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A Novel Organogel System Capable of Enhancing Skin Penetration Characteristics of Acyclovir

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ABSTRACT – Topical preparations such as cream for Acyclovir (ACV), a potent anti-viral agent for the treatment of herpes simplex and herpes zoster, have been marketed in the world since 1993. However, the skin penetration rate of ACV from generic cream formulations sold in Europe has been found to be lower than the original Zovirax® cream. In this study, we formulated ACV into a novel organogel system and compared the skin penetration characteristics with Zovirax® cream. The rate and amount of skin penetration of ACV from the organogels were 6.3-fold greater than those obtained with Zovirax® at an ACV concentration of 5%. The solubilizing effect of oil phase and anti-nucleation effect exhibited by sodium alginate contained in water phase are most likely attributed to enhanced ACV skin penetration property.

Key words – Acyclovir, Organogel, Skin penetration

Acyclovir (ACV), [9-(2-hydroxyethoxymethyl) guanine] is a well-known potent and selective anti-viral agent for herpes simplex and herpes zoster viruses and it has been generally administrated orally as well as topically.[1] Since 1993, many topical generic products of Glaxo Smith Kline's ACV 5% cream (Zovirax®) have been marketed all over the world. Trottet et al. have compared the skin penetration characteristics of 139 generic cream products of ACV sold in Europe and showed that Zovirax® cream was proven to be superior in terms of skin penetration ability of ACV among the products tested.[2] In vitro skin penentration study has been recognized as a convenient means to study the bioequivalence of topical products for systemic effects.[3] Based on these backgrounds, we compared the skin penetration characteristics of a novel ACV organogel system with Zovirax® (Glaxo Smith Kline, marketed by Dong-A Pharmaceutical company, Korea).

Experimental

Materials

ACV was donated from Dong Gu Pharmaceutical company (Seoul, Korea). Gelucire 44/14®, Plurol Oleique® and Lauroglycol 90® were obtained from Gatteffossè (France). Sodium alginate was purchased from Junsei Chemical Co. Ltd. (Japan) and all other solvents reagents were of reagent grade and used as received.

Preparation of ACV organogel

Oil phase, composed of Gelucire 44/14®, Plurol oleique® and Lauroglycol 90®, was melt at 60°C. ACV was added to the oil phase and mixed with stirring for 30 min. Water phase was prepared by mixing sodium alginate (2.5%) and glycerin in distilled water at room temperature and heated to 60°C. The oil phase was added to the water phase and mixed for 30 min. This ACV organogel formulation was cooled down to room temperature and matured for 48 h until skin penetration study.

Skin permeation study

Male Sprague-Dawley rats (12-14 weeks old, weighing 200±10 g) were used for in vitro skin penetration study. After the dorsal skin was separated carefully and the underlying subcutaneous tissue was surgically removed, the skin tissue was rinsed with saline solution. Prepared skin samples were stored in a deep freezer (−70°C) until skin penetration experiments. One gram of the organogel sample was loaded onto the donor compartment of Franz diffusion cells, maintained at 37±0.5°C, with a penetration area of 2.00 cm^2. PBS (pH 7.4) was used as a receptor solution.

HPLC analysis condition

Reverse phase μ-Bondapak (C_{18}, 4.6×150 mm, 5 μm, Waters, MA, USA) column was used for analysis of ACV. The composition of mobile phase was the mixture of 1% acetic acid and acetonitrile (98 : 2, (v/v)) with a flow rate of 1.2 mL/

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min. Detection wavelength was 254 nm and injection volume was 20 μL.

Results and Discussion

The skin penetration characteristics of ACV in the organogel formulation with various concentrations of ACV ranged from 0.5 to 7%. As shown in Figure 1, the skin penetration rate of ACV increased gradually with increasing ACV concentrations within the organogel. The skin penetration rate of ACV from the organogel having ACV concentrations of 5 and 7% was similar. The skin penetration rate and amount of ACV from the organogel was 6.3-fold greater than that from Zovirax® at an ACV concentration of 5% (Figure 2). The total penetrated amount of ACV from the organogel after 6 h was 33.2 μg/cm^2, but that of ACV from Zovirax® was only 5.28 μg/cm^2. The flux value of ACV from the organogel was 5.53 μg/cm^2/hr while that of Zovirax® was 0.88 μg/cm^2/hr, respectively. The flux of ACV from Zovirax® was similar to that of the organogel containing 0.5% of ACV.

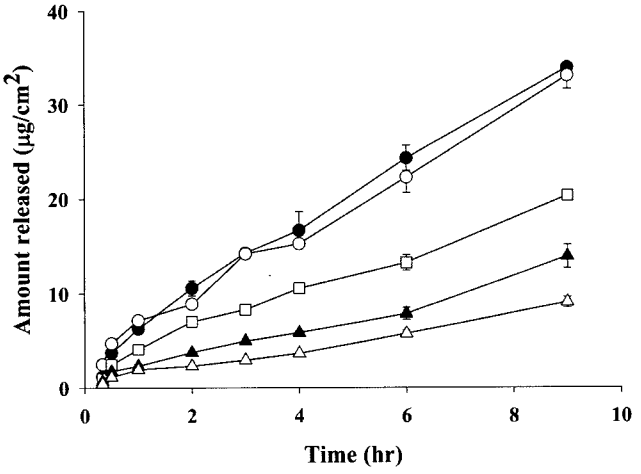

Figure 1–Effect of concentration on the skin penetration of acyclovir from organogel. Each data point indicates mean±S.E. (n=3). △, 0.5% ACV; , 1% ACV; □, 2% ACV; ○, 5% ACV; ●, 7% ACV.

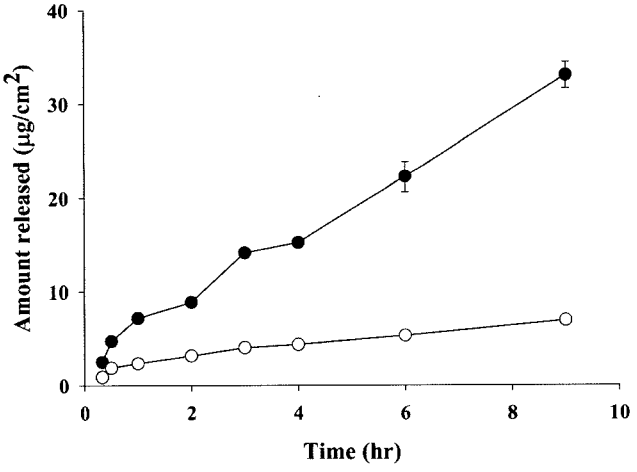

Figure 2–Comparison of skin penetration of acyclovir from the organogel and commercially available Zovirax® cream at an acyclovir concentration of 5%. Each data point indicates mean±S.E. (n=3). ○, 5% Zovirax® cream; ●, 5% organogel.

When we examined the microscopic images of Zovirax® cream and the present organogel, insolubilized ACV crystals were obviously observed and the amount of drug crystals found in Zovirax® was considerably greater than in the organogel. In addition, the crystal size of ACV in the organogel was much smaller than that observed in Zovirax® (data not shown). It is thus speculated that the solubility of ACV in the organogel was higher than in Zovirax®. Accordingly, this apparently increased solubility of ACV in the organogel may be attributed to the enhanced skin penetration of ACV. The increased solubility of ACV in the organogel may come from the solubilizing effect of the oil phase and anti-nucleation effect of the polymer dispersed in water phase. The anti-nucleation effect inhibiting the growth of drug crystal is somewhat in agreement with Kondo *et al.* who studied the mechanism of anti-nucleation effect of hydrophilic polymers.[4-7] The present study demonstrated that the organogel system composed of oil phase and sodium alginate contained in water phase could be a promising skin penetration enhancing formulation for ACV. The solubilizing effect of oil phase and anti-nucleation effect exhibited by sodium alginate is most likely the reason for its enhanced ACV skin penetration property.

Acknowledgements

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