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Effects of Glycerin and PEG 400 in Donor and Receptor Solutions upon Skin Permeation of Drug

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In vitro 경피흡수 실험시 Donor 와 Receptor 용액중의 글리세린과 PEG 400이 약물의 경피투과도에 미치는영향

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Effects of glycerin and PEG 400 in donor and receptor solutions upon skin permeation of drug were investigated. Deoxycortisone was used as a model compound. *In vitro* skin permeation study with freshly excised hairless mouse skin was performed and the steady-state skin permeation rates of the drug were determined in different fractions of glycerin or PEG 400 in donor and receptor solutions. Glycerin in donor solution didn't show any effect on the skin permeation rate of deoxycortisone. However glycerin in receptor solution showed significant effect on the skin permeation rate of the drug. In glycerin, there's a critical concentration for balancing hydration and dehydration of skin. At low concentration, less than 20 %, glycerin showed the enhancement of the flux due to the hydration effect of skin. At high concentration, more than 30 %, glycerin retard the permeation rate which might be due to the dehydration effect on the dermis layer. Since dermis has more water content than the stratum corneum, the steady state skin permeation rates were more influenced when glycerin was in receptor solution than that of in donor solution. PEG 400 aqueous solutions doesn't affect the steady state permeation rate of deoxycortisone significantly.

Keywords—Skin permeation, Deoxycortisone, Glycerin, PEG 400, Receptor solution, Donor solution

Glycerin (propane-1,2,3-triol) has been used primarily for its humectant and emollient properties in topical pharmaceutical formulations.[1] The humectant glycerol when applied topically can retain the water and reduce the water evaporation.[2] There are several reports that the humectant properties of glycerol may come from the ability to bind water to itself.[2] Batt et al., reported that glycerin may interact with stratum corneum lipid structures or proteins, altering their water binding or hydrophobic properties.[3] In addition to its moisturizing effect on the skin, glycerin has been used as a stabilizing agent for unstable compounds such as vitamin C.[4,5]

As a stabilizing medium for vitamin C during skin permeation study, glycerin solution has been used since glycerin solution showed more stabilizing effect than the other polymeric solutions such as propylene glycol and PEG 400.[6] However we noticed that the skin permeation rate of the drug was significantly influenced by the volume fraction of glycerin in receptor solutions. Since the physical and chemical properties of the vehicle play a major role in det-

ermining the rate of uptake and penetration of the drug through the skin,[7,8] we investigated the effect of glycerin in donor and receptor solutions upon skin permeation rate of drug. As a comparison, we also investigated the effect of PEG 400 in receptor solution. Deoxycortisone was selected as a model drug.

MATERIALS AND EXPERIMENTAL METHODS

Deoxycortisone and glycerin were obtained from Sigma Chemical Co. (St. Louis, Mo, USA). Silicone Fluid (Dow Corning 360, 20 cp) and PEG 400 (Dow Corning) were used as obtained. All other chemicals were regent grade. The solvent used in HPLC assay was HPLC grade.

Permeation Study and HPLC anaysis

Glycerin as a Donor Solution

Glycerin aqueous solutions with different fractions (0-50%, v/v) were prepared. Excess crystals of deoxycortisone were put into each solution and equilibrated for 24 hr in a shaking water bath at 37°C. The saturated solutions of deoxycortisone were used as a donor solution. Forty percent PEG 400 aqueous solution was used as a receptor solution. Skin permeation study was performed under *in vitro* conditions as described previously.[9] In brief, a freshly excised full thickness of abdominal skin of a female hairless mouse (5-7 weeks old, Jackson Lab., HRS/J strain) was mounted between the half cells of the in vitro skin permeation system (n=3-6). The hydrodynamic characteristics of this diffusion cell has already been established previously.[10] Then the selected donor and receptor solutions were charged in each cell compartment. The volume of donor and receptor cell was 3.5 m*l* respectively. At predetermined time intervals, 30 μ*l* of receptor solution was withdrawn and assayed for the drug concentration with HPLC. The total amount of drug which permeated through the skin was plotted as a function of time. Permeation rate and lag time were determined from the steady-state permeation profile and the time intercept of the profile respectively. A HPLC analysis was employed to quantitate the amount of the drug permeated through the skin. Acetonotrile : water = 55:45 was selected as a mobile phase. β-Bondapak C_{18} reverse phase (4×30 mm) column was used.

Glycerin and PEG 400 as a Receptor Solution

Excess deoxycortisone was put into a silicone fluid and equilibrated for 24 hr in a shaking water bath at 37°C. The saturated solution of deoxycortisone in silicone fluid was used as a donor solution. Silicone fluid was selected because it has a good solubility of deoxycortisone and has no interaction with skin membrane and thus shows no alteration effect on the skin permeation rate of drug. Different fractions of either glycerin or PEG 400 (v/v) were prepared and used as a receptor solution. Skin permeation study was conducted as described above.

RESULTS AND DISCUSSION

Solubilities of deoxycortisone in a different volume fraction of glycerin solutions were listed in Table 1. As the volume fraction of glycerin (%, v/v) increases, the solubility of the drug propotionally increases. Glycerin acts as a co-solvent for this lipophilic deoxycortisone.

Fig. 1. shows the effect of glycerin as a donor solution upon the skin permeation of the drug. As a receptor solution, 40 % PEG 400 aqueous

Table 1—*Solubilities of Deoxycortisone in Different Volumn Fraction of Aqueous Glycerin Solution.*

Volume fraction of glyerin (% v/v)	Solubility of deoxycortisone(μg/m*l*)
0	106.9±0.64
10	191.6±2.99
20	216.0±7.71
40	517.5±10.40
50	675.8±30.25

solution was used. There was no significant effect of glycerin on the skin permeation of the drug. Although the solubility of deoxycortisone is quite different in the different fractions of glycerin solutions, the permeation rates and the lag times are similiar. These result may suggest that glycerin in donor solution doesn't change the property of the skin such as the the solubility of the deoxycortisone in the skin or the diffusivity of the drug through the skin during 12 hour skin permeation study.

Fig. 2. shows the effect of glycerin in receptor solution on the skin permeation of deoxycortisone. Each receptor solution has high enough solubility to maintain the sink condition. Although the driving force for the skin permeation was same as we control the donor solution concentration, the permeation profiles of the drug with different volume fractions of glycerin (0-50 %) in the receptor solutions show a remarkable difference. Ten percent and twenty percent glycerin receptor solutions show higher permeation rate than those of water, 40 % and 50 % solutions. The lag times in each profile and the permeation rate are different suggesting glycerin in receptor solution may influence the diffusivity of the drug through the skin. As glycerin acts as a humectant in low concentrationa, the higher permeation rate observed might be due to the hydration effect on the dermis which consists of an aqueous phase. By hydrating the dermal side of skin, glycerin helps the lipophilic deoxycortisone permeate through the skin. Since hydration enhance the permeation rate.[11-13]

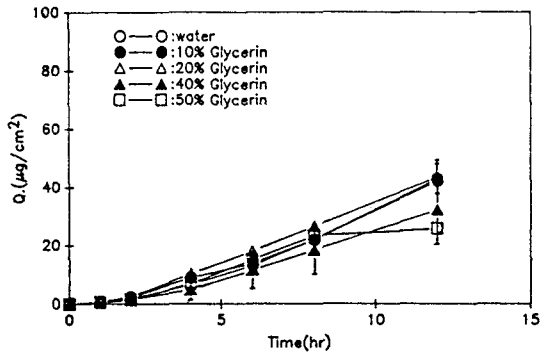

Figure 1—Effect of glycerin in donor solution on the skin permeation of deoxycortisone. Receptor solution : 40% PEG 400 aqueous solution.

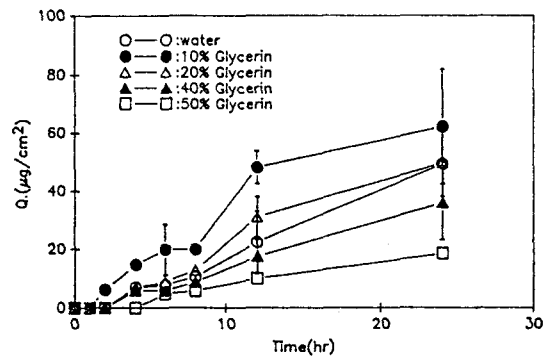

Figure 2—Effect of glycerin in receptor solution on the skin permeation of deoxycortisone. Donor solution : Silicone Fluid was saturated with deoxycortisone.

Fig. 3. shows the comparison of the effect of glycerin either in the donor or in receptor solution on the steady state permeation rate. The steady state flux were plotted as a function of glycerin concentrations. There is no significant change in steady state flux with different fractions of glycerin in the donor solution. However, the effect of glycerin in the receptor solution is somewhat significant as discussed above. Since the stratum corneum contains 15 % less than the dermis, glycerin doesn't show any effect on

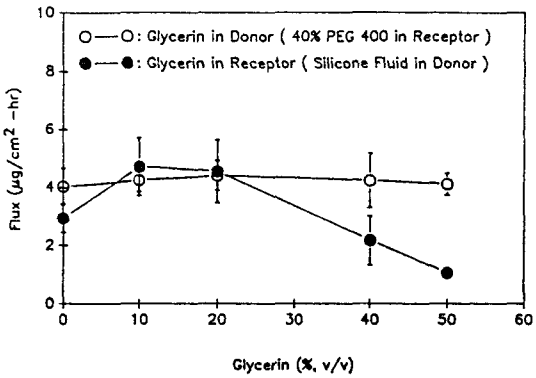

Figure 3—Influence of glycerin in donor and receptor solution upon skin permeation of deoxycortisone.

the stratum corneum while there's a significant effect on the dermis side. This enhancement may be attributed to skin moistening by glycerin on the skin. Glycerin which has three hydroxy functional groups in the molecule might form hydrogen bonds with water molecule in the skin. When the glycerin fraction further increased, the permeation rate decreased. This may suggest the existence of a critical concentration of glycerin for determining hydration and dehydration of the skin. At high concentration, glycerin might absorb water from a skin tissue, and makes the skin structure more tight resulted in low permeation rate.

The effect of PEG 400 in the receptor solution on the skin permeation of deoxycortisone is also investigated. Fig. 4. shows the effect of PEG 400

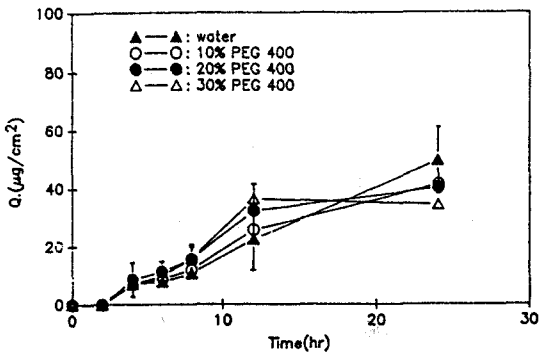

Figure 4—Effect of PEG 400 in receptor solution upon skin permeation of deoxycortisone.

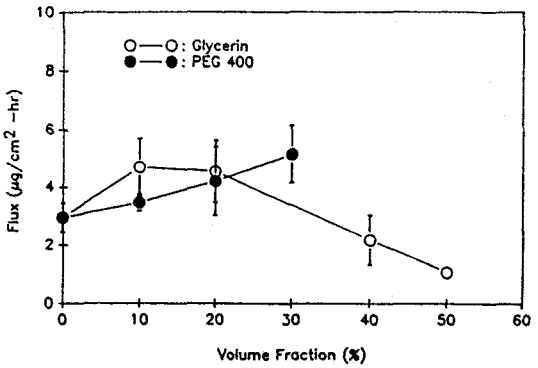

Figure 5—Comparison of the effect of glycerin and PEG 400 upon steady state skin permeation rate of deoxycortisone.

in the receptor solution. Silicone fluid saturated with desoxycorticone was used as the donor solution. Permeation profiles indicate that PEG 400 in the receptor solution does not influence the permeation rate and the lag time. Tojo et al., [14] previously reported the effect of PEG 400 in a donor solution on the skin permeability of progesterone. There was no change on skin permeation rate of progesterone with different fraction of PEG 400 as a donor solution.

The effect of glycerin and PEG 400 in the receptor solution upon steady state flux were compared in Fig.5. Up to 20 % of glycerin solution, the steady state permeation rate is similiar with the one of PEG 400 solutions. However at higher than 20 % of glycerin solution, the flux become significantly decreased due to the dehydration effect on the skin.

Based on our experimental results, we recommend that unless there's a special requirement to use glycerin as a stabilizing medium, PEG 400 aqueous solution is preferable as a co-solvent for the lipophilic drug during the skin permeation study.

CONCLUSION

Glycerin in the receptor solution can significantly influence the skin permeation rate of the drug. At low concentration, 10 to 20 %, glycerin enhanced the permeation rate while at high concentration, 40 to 50 %, glycerin retarded the permeation rate of the deoxycortisone. PEG 400 aqueo s solution in receptor solution doesn't significantly affect the steady state permeation rate of the drug.

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