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Permeation Studies of Miconazole Nitrate (Mn) Gel Containing Dimethyl Sulfoxide as an Enhancer Using Franz-Type Diffusion Cell

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ABSTRACT

Miconazole nitrate is one of the broad-spectrum antifungal compounds used to treat fungal infections where it is used as a topical and transdermal formulation. The main problem of this drug in topical treatment is its low skin penetration. One of the efforts to improve miconazole nitrate skin permeation is by the addition of enhancers such as dimethyl sulfoxide (DMSO). The present study was aimed to assess the impact of various concentrations of DMSO on the *in vitro* release and skin permeation of miconazole from gel preparation using Franz-type Diffusion Cell. Four formulations were prepared of varying DMSO concentrations (3%, 5%, and 7%) and negative control. The evaluation of their physical characteristics, including homogeneity, organoleptic properties, spreadability, pH, viscosity and skin penetration tests were done. The permeation test was conducted in Franz-Type diffusion cell using rabbit skin for 8 hours. The results of the physical evaluation showed that the gel's spreadability ranged from 6.14 ± 0.21 to 6.67 ± 0.16 g cm/s. The average pH of the gels ranged from 5.5 - 5.9, and the gel's viscosity was about 6996 ± 00.00 – 6996 ± 28.07 cps. The result of the permeation test showed that each gel formula was 2.83%, 27.52%, 41.96%, and 52.76% respectively. The gel containing 7% dimethyl sulfoxide (F3) had the most significant percentage of permeation after 8 hours, 52.76%, while the negative control 2.83% permeation. Dimethyl sulfoxide improved the skin permeation profile of miconazole nitrate gel, F3 show the most excellent skin permeation profile.

Keywords: Gel, Dimethyl sulfoxide, Enhancer, Miconazole nitrate, Antifungal.

Introduction

An enhancer is a substance that can increase penetration of a drug into the skin.[1] There are four mechanisms of action of skin penetration of enhancer; namely, the first mechanism is solvents that the enhancers work with dissolving network components on the skin. The second mechanism is through interactions between enhancers and lipids intercellular thus causing disruption of skin structure and increasing diffusion drugs via lipids. The third mechanism is the interaction between the enhancer with intracellular protein to increase penetration through the corneocyte layer. The fourth mechanism is growing partition for drugs such as co-enhancers and co-solvents into the stratum corneum.[2]

Dimethyl sulfoxide (DMSO) is one of a sulfoxide class enhancer that can increase skin permeation by changing the stratum corneum's protein structure effectively.[3] The effect of the DMSO enhancer depends on the concentration and also the co-solvent used. However, using too high a concentration of DMSO can cause erythema and spot on the stratum corneum.[4] DMSO has been extensively used as permeation enhancers in the permeation of hydrophilic and lipophilic drugs.[5] A skin irritation assay performed in rabbit according to the OECD TG 404 revealed no more than a very slight or well-defined erythema, which disappeared in 3 days and also returned to normal after discontinuation of treatment.[6] This profile of DMSO makes it an interesting excipient to work with especially in case of transdermal formulation as it can enhancing drug permeability. Miconazole nitrate (MN) is usually applied to the skin or mucous membranes to treat fungal infections. This agent is used mainly for the treatment of mycotic skin diseases. Miconazole nitrate's bioavailability is very low because it is challenging to dissolve and has a small absorption (about <1 ng/mL).[7] Therefore, as an antifungal agent, it is administered topically, but this drug's main problem in topical treatment is low skin penetration.[9]

Previous research using dimethyl sulfoxide as a Penetration Enhancer of Piroxicam Gel.[5] Another approach has been used dimethyl sulfoxide to enhanced percutaneous permeability of Acyclovir gel formulation.[6] The Previous research showed that MN in nanoemulsion dosage form has a higher cumulative percentage absorption than the cream dosage form. Caused probably due to the nanoemulsion formula having a smaller particle size than the cream to cross the stratum corneum and increase drug penetration.[10]

This study was aimed to evaluate the physical characteristics and the penetration ability of gel containing dimethyl sulfoxide (DMSO) as an enhancer using Franz-type diffusion cell.

Materials and Methods

Miconazole nitrate was purchased from Kimia Farma Watudakon Jombang East Java, Indonesia. Carbopol 940, Triethanolamine, Dimethyl sulfoxide, Methanol, Chloroform and Phosphate buffer solution were purchased from Merck, Indonesia. Propylene glycol was obtained from DCC, Singapore. Methyl paraben and Propyl paraben were obtained from UENO, Thailand. NaCl 0.9% solution was purchased from Widarta, Indonesia.

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The formula of Miconazole Nitrate Gel
The Formula of Miconazole Nitrate Gel showed in Table 1.

Table 1: Formula of Miconazole Nitrate Gel

Material	F0 (%)	F1 (%)	F2 (%)	F3 (%)
Mikonazole nitrate	2	2	2	2
Carbopol 940	1	1	1	1
TEA	1	1	1	1
DMSO	0	3	5	7
Tween 80	5	5	5	5
Propylene glycol	5	5	5	5
Methyl paraben	0.2	0.2	0.2	0.2
Propyl paraben	0.1	0.1	0.1	0.1
Aquadest	ad 100	ad 100	ad 100	ad 100

Preparation of Miconazole Nitrate Gel
The sample dissolved in DMSO solution in water, and then methyl paraben was dissolved in the mixture. The distilled water was heated up to 70^{o}C. Then, the carbopol was swelled by using distilled water for ± 30 minutes and stir it continuously until the entire carbopol dissolved. Mix the materials one by one until it all becomes homogeneous.[11]

Organoleptic test
The organoleptic tests, including odor, color, and consistency, were carried out visually by three assessors.[9] The criteria of each tests were the Gel is usually clear with a semi-solid consistency and has a distinctive odor.[18]

Homogeneity Test
The homogeneity test was carried out by applying gel to the object-glass and then affixing it with another glass object. The presence or absence of coarse grains was observed using microscope.[13]

pH measurement
The pH measurements were done using a digital pH meter (Mettler Toledo). Gel (0.5g) was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel formulation until the constant reading was observed. The measurement determination of pH of each formulation were measured in three replicate.[9]

Spreadability test
A weighed quantity (350 mg) of gel was taken on a glass plate (10x5 cm). Another glass plate (10x5 cm and 5.8±1 g) was dropped from a distance 5 cm. The diameter of the circle of spread was measured after 1 min.[14]

Viscosity test
The viscosity of each formulations was determined at ambient temperature using Brookfield digital viscometer with spindle no.7 at 50 rpm (revolutions per minute), and the results was recorded.[10]

In vitro skin permeation of miconazole nitrate gel
The drug release kinetics studied using a modified Franz-type diffusion cell. Male rabbits weighing 1.8 kg were chosen for the in vitro studies.[14] Hairs on the abdominal region were removed by the razor knife (Gillette Brand) with no break of the stratum corneum. During the experiment period, animals that anesthetized with chloroform and abdominal skin was established. The fatty material adhered to the dermis was carefully peeled off. Miconazole nitrate nanoemulsion was applied to the surface of the skin in the donor compartment, The samples were withdrawn at different time intervals as much as 0.5 mL from the receptor compartment and analyzing of drug content using a UV-Visible spectrophotometer at a wavelength of 272 nm.[10]

Statistical analysis
The research data were analyzed using the SPSS version 17.0. Data were analyzed using the Shapiro-Wilk method to determine normality and also carried out a homogeneity test. Then proceeded to use the One Way ANOVA method to determine the average difference between groups. Observed differences were further analysed using the Post Hoc Tukey HSD test to see the real difference between treatments.

Results and Discussion

The results of spreadability test
Spreadability plays a considerable role in patient compliance and ensures a uniform gel application to a larger skin area. The low value of the gel's spreadability coefficient of the gel was sufficient, suggesting easy spreading and no signs of grittiness. The lower value of spreadability indicates the lesser work required to spread the gel over the skin, which means easily spread formulation was by applying a small amount of shear. The spreadability of gel were ranging from 6.14 ± 0.21 to 6.67 ± 0.16 g.cm/s. The greater dispersibility, the easier the formula applied to the skin surface. Good spreadability about 5-7 cm.[17]

The result of In vitro skin permeation of miconazole nitrate gel
The drug release kinetics was studied using a modified Franz-type diffusion cell. The cumulative amount of penetration shows in Figure 1.
The cumulative amount of miconazole nitrate penetrated through rabbit skin during the 8 hours test of each gel formulation was 2.83%, 27.52%, 41.96% and 52.76%, respectively. This result confirms that the release of miconazole nitrate from the gel bases was greater in F3 than other formulations. The results also showed a significant difference between the gel formulas in the release of miconazole nitrate after 480 minutes. DMSO may also extract lipids, making the horny layer more permeable by forming aqueous channels. The mechanism of sulphoxide as a penetration enhancer is used widely to denature the protein. On application to human skin, it has been shown to change the intercellular keratin conformation from α-helical to ß-sheet.[2]

Table 2: The results of measuring the viscosity and pH of the preparation

Storage time	pH				Viscosity (cps)			
(weeks)	F0	F1	F2	F3	F0	F1	F2	F3
0	5.9 ± 0.2	5.9 ± 0.2	5.8 ± 0.2	5.8 ± 0.2	6996 ± 18.85	6996 ± 18.77	6996 ± 00.00	6996 ± 00.00
2	5.7 ± 0.2	5.8 ± 0.1	5.6 ± 0.1	5.8 ± 0.2	6996 ± 18.85	6996 ± 18.77	6996 ± 00.00	6996 ± 00.00
4	5.5 ± 0.1	5.6 ± 0.1	5.6 ± 0.1	5.6 ± 0.3	6996 ± 18.85	6996 ± 18.77	6996 ± 28.05	6996 ± 00.00
6	5.5 ± 0.3	5.6 ± 0.3	5.5 ± 0.1	5.5 ± 0.1	6996 ± 18.85	6996 ± 18.75	6996 ± 28.07	6996 ± 28.07
8	5.7 ± 0.2	5.8 ± 0.2	5.6 ± 0.1	5.8 ± 0.2	6996 ± 18.85	6996 ± 18.77	6996 ± 28.07	6996 ± 28.07

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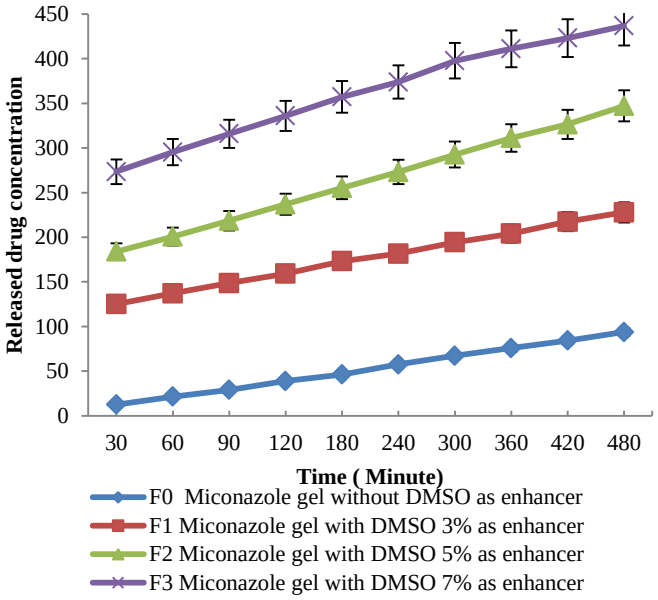

Figure 1: Graph of a penetration test of Miconazole gel in phosphate buffer pH 7.4 at 37°C.

Conclusion

Dimethyl sulfoxide can improve the permeation profile of miconazole nitrate from topical gel formulation. The formula containing 7% dimethyl sulfoxide showed the most excellent permeation profile.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them

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