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# Skin Permeation Enhancement of Drugs by Lipophilic and Hydrophilic Vehicles

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The in vitro skin permeability of 16 drugs with a wide span of lipophilicity (log P ranging from −0.95 to 4.40) was evaluated with an ethanol/panasate 800 (tricaprylin, P-800) (40/60) lipophilic binary vehicle and an ethanol/water (60/40) hydrophilic binary vehicle with lauric acid. The skin permeability of the drugs was enhanced by the use of the ethanol/P-800 (40/60) binary vehicle or the ethanol/water (60/40) binary vehicle with lauric acid; permeation rate was increased and lag time was decreased. The relationship between lipophilicity and skin permeation rate of the drugs showed parabolic shapes with their peaks at much greater hydrophilic range compared with other past references. In the in vivo skin absorption of theophylline using abdominal rat skin, the ethanol/P-800 (40/60)-7% (w/w) ethycellulose gel produced a good feature as a sustained-release preparation, and the ethanol/water (60/40)-3 % (w/w) HPMC gel with lauric acid showed the highest BA value. The results suggest that the lipophilicity of a drug is a main factor for prediction of the skin permeability of the drug and that the ethanol/P-800 (40/60) binary vehicle and ethanol/water (60/40) binary vehicle with lauric acid would be good candidates for clinical transdermal application of hydrophilic drugs.

The advantages of transdermal administration are avoiding hepatic first-pass effect, minimizing inter- and intrapatient variation, maintaining steady-state plasma level to provide long-term therapy from a single dose, and allowing a shift termination of drug input can be realized. For the potential use of a drug as a transdermal delivery system, two limiting factoer (a long lag time and a low steady-state flux) must be overcome. The method for overcoming these obstacles is to select an optimal vehicle system or to use a permeation enhancer. We developed a lipophilic vehicle for skin permeation enhancement of a drug. The in vitro skin permeation results of ketoprofen showed that ethanol plays a role in a long lag time and a high permeation rate, and that panasate 800 (caprylic triglyceride, P-800) plays a role in reducing lag time.[1] P-800 is a neutral oil that is not miscible with water and is stable toward oxidation compared with natural vegetable oils. It has been also suggested that an ethanol/P-800 (40/60) lipophilic binary vehicle improved both the permeation rate and the lag time, and the mutual effect was concluded to be due to the increase of diffusivity of a drug by P-800 and the increase of partition of a drug into skin tissue by ethanol.[1,2] In a previous report,[4] we suggested that an ethanol/water (60/40) hydrophilic binary vehicle increased the permeability of tegafur, but the permeability, the lag time (6.3 h) and the permeation rate (0.6%/h) were insufficient. The addition of fatty acids or fatty alcohols as permeation enhancers to the binary vehicle dramatically enhanced the permeability of tegafur. The highest enhancement effect was obtained with lauric acid. However, the above binary vehicles as solution states

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demand a practical dosage form for clinical use.

Generally, the skin can be considered as a trilaminate structure, consisting of the outer hydrophobic stratum corneum, the underlying viable hydrophilic epidermis, and dermis. The amphiphilic nature of the skin dictates that its permeability will be highly dependent on the lipophilicity of a penetrant.

In the present study, we evaluated the effects of the ethanol/P-800 (40/60) lipophilic binary vehicle and ethanol/water (60/40) hydrophilic binary vehicle with lauric acid on the skin permeation of various drugs having a wide range of lipophilicity as indicated by the n-octanol/water partition coefficient P (log P, −0.95~4.40). We selected 16 drugs, including anti-cancer drugs, xanthines,local anesthetics, and anti-inflammatory drugs, as model drugs with different log P values. The relationships between lipophilicities of the drugs and in vitro skin permeabilities were studied. Furthermore, we developed a trial to prepare a lipophilic ethylcellulose gel using the ethanol/P-800 (40/60) binary vehicle and a hydrophilic hydroxypropylmethylcellulose (HPMC) gel using the ethanol/water (60/40) binary vehicle containing lauric acid. we selected theophylline as a hydrophilic model drug, and evaluated the in vivo absorption of the drug from the two gel preparations.

## Materials and Methods

### Materials

Tegafur was obtained from Taiho Pharmaceutical Company (Tokushima, Japan). Alclofenac, ketoprofen and ibuprofen were gifts from Hisamitsu Company (Saga, Japan). Propentofylline and pentoxifylline were kindly supplied from Hoechst-Japan Company (Tokyo, Japan). The following drugs were purchased from the companies described in parentheses: 5-fluorouracil and caffeine (Wako Pure Chemicals, Japan); lidocaine HCl and salicyluric acid (Sigma Company, St. Louis, MO); and theophylline, antipyrine, procaine HCl, tetracaine HCl, dibucaine HCl, salicylic acid, ethylcellulose (8~120 cP grade), and lauric acid (Nacalai Tesque Company, Kyoto, Japan). HPMC (Metolose 65H-4000) was kindly supplied by Shin Etsu Chemical Company (Tokyo, Japan). Panasate 800 (P-800) as tricaprylin was kindly supplied by Nihon Yushi Company (Tokyo, Japan). All other chemicals were of reagent grade.

### Preparation of Ethanol/P-800-Ethylcellulose Gel

Ethanol/P-800 (40/60)-ethylcellulose gels containing 0.5% (w/w) theophylline were prepared by three roll mill method. Ethylcellulose was mixed with P-800, and then the mixture was mechanically conducted with a three roll mill (Erweka AR400, Erweka Apparatus GMBH, Ottostr, Germany) until the mixture became transparent and produced a viscous P-800-ethylcellulose gel. Ethanol/P-800 (40/60)-ethylcellulose gel containing0.5% (w/w) theophylline was prepared by the addition of ethanol containing the drug to the P-800-ethylcellulose, followed by mixing with a mortar and pestle.

### Preparation of Ethanol/Water-HPMC Gel

HPMC was added to ethanol/water (60/40) bi-nary vehicle, and then the mixture was mechanically stirred with a propeller (MDC Stirrer 2S type, Tokyo Rikakikai Company, Tokyo, Japan) at 200 rpm to produce a transparent ethanol/water (60/40)-HPMC gel. Ethanol/water (60/40)-HPMC gel containing 0.5% (w/w) theophylline and 4% (w/w) lauric acid was prepared by dissolving the drug and lauric acid to the above gel.

### *In Vitro* Skin Permeation Studies

The in vitro experiments were performed according to the method given in our previous report.[1] Briefly, the excised skin of hairless female mouse was obtained from 8~9-weeks-old,

27~33-g animals. Vertically assembled diffusion cells with an effective diffutional area of 0.785 $cm^2$ and downstream volume of 5 mL were used. The above skin was mounted on the diffusion cell, and the receiver compartment was filled with 5 mL of 50 mM phosphate buffer saline (PBS) at pH 7.4 maintained at 37℃. The donor compartment was charged with 0.5 mL of 0.5% (w/w) drug preparation at 37℃ and capped. Five hundred-microliter aliquots were withdrawn from the receiver compartment periodically for 26 h and replaced with equal volume of fresh PBS maintained at 37℃.

The sample solution was filtered through a membrane filter (pore size, 0.2 μm; Tosoh W-13-2; Tosoh Company, Japan) and injected onto the HPLC. The HPLC (Shimadzu Company, Kyoto, Japan) consisted of a solvent delivery pump (LC-9A), a column (Shimpack CLS-ODS, 0.6×15 cm), a UV detector (SPD-6A), and an integrater (C-R 6A). In all cases, the flow rate and column temperature were kept at 1.5 mL and 40℃, respectively. Mobile phases and UV conditions for each drug are listed in Table I. The correction of concentration against each sample point was also undertaken.

**Table I**—HPLC Methods Employed for Determination of Concentration of Drugs in In Vitro Experiments

| Drugs | Mobile phase[a)] | UV detection (nm) |
|---|---|---|
| Anti-cancerDrugs | | |
| 5-Fluorouracil (FU) | A : C(1 : 90) | 280 |
| Tagafur (TEG) | A : C(17 : 83) | 280 |
| Xanthines | | |
| Caffeine (CF) | A : C(18 : 82) | 273 |
| Theophylline (TP) | A : C(12 : 88) | 273 |
| Pentoxifylline (PT) | A : C(30 : 70) | 273 |
| Propentofylline (PP) | A : C(45 : 55) | 273 |
| Local Anesthetics | | |
| Procaine HCL (PC) | A : B : D (10 : 3 : 87) | 290 |
| Lidocaine HCl (LC) | A : B : D (19 : 3 : 78) | 210 |
| Tetracaine HCl (TC) | A : B : D (31 : 8 : 61) | 290 |
| Dibucaine HCl (DC) | A : B : D (38 : 8 : 54) | 240 |
| Anti-inflammaatory Drugs | | |
| Antipyrine (AP) | A : D(28 : 72) | 254 |
| Salicyluric acid (SU) | A : C(15 : 85) | 300 |
| Salicylic acid (SU) | A : C(17 : 83) | 300 |
| Alclofenac (ALC) | A : C(27 : 75) | 220 |
| Ketoprofen (KP) | A : C(30 : 70) | 258 |
| Ibuprofen (IBU) | A : C(34 : 66) | 220 |

[a)]Expressed as volume fraction; A : Acetonitrile; B : MeOH; C : pH 7.0, 10 mM Phosphate Buffer; D : 0.5 mM Phosphoric Acid.

### *In Vivo* Skin Permeation Studies

The abdominal hair of a rat (Wistar strain, 7 weeks old, 180~220 g, Nihon SLC, Shizuoka, Japan) was removed with clippers on the day before the experiments. Pentobarbital was administered intraperitoneally at a dose of 50 mg/kg to induce continuous anesthesia during the experiment, and the animal was restrained in the supine position on a plate maintained at 37℃. We used a specially made glass cell with an effective diffusional area of 3.14 $cm^2$. The glass cell was attached to the hair-free abdominal region of the rat using an adhesive (Aron Alpha, Toa Gosei Chemical Company, Ltd., Tokyo, Japan), and then the cell was charged with 0.5 g of 0.5% (w/w) drug preparation at 37℃ and capped. Two hundred fifty-microliter blood samples were collected periodically from the jugular vein for 26 h. The blood samples were centrifuged at 12000 rpm for 5 min, and 0.1 mL plasma samples were used for analysis.

The concentration of theophylline in each plasma sample was determined by HPLC. To 0.1 mL of plasma, 0.1 mL of caffeine solution (20 μg/mL) as an internal standard and 8 mL of dichloromethane were added. The mixture was extracted by shaking for 20 min, followed by centrifugation at 2500 rpm for 20 min. Seven mL of organic layer was collected and evaporated under a nitrogen gas stream at 45℃ to remove the solvent. The residue was dissolved in 0.2 mL of the above mobile phase, and 20 μl of the solution was injected into the HPLC. The other conditions of HPLC were the same as described above.

**Determination of n-Octanol/Water Partition Coefficient**

The logarithms of n-octanol/water partition coefficient (log P) were obtained either from references[5-8] or by the calculation.[9] The calculation was made with Hansch π values.[7]

**Calculation of Permeation Parameters**

For each diffusion cell, the cumulative permeation percentage (%) of drugs versus time (h) was plotted. The in vitro permeation rate (%/h) and lag time (h) could be calculated from the slopes and intercepts, respectively, on the time axis of the linear portion of the plots. In vivo bioavailability (BA, %) was calculated by comparing the areas under the plasma concentration-time curves (AUC) obtained after intravenous and dermal administration. Individual AUCs were calculated using the trapezoidal rule for 0 ~24 h. Four experiments per group were performed. All data were expressed as the mean standard deviation (S.D.).

## Results and Discussion

***In Vitro* Skin Permeability of Drugs from Ethanol/P-800 Lipophilic Binary Vehicle**

The in vitro permeabilities of 16 drugs through excised hairless mouse skin were examined with ethanol, P-800, and the ethanol/P-800 (40/60) binary vehicle. The permeation profiles of 5-fluorouracil, procaine HCl, propentofylline, and ibuprofen are shown in Fig. 1 as typical examples. The corresponding permeation parameters and log P of the drugs are summarized in Table II.

The skin permeabilities of all drugs were remarkably enhanced by the ethanol/P-800 (40/60) binary vehicle compared with ethanol or P-800 as single vehicles. These results are in agreement with our previous results that skin permeation of ketoprofen,[1] alclofenac,[2] or tegafur[4] was enhanced by the combination vehicle of ethanol and P-800 compared with each single vehicle. In those reports, we concluded that the mutual enhancement effect of the ethanol/P-800 binary vehicle was due to ethanol increasing the permeation rate by increasing the partition of the drugs to the skin and by reducing the barrier function of the stratum corneum; also P-800 reduces the lag time, by increasing the diffusion of the drugs in the stratum corneum and viable skin.[2] In the present study, it was suggested that the ethanol/P-800 (40/60) binary vehicle is also effective at improving the permeability of a wide span of drugs with different lipophilicity.

***In Vitro* Skin Permeability of Drugs from Ethanol/Water Hydrophilic Binary Vehicle with or without Lauric Acid**

Table III represents the permeation parameters of 16 drugs with a wide span of log P, for the ethanol/water (60/40) binary vehicle with or without lauric acid. With an ethanol/water (60/40) binary vehicle, lag times ranging from 2.0 to 9.9 h and permeation rates ranging from 0.12 to 1. 90%/h were observed for most drugs. The addition of lauric acid to the binary vehicle remarkably enhanced the skin permeability of almost all the drugs (except such drugs as ibuprofen or ketoprofen) compared with the binary vehicle alone. The lag times were reduced to under 2.9 h for all drugs. The greatest permeation rate was observed for 5-fluorouracil, which had the highest hydrophilicity of all the drugs examined in this study, whereas dibucaine with the highest lipophilicity showed the lowest value. We recently demonstrated a good and linear relationship between the solubility parameter and the permeation coefficient of nine steroidal drugs with almost the same molecular weight and similar chemical structure.[10] In that paper, we concluded that the partition of the drugs from the ethanol/water (60/40) binary vehicle increases as the lipophilicity of the drugs increases, because the lipo-

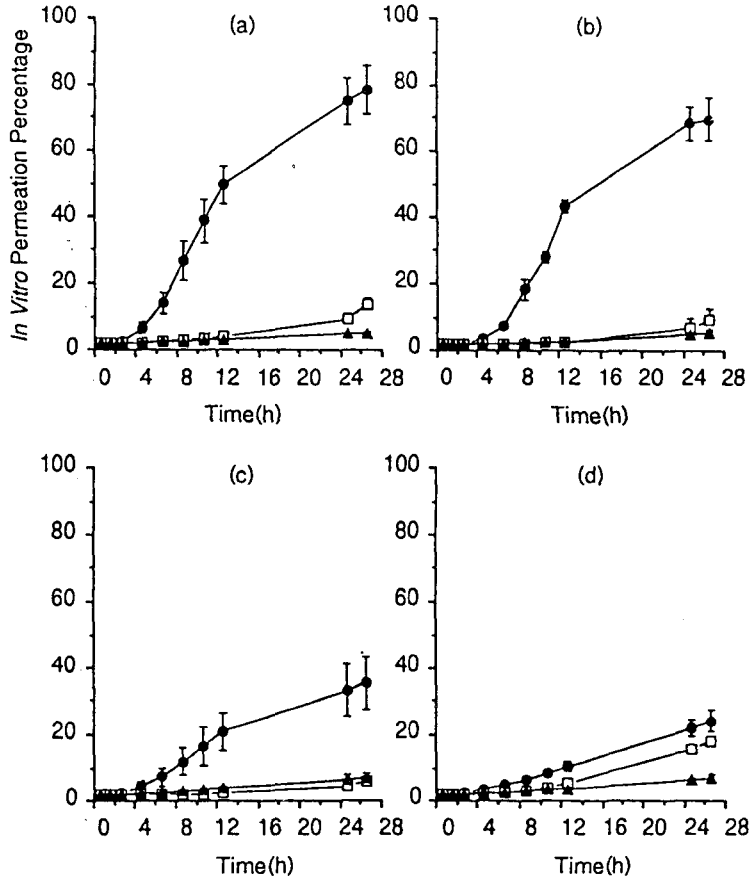


**Figure 1**—In vitro skin permeation profiles of FU (a), PC (b), PP (c) and IBU(d) across excised hairless mouse skin from ethanol, P-800 and ethanol/P-800 (40/60) binary vehicle.
Key : □; Ethanol, ▲; P-800, ●; Ethanol/P-800 (40/60).
Each point and vertical line represent the mean and S.D. of four experiments.

philicity of the skin is higher than that of the binary vehicle. However, a reverse correlation between the enhancement ratio and log P was obtained in the present study. For explaining the above phenomenon, it will be necessary to elucidate the cooperative enhancing mechanism of lauric acid and the binary vehicle on drug permeability in relation to the total considerations of the barrier function, partition property and permeation route of the skin.

**Relationship between Lipophilicity and Skin Permeability of Drugs**[9,11]

Fig. 2 and 3 represent the relationship between lipophilicity and permeation rate of the drugs from the ethanol/P-800 (40/60) binary vehicle (Fig. 2) and from the ethanol/water (60/40) binary vehicle with lauric acid (Fig. 3).

The permeation rate of the drugs across excised hairless mouse skin increased with an increase in the hydrophilicity of the drugs; this was also observed with the ethanol/water (60/40) binary vehicle with lauric acid. The relationship between log P and the permeation rate of the drugs yielded good parabolic shapes in both the ethanol/P-800 (40/60) (Eq. 1) and the ethanol/water (60/40) binary vehicle with lauric acid (Eq.

**Table II**—Lipophilicity and In Vitro Skin Permeation Parameters of Various Drugs across Excised Hairless Mouse Skin from Ethanol/P-800 (40/60) Binary Vehicle

| Drugs | log P | Permeation rate(%/h) | Permeation percent (% at 12 h) | Lagtime (h) |
|---|---|---|---|---|
| FU | −0.95 | 7.2(0.6) | 54.4(5.2) | 2.2(0.5) |
| TEG | −0.48 | 8.0(0.7) | 56.8(5.4) | 2.2(0.7) |
| CF | −0.07 | 5.2(0.4) | 47.2(3.4) | 3.1(0.3) |
| TP | −0.02 | 5.9(0.5) | 47.7(4.5) | 2.9(0.4) |
| PT | 0.72 | 4.1(0.4) | 32.7(4.0) | 3.8(0.5) |
| PP | 1.72 | 2.1(0.3) | 18.8(5.5) | 3.5(0.5) |
| PC | 1.87 | 5.0(0.4) | 41.5(1.8) | 4.4(0.7) |
| LC | 2.26 | 2.3(0.3) | 19.4(4.6) | 3.8(0.5) |
| TC | 3.73 | 1.0(0.2) | 5.1(1.3) | 4.0(0.7) |
| DC | 4.40 | 0.5(0.1) | 4.7(1.3) | 4.2(0.4) |
| AP | 0.23 | 7.0(0.6) | 47.7(4.5) | 3.5(0.6) |
| SU | 1.13 | 6.4(0.7) | 57.5(8.3) | 2.8(0.3) |
| SD | 2.25 | 3.3(0.4) | 33.2(4.6) | 1.5(0.3) |
| ALC | 2.48 | 2.8(0.2) | 25.4(3.3) | 3.0(0.5) |
| KP | 2.94 | 1.9(0.2) | 16.1(2.3) | 3.7(0.4) |
| IBU | 3.51 | 1.2(0.2) | 7.7(0.6) | 2.2(0.4) |

Each value represents the mean (S.D.) of four experiments.

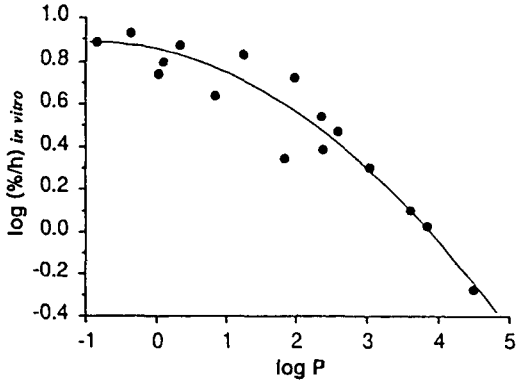


**Figure 2**—Relationship between log P and in vitro permeation rate of 16 drugs from ethanol/P-800 (40/60) binary vehicle.

2), which are described in the following regression equations:

$$\log(\%/h) = 0.81 - 0.07(\log P) - 0.04(\log P)^2 \quad (r = 0.916,\ n = 16) \quad (1)$$

**Table III**—In Vitro Skin Permeation Parameters of Various Drugs from Ethanol/Water(60/40) Binary Vehicle with or without 4%(w/w) Lauric Acid

| Drugs | Permeation rate (%/h) | | Lag time (h) | | Enhance-ratio |
|---|---|---|---|---|---|
| | I | II | I | II | |
| FU | 0.36(0.06) | 8.06(1.62) | 6.3(0.8) | 2.4(0.3) | 22.4 |
| TEG | 0.64(0.04) | 7.40(0.62) | 6.3(0.5) | 2.1(0.7) | 11.6 |
| CF | 0.35(0.06) | 5.69(0.64) | 5.0(0.8) | 1.8(0.3) | 16.3 |
| TP | 0.34(0.04) | 6.68(1.01) | 6.4(1.0) | 1.2(0.2) | 19.7 |
| PT | 0.23(0.03) | 4.17(0.88) | 9.3(1.6) | 2.1(0.2) | 18.1 |
| PP | 0.18(0.04) | 3.39(0.42) | 9.3(1.4) | 2.9(0.4) | 18.8 |
| PC | 0.31(0.07) | 3.83(0.71) | 8.3(1.1) | 1.3(0.3) | 12.4 |
| LC | 0.23(0.04) | 1.83(0.14) | 9.3(1.6) | 0.8(0.2) | 8.0 |
| TC | 0.15(0.01) | 0.31(0.05) | 9.8(1.8) | 2.8(0.5) | 2.1 |
| DC | 0.12(0.01) | 0.21(0.04) | 9.9(2.2) | 2.8(0.6) | 1.8 |
| AP | 0.29(0.04) | 6.37(1.05) | 6.8(1.3) | 2.9(0.7) | 22.0 |
| SU | 0.36(0.03) | 5.89(0.64) | 6.8(0.7) | 2.9(0.5) | 16.4 |
| SD | 1.67(0.22) | 6.07(0.85) | 2.0(0.3) | 1.8(0.4) | 3.6 |
| ALC | 1.81(0.24) | 4.34(0.52) | 4.1(0.6) | 1.2(0.3) | 2.4 |
| KP | 1.43(0.42) | 2.31(0.35) | 4.7(1.2) | 2.6(0.4) | 1.6 |
| IBU | 1.90(0.23) | 2.04(0.43) | 2.2(0.3) | 2.2(0.2) | 1.1 |

I : Ethanol/Water(60/40) Binary vehicle; II : Ethanol/Water(60/40) Binary vehicle containing 4%(w/w) Lauric acid; Enhancement Ratio=Permeation rate(II)/Permeation rate (I); Each value represents the mean(S.D.) of four experiments.

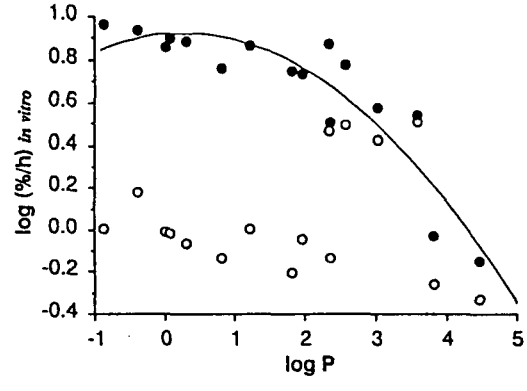


**Figure 3**—Relationship between log P and in vitro permeation rate of 16 drugs from ethanol/water (60/40) binary vehicle with lauric acid.
Key : ●; Ethanol/Water (60/40) with lauric acid, ○; Ethanol/Water (60/40) binary vehicle

$$\log(\%/h) = 0.85 + 0.03(\log P) - 0.08(\log P)^2 \quad (r = 0.916,\ n = 16) \quad (2)$$

Maximum values of permeation rates were obtained with a log P of −0.88 for the ethanol/P-800 binary vehicle and a log P of 0.19 for the ethanol/water binary vehicle with lauric acid with eqs 1 and 2, respectively. Therefore, it was considered that the above two binary vehicles would be successful at enhancing the skin permeation of relatively hydrophilic drugs.

Generally, the skin is considered as a heterogeneous structure, composed of a comparatively lipophilic stratum corneum and hydrophilic viable skin (epidermis and dermis). Therefore, for hydrophilic penetrants, partitioning into the stratum corneum becomes the rate-determining step of skin permeation. By contrast, for penetrants with a high lipophilicity, partitioning out of the stratum corneum into the viable epidermis becomes important. The heterogeneous skin, composed of alternative aqueous and lipidic phases, leads one to assume that a parabolic relationship may be obtained between lipophilicity and skin permeability of drugs if drugs with a wide range of lipophilic character are examined. It has already been reported that skin permeabilities of homologous salicylate and nonsteroidal anti-inflammatory drug series show a parabolic relationship to log P value, with peaks at log P of 2.24 and 2.43.[8] Many authors[8,12-16] also have reported that the relationship between skin permeability and lipophilicity showed a characteristic parabolic shape with the maximum occurring at a log P of 2~3. Their parabolic shapes, with maximum in amphiphilic drugs of log P 2~3, indicate that large skin permeations for clinical use cannot be expected for re latively hydrophilic drugs, and the stratum corneum is a permeation barrier for hydrophilic drugs.

In the present study, however, we could obtain parabolic relationship, with maximum peaks of log P at −0.88 and 0.19, which are inclined toward a much greater hydrophilic range when compared with the previous reports. It was concluded that the lipophilicity of a drug is the main factor for prediction of the skin permeability of the drug from the above two vehicles, and these vehicles more effectively enhance the skin permeability of a hydrophilic drug.

***In Vivo* Skin Permeation of Theophylline from Ethanol/P-800-Ethylcellulose Gel[17]**

Fig. 4 represents the plasma concentration-time profiles of theophylline after transdermal administration of the ethanol/P-800 (40/60) binary vehicle and the binary vehicle-ethylcellulose gel preparations. The corresponding BA parameters are summarized in Table **IV**.

In the case of the ethanol/P-800 (40/60) binary vehicle, the plasma concentration of theophylline reached a maximum value at 6 h after transdermal administration of the drug, and then rapidly declined. For the ethylcellulose gel preparations, the $C_{max}$ values decreased and the times ($T_{max}$)

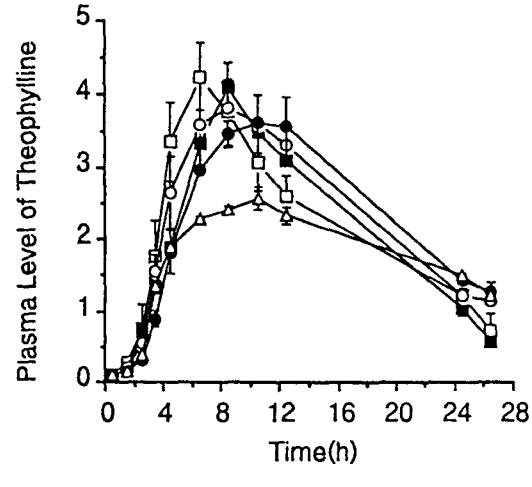


**Figure 4**—Plasma levels of theophylline across abdominal rat skin from ethanol/P-800 (40/60)-ethylcellulose gel preparations.
Content of ethylcellulose, Key : □; 0%, ■; 3%, ○; 5%, ●; 7%, △; 10%. Each point and vertical line represent the mean and S.D. of four experiments.

**Table IV**—In Vivo Skin Absorption Parameters of Theophylline across Abdominal Rat Skin from Ethanol/P-800 (40/60)-Ethylcellulose Gel Preparations

| Content of ethylcellulose (%, w/w) | $C_{max}$(μg/ml) | $T_{max}$ (h) | AUC(0-24 h) | Absolute BA (%) at 24 h |
|---|---|---|---|---|
| 0% | 4.2(0.5) | 6 | 55.9(7.5) | 65.7(7.3) |
| 3% | 4.0(0.4) | 8 | 52.3(1.3) | 64.8(1.6) |
| 5% | 3.7(0.1) | 8 | 58.8(2.7) | 72.9(3.3) |
| 7% | 3.5(0.4) | 10 | 55.3(4.8) | 68.6(5.9) |
| 10% | 2.5(0.2) | 10 | 42.3(1.3) | 52.4(1.6) |

Each value represents the mean(S.D.) of four experiments.

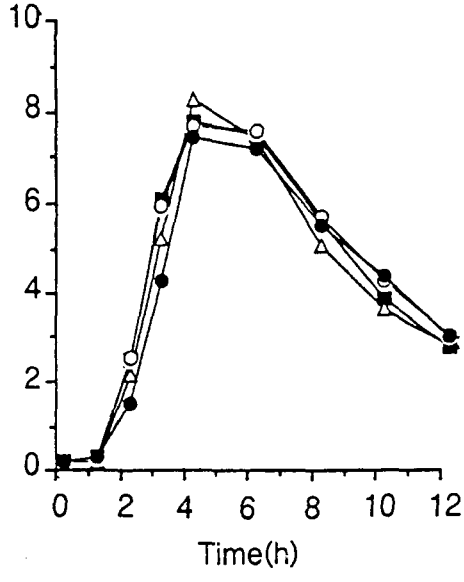


**Figure 5**—Plasma levels of theophylline across abdominal rat skin from ethanol/water (60/40)-HPMC gel preparations with 4% lauric acid.
Content of HPMC, Key : △; 0%, ■; 2%, ○; 3%, ●; 4%. Each point represents the mean of four experiments.
Acid

to reach $C_{max}$ were delayed with an increase in the content of ethylcellulose in the gels. Almost the same BA values (61.1~71.9) were obtained with 0~7%(w/w) ethylcellulose gels, and 7%(w/w) ethylcellulose gel preparation produced the best sustained-releasing profile. Unfortunately, 10%(w/w) ethylcellulose gel showed a low BA value in spite of the construction of a better pat-tern as a sustained-release preparation. This

**Table V**—In Vivo Skin Absorption Parameters of Theophylline across Abdominal Rat Skin from Ethanol/water (60/40)-HPM Gel Preparations with 4%(w/w) Lauric Acid

| HPMC content (%, w/w) | $C_{max}$(μg/ml) | $T_{max}$(h) | AUC | | Absolute BA(%) | |
|---|---|---|---|---|---|---|
| | | | 0-12 h | 0-24 h | at 12 h | at 24 h |
| 0% | 8.1(0.5) | 4 | 52.9(5.6) | 69.6(6.3) | 65.6(6.9) | 86.3(7.8) |
| 2% | 7.6(1.4) | 4 | 55.1(7.1) | 71.9(7.0) | 68.3(8.8) | 89.1(8.6) |
| 3% | 7.5(1.0) | 4 | 56.4(7.2) | 74.8(7.4) | 69.9(9.0) | 92.7(9.2) |
| 4% | 7.3(0.7) | 4 | 52.2(7.6) | 71.7(7.8) | 64.7(9.2) | 88.1(9.7) |

Each value represents the mean(S.D.) of four experiments.

fact was based on the difficulty of application to the skin as a result of its high viscosity.

### *In Vivo* Skin Permeation of Theophylline from Ethanol/Water-HPMC Gel[18]

Fig. 5 represents the plasma concentration-time profiles of theophylline using the ethanol/water (60/40) binary vehicle and the binary vehicle-HPMC gel preparations with lauric acid. The corresponding BA parameters are summarized in Table V.

The *in vivo* permeations of theophylline from the ethanol/water (60/40)-HPMC gel preparations with lauric acid and with various concentrations of HPMC showed essentially same patterns as that from the ethanol/water (60/40) binary vehicle with lauric acid. Especially, the ethanol/water (60/40)-3%(w/w) HPMC gel with lauric acid indicated the greatest BA (92.7%) and a good application on the skin surface.

## Conclusion

The skin permeation of various drugs covering a wide span of lipophilicity was enhanced by the use of an ethanol/P-800 (40/60) lipophilic binary vehicle or an ethanol/water (60/40) hydrophilic binary vehicle with lauric acid; permeation rate was increased and lag time was decreased. The relationship between lipophilicity and skin permeation rate of the drugs showed a parabolic shape with a peak at a more hydrophilic range

compared with other past references. In the in vivo skin absorption of theophylline using abdominal rat skin, the ethanol/P-800 (40/60)-7% (w/w) ethycellulose gel produced a good feature as a sustained-release preparation, and the ethanol/water (60/40)-3% (w/w) HPMC gel with lauric acid showed the highest BA value. We suggest that the ethanol/P-800 (40/60) binary vehicle and ethanol/water (60/40) binary vehicle with lauric acid could be considered as potential candidates for clinical transdermal application of a hydrophilic drug.

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