Transcutol was selected as a surfactant due to its higher solubility compared to the other surfactants tested. Moreover, Transcutol was known to enhance the permeability of various drugs (Hong et al., 2006). The short-chain alcohols including ethanol are known be suitable as a cosurfactant, since the small volume of them could be easily inserted into the interfacial layer, forming tight interfacial film (Lee et al., 2003). Ethanol has been widely known as a permeation enhancer, and phosphatidyl choline (PC) also has been

reported for permeation enhancing effect (Kim et al., 2002). Thus, the mixture of ethanol and PC at 3:2 weight ratio was used as a cosurfactant.

Phase studies

The purpose of the construction of pseudo-ternary phase diagrams was to find out the existence range of microemulsion. The pseudo-ternary phase diagrams with 1:1 weight ratio of surfactant (Transcutol) to cosurfactant (the mixture of ethanol and PC at 3:2 ratio) is described in Fig. 1. The translucent microemulsion region is presented in the phase diagrams. The rest of the region on the phase diagram represents the turbid and conventional emulsions based on visual observation.

Preparation and characterization of microemulsion and MBH

Microemulsion formulation F1 was selected from the phase diagram in Fig. 1. In the topical delivery of antifungal agents, only a small surface area of skin is used for the application, thus the formulations with higher solubulization of itraconazole would be preferred. Microemulsion loaded with 0.02% (w/w) of itraconazole was successfully prepared, whose content of oil, surfactant, cosurfactant and aqueous phase is described in Table II. The solubility of itraconazole in F1 was about 200 times higher than its aqueous solubility (<0.2 µg/mL). However, formulations with higher drug loading (1% and 1.5%) were also prepared as it has been reported that 1-2% of itraconazole vaginal creams were well tolerated in the clinical investigations (Francois et al., 2003), which were well above the drug solubility of the current formulation. It is known that the particle size distribution is one of the most important characteristics of emulsion for the evaluation of its stability and also *in vivo* fate of emulsion (Hong et al., 2006). The smaller particle size of itraconazole microemulsion (F1) was obtained with 1:1 ratio of surfactant to cosurfactant (Table III).

As the viscosity of F1 was too low (less than 15 cP) for the topical application, 0.7% of Carbopol 940 or xanthan gum was added to prepare MBHs, which are more suitable for topical administration (Lapasin et al., 2001). MBHs prepared with xanthan gum (F1-1) showed lower viscosity than those with
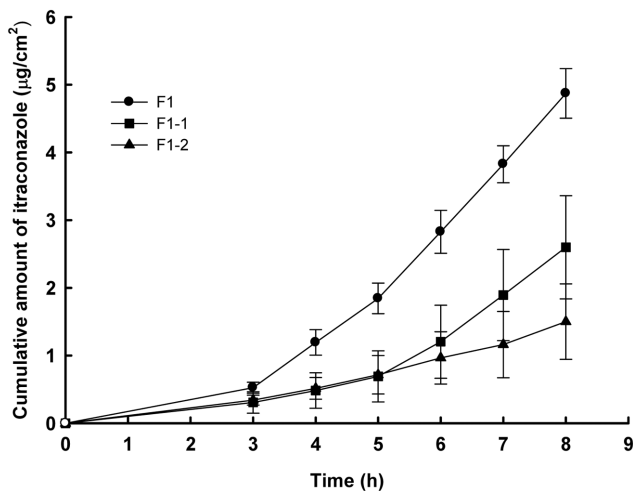
Table III. *Solubility of Itraconazole in Microemulsion and Viscosity of Prepared MBH Formulations. Viscosity (100 rpm, 25±0.5ºC)*

	F1	F1-1	F1-2
Solubility (mg/g)	0.235	-	-
Vesicle size (nm)	56.08±10.73	-	-
Viscosity (cP)	11.52	116.1	1692

Carbopol 940 (F1-2) (Table III).

In vitro skin permeation studies

Fig. 2 shows the *in vitro* permeation profiles of itraconazole (0.02%) through hairless mouse skins from various vehicles, which was conducted using the static vertical Franz diffusion cells in occlusive conditions at 37ºC. The permeation parameters of the formulations were presented in Table IV. It was observed that the microemulsion (F1) showed higher drug permeation profile compared to its corresponding MBHs (F1-1 and F1-2) and the F1-2 showed low permeation profile than that of F1-1, this could be due to the low flux and high viscosity of F1-2 compared to that of F1-1 (Table IIIs and IV). Moreover, the lag time was significantly different between the microemulsion and its corresponding MBHs (Table IV). Despite the lowest flux of Carbopol-based MBH (F1-2), the shorter lag time was observed with them. The skin deposition of itraconazole determined after the 8 hr permeation study revealed that the prepared MBHs were as good as microemulsion in facilitating the drug penetration into the skin (Fig. 3). There are several mechanisms which could explain the ability of MBH to modulate drug transfer across the skin. One of the mechanism by which MBH may contribute to transdermal

Figure 3. Amount of itraconazole retained in the skin at the end of 8 h of *in vitro* permeation studies from various formulations (n=3). *; $p < 0.05$

drug delivery may be ascribed to the good adhesiveness to skin due to the suitable viscosity of MBHs. Moreover, Carbopol 940 and Xanthan gum in MBH could enhance the skin permeation of itraconazole because of the tight contact of the preparation with skin and delayed release time (Chen et al., 2006; Zhu et al., 2009). Moreover, it has been reported that the components of the microemulsion also would contribute to the enhanced drug transport across the skin (Zhu et al., 2008). In this study, Transcutol was used as a surfactant and has been reported for its skin penetration-enhancing effect (Mura et al., 2000). The mixture of ethanol and PC were used as a cosurfactant, and ethanol is known for its penetration-enhancing effect by altering the skin texture (Williams and Barry, 2004). Moreover, PC belongs to the sub-class of phospholipids, which is one of the main components of biological membrane, and is also reported for permeation-enhancing effect (Dreher et al., 1997; Kim et al., 2002). Additionally, the characteristics of microemulsion such as high drug concentration, the small droplet diameter and the reaction between the surfactants and skin stratum corneum may also have contributed to the permeation-enhancement even though the droplets of microemulsion were located in the gel network of Carbopol 940 or Xanthan gum (Kreildgaard, 2002; Zhu et al., 2009; Chen et al., 2006). Since the Carbopol-based MBH (F1-2) showed short lag time and sufficient viscosity for the topical application than that of others, it was selected for further studies.

To determine the effect of the itraconazole loading in the MBH on the hairless mouse skin permeation and deposition, the *in vitro* permeation study was conducted with F1-2 prepared with three different drug loading (0.02, 1% and 1.5% *w/w*). Fig. 4 shows the effect of the amount of drug loading in MBH on the permeation profile. It was observed that up to 8 h
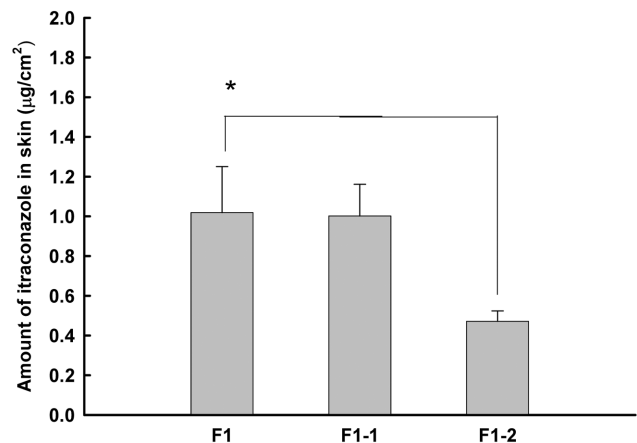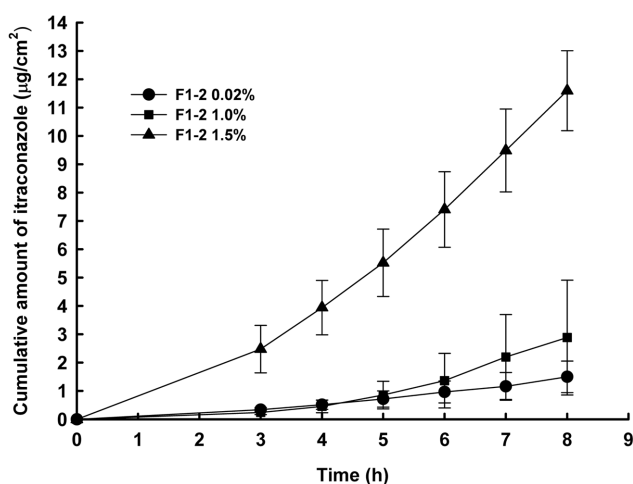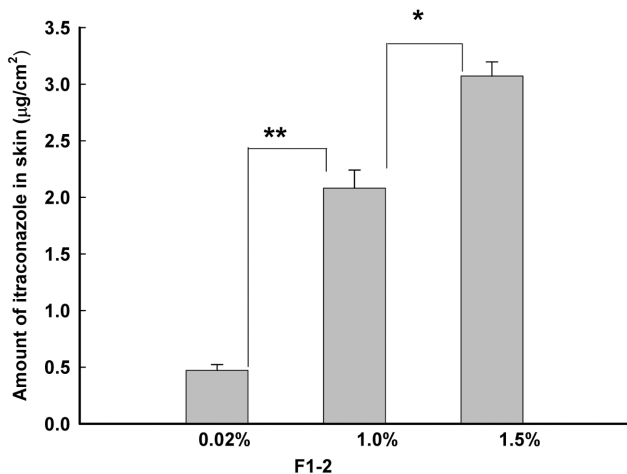

Figure 2. Permeation profiles of itraconazole through hairless mouse skin from microemulsion and MBH formulations containing 0.02% of itraconazole (n=3).

Table IV. *In vitro Permeation Parameters of Itraconazole from the Formulations Across the Hairless Mouse Skin*

Formulation	Flux ($\mu g/cm^2/h$)	Lag time (h)
F1	1.008 ± 0.05	3.18 ± 0.19
F1-1	0.641 ± 0.13	4.01 ± 0.42
F1-2	0.255 ± 0.09	2.24 ± 0.10

Each value is the mean ± S.D. (n=3)

Figure 4. Permeation profiles of itraconazole through the hairless mouse skin from microemulsion-based hydrogel F1-2 with different amount of drug loading (0.02, 1 and 1.5% *w/w*) (n=3).

Figure 6. Amount of itraconazole retained in skin at the end of *in vivo* skin deposition studies from 1.5% drug loaded MBH (F1-2) (n=3).
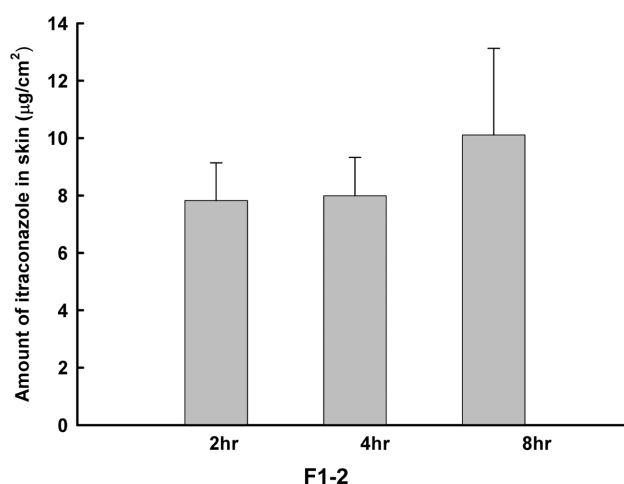

Figure 5. Amount of itraconazole retained in skin at the end of *in vitro* permeation studies from microemulsion-based hydrogel (F1-2) prepared with different amount of drug loading (0.02, 1 and 1.5% *w/w*) (n=3). *; $p<0.01$ Significant difference. **; $p<0.001$

there was no significant difference in the permeation profile between 0.02% and 1% drug loaded MBH (F1-2), but in 1.5% drug loaded MBH showed significantly increased permeation profile (Fig. 4). The amount of drug retained in the skin at the end of 8 h revealed that the drug deposition significantly increased with higher drug loading in F1-2 (Fig. 5). Thus, the formulation contain 1.5% drug loaded were selected to evaluate *in vivo* for further studies.

In vivo skin deposition studies

As the carbopol based 1.5% drug loaded MBH showed optimum permeation profile and skin drug content, we evaluated the *in vivo* performance of F1-2 (1.5%). Itraconazole was not

detected in the blood samples collected at all time points (2, 4 and 8 h). The skin drug content from F1-2 after *in vivo* deposition study for up to 8 h is profiled in Fig. 6. It was observed that the F1-2 reached the maximum skin drug content in 2 h and there was no significant increase in the skin drug content observed. The presence of the higher amount of surfactant could be the reason for the higher skin drug content at 2 h for F1-2 (Mura et al., 2000). These results showed that F1-2 could be used as a potential MBH topical formulation for itraconazole.

Conclusions

In this study, the microemulsion composed of benzyl alcohol (oil), Transcutol (surfactant) and the mixture of ethanol and PC as a cosurfactant was prepared using phase diagram. MBHs were successfully prepared by adding carbopol or xanthan gum for the topical delivery of itraconazole. The *in vitro* and *in vivo* permeation studies revealed that the prepared MBHs could be used as a potential carrier for the topical delivery of itraconazole.

Acknowledgements

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