Prediction of Skin Permeability of Drugs. I. Comparison with Artificial Membrane

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In order to measure the contribution of lipid and pore (aqueous) pathways to the total skin permeation of drugs, and to establish a predictive method for the steady state permeation rate of drugs, the relationship between permeability through excised hairless rat skin and some physicochemical properties of several drugs were compared with those through polydimethylsiloxane (silicone) and poly(2-hydroxyethyl methacrylate) (pHEMA) membranes, as typical solution-diffusion and porous membranes, respectively. A linear relationship was found between the permeability coefficients of drugs for the silicone membrane and their octanol/water partition coefficients. For the pHEMA membrane, the permeability coefficients were almost constant independent of the partition coefficient. On the other hand, the skin permeation properties could be classified into two types: one involves the case of lipophilic drugs, where the permeability coefficient is correlated to the partition coefficient, similar to the silicone membrane; and the other involves hydrophilic drugs, where the permeability coefficients were almost constant, similar to pHEMA membrane. From the above results, the stratum corneum, the main barrier in skin, could be described as a membrane having two parallel permeation pathways: lipid and pore pathways. An equation for predicting the steady state permeation rate of drugs was derived based on this skin permeation model.

Keywords skin permeability; lipid pathway; pore pathway; physicochemical properties

Introduction

Transdermal drug delivery is one of the most promising approaches among various new drug delivery systems. However, only certain drugs can be effectively delivered through the skin. Therefore, a criterion to predict skin permeability of candidate drugs for transdermal drug delivery is desired.

Primary resistance to skin permeation is in the stratum corneum, the skin's uppermost layer.[1] Skin permeation has been treated as a transport process through a homogeneous membrane based on a solution-diffusion theory.[2] This theory was supported by a relationship between skin permeability and the physicochemical properties of limited lipophilic drugs,[3–5] but the relatively high permeability of ionic and polar solutes, such as tetraethylammonium bromide and glucose, could not be explained by the theory.[6,7] Recently, it has been recognized that the stratum corneum is a heterogeneous membrane consisting of a mosaic of cornified cells containing cross-linked keratin filaments and intercellular lipid-containing regions,[8] suggesting that there are distinct lipophilic and hydrophilic pathways in the stratum corneum.[6,7] Therefore, in predicting skin permeability of drugs, it is important to assess the contribution of each pathway to the permeability.

The primary objectives of the present study are (i) to measure the contribution of both the lipophilic pathway (lipid pathway), which can be described based on the solution-diffusion theory, and the hydrophilic pathway (pore pathway), which can be explained by the pore theory, to the total skin permeability; and (ii) to establish a predictive method for the steady state permeation rate of drugs based on this assumption. In pursuit of these aims, we used a number of drugs with a variety of physicochemical properties. Drug permeability through excised hairless rat skin was compared with that through polydimethylsiloxane (silicone) and poly(2-hydroxyethyl methacrylate) (pHEMA) membranes, as typical solution-diffusion and porous membranes, respectively. Several researchers have already reported the relationship between artifitial and/or skin membrane permeability and physicochemical properties of compounds.[3–5,9,10] However, limited drugs and basic compounds such as steroids and alkanols were mainly used to obtain the relationship. Therefore, we tried to reconstruct the relationship using a variety of practical drugs.

Materials and Methods

Materials Indomethacin (IDM), isosorbide dinitrate (ISDN) and flurbiprofen (FP) were gifts from Toko Yakuhin Industries Co. (Tokyo, Japan) and ibuprofen (IP) and nicorandil (NR) were from Nisshin Flour Milling Co. (Tokyo). Ketoprofen (KP), dopamine hydrochloride (DPH) and diclofenac sodium (DC-Na) were kindly supplied by Nissan Chemical Industries Co. (Tokyo), Nikken Chemicals Co. (Tokyo) and Hamari Yakuhin Industries Co. (Osaka, Japan), respectively. Lidocaine (LC), antipyrine (ANP), 5-fluorouracil (5-FU) and cyclobarbital (CB) were obtained from Tokyo Kasei Kogyo Co. (Tokyo) and aminopyrine (AMP) and β-estradiol (ED) were from Wako Pure Chemical Industrial Co. (Osaka), and dl-isoproterenol hydrochloride (IPH) and l-dopa (L-DP) were from Sigma Chemical Co. (St. Louis, MO, USA). Morphine hydrochloride (MPH) was purchased from Takeda Yakuhin Industries Co. (Osaka). All the above drugs were used without further purification. Other chemicals and solvents were of reagent grade and obtained commercially.

Membrane Preparation Non-reinforced polydimethylsiloxane sheeting (Silastic®, Dow Corning, Midland, MI, USA, 0.015 cm thick) was used as a silicone membrane.

pHEMA membrane was synthesized by a radical polymerization of 2-hydroxyethyl methacrylate (Tokyo Kasei Kogyo Co.) with azobis(isobutyronitrile) (Tokyo Kasei Kogyo Co.) as an initiator.[11] After complete polymerization, the membranes were repeatedly soaked in water until use. The thickness of the swollen membrane was about 0.05 cm.

A 4.5 cm^2 section of abdominal skin from male hairless rats (WBN/ILA-Ht, 6—7 weeks old, 150—160 g weight, Saitama Laboratory Animals, Saitama, Japan) was excised immediately before the skin permeation experiments. Either intact or stripped skin was used. The stripped skin was prepared by 20 times stripping using cellophane tape (Nichiban Co., Tokyo).[12]

Membrane Permeation Procedure Membrane permeation experiments were done according to the method of Okumura *et al.*[13] The receiver compartment of each cell was filled with distilled water and the donor compartment with a drug suspension in distilled water (at 2—10 times higher concentration than the solubility of each drug) to assure constant thermodynamic activity throughout the course of the experiment. Each experiment was carried out for 5 h (silicone) or 7 h (pHEMA) to achieve

a steady state permeation rate. Skin permeation was done for 8 h. In cases using highly hydrophilic drugs, the mean permeation rate from 4 to 8 h was treated as the steady state permeation rate because steady state permeation could not be achieved throughout the experiment. A sink condition was always maintained in the receiver compartment.

The effect of permeation-resistance in the dermis on the overall skin permeability of highly lipophilic drugs was corrected by calculating the permeability coefficient of the stratum corneum from the permeation data of stripped skin. The possibility of skin metabolism of drugs during the permeation experiment was checked by measuring metabolic activity against each drug in skin homogenates. All drugs used in this study were almost stable in the skin homogenates over 24 h.

Determination of Solubility and Partition Coefficient The solubility of drugs in water, octanol and isooctane was determined by following the method of Sato *et al.*[14] A cellulose acetate-membrane filter (0.2 μm pore size, Toyo Roshi, Tokyo) and FR-20 membrane filter (0.2 μm pore size, Fuji Photo Film Co., Tokyo) were used in cases of water and octanol or isooctane, respectively. Distilled water or methanol were used as diluting solvents. In the case of isooctane, the solvent (isooctane) was evaporated to dryness; subsequently, methanol or water was added.

The octanol/water partition coefficient of drugs (K_{ow}) was calculated as the solubility ratio in octanol/water at 37 °C.

Analysis of Drug Concentration The HPLC system for analyzing drug concentrations consisted of a pump (LC-6A, Shimadzu, Kyoto, Japan), either an ultraviolet (SPD-6A, Shimadzu) or fluorescent detector (RF-535, Shimadzu), a 4.6 mm × 250 mm stainless-steel column packed with Nucleosil 5C18 (Macherey Nagel, Germany), and an integrator (C-R6A, Shimadzu). In all cases, the flow rate of the mobile phase was 1.0 ml/min.

TABLE I. HPLC Conditions for the Analysis of Drugs Used in This Experiment

Drug	Mobile phase	Detection (nm)	Internal standard
ED	Acetonitrile : water (60 : 40)	Ex. 290 Em. 310	—[a]
IP	Methanol : 0.1% phosphoric acid (80 : 20)	UV 262	*p*-Hydroxybenzoic acid butyl ester
FP	Acetonitrile : 0.1% phosphoric acid (60 : 40)	UV 245	*p*-Hydroxybenzoic acid hexyl ester
IDM	Methanol : 0.1% phosphoric acid (80 : 20)	UV 262	*p*-Hydroxybenzoic acid ethyl ester
KP	Methanol : 0.1% phosphoric acid (75 : 25)	UV 254	*p*-Hydroxybenzoic acid amyl ester
LC	Acetonitrile : 0.1% phosphoric acid (33 : 67) + 5 mM sodium 1-hexanesulfonate	UV 245	*p*-Hydroxybenzoic acid methyl ester
ISDN	Acetonitrile : water (55 : 45)	UV 220	*p*-Hydroxybenzoic acid ethyl ester
CB	Acetonitrile : 0.1% phosphoric acid (35 : 65)	UV 205	—[a]
AMP	Acetonitrile : 0.1% phosphoric acid (40 : 60) + 5 mM sodium dodecylsulfate	UV 254	*p*-Hydroxybenzoic acid methyl ester
5-FU	Acetonitrile : 0.1% phosphoric acid (2 : 98)	UV 265	—[a]
DC-Na	Methanol : 0.1% phosphoric acid (75 : 25)	UV 286	*p*-Hydroxybenzoic acid butyl ester
NR	Acetonitrile : water (33 : 67)	UV 254	*p*-Hydroxybenzoic acid methyl ester
ANP	Acetonitrile : 0.1% phosphoric acid (30 : 70) + 5 mM tetra-*n*-butylammonium hydrogensulfate	UV 245	*p*-Hydroxybenzoic acid methyl ester
MPH	Acetonitrile : 0.1% phosphoric acid (40 : 60) + 5 mM sodium dodecylsulfate	UV 230	—[a]
IPH	Acetonitrile : 0.1% phosphoric acid (45 : 55) + 5 mM sodium dodecylsulfate	UV 280	—[a]
DPH	Acetonitrile : 0.1% phosphoric acid (35 : 65) + 5 mM sodium dodecylsulfate	UV 280	—[a]
L-DP	Acetonitrile : 0.1% phosphoric acid (35 : 65) + 5 mM sodium dodecylsulfate	UV 280	—[a]

a) Absolute calibration method was used.

Other conditions are listed in Table I.

Determination of Melting Temperature and Thermodynamic Activity The melting temperature (T_m) and heat of the fusion of the drugs were determined with differential scanning calorimetry (DSC-8230B, Rigaku Co., Tokyo). A weighed sample (1—3mg) was packed in an aluminum pan. An empty pan was used as a reference. Each sample was heated at a rate of 3 °C/min from room temperature to each melting point plus 15 °C (sensitivity of 4 mcal/s). The molar heat of fusion (ΔH) was calculated from the area of the melting endotherm and moles of each sample used by calibrating with metallic indium. The thermodynamic activity of crystalline drug (a) was calculated according to the following equation:

$$\ln a = \Delta H/\boldsymbol{R}(1/T_m - 1/T) \quad (1)$$

where $\boldsymbol{R}$ and T are the gas constant (1.987 cal deg^{-1} mol^{-1}) and the experimental temperature (310.15 K).

Theory. Solution-Diffusion Theory Permeation of a drug through a solution-diffusion membrane can be described by a physical model as shown in Fig. 1. This model suggests that a steady state permeation rate (dQ/dt) is mathematically expressed by Eq. 2 based on Fick's first law:

$$dQ/dt = D_m \Delta C/L \quad (2)$$

where D_m is the diffusion coefficient of a drug in the membrane, ΔC is the concentration differential of the drug in the membrane, and L is the membrane thickness. If the concentration of the drug in the donor compartment is greater than the solubility and a sink condition is maintained in the receiver compartment throughout the permeation experiment, ΔC in Eq. 2 can be replaced with a product of the solubility of the drug in the donor solvent (C_v) and membrane/donor vehicle partition coefficient of the drug (K):

$$dQ/dt = D_m K C_v/L \quad (3)$$

Introducing the terms of the thermodynamic activity, the following equation was derived as proposed by T. Higuchi[2]:

$$dQ/dt = D_m a_v/\gamma_m L \quad (4)$$

where a_v is the thermodynamic activity of the drug in the vehicle (donor solvent), and γ_m is the activity coefficient of the drug in the membrane. On the other hand, the permeability coefficient of the drug (P) is given by:

$$P = D_m K/L \quad (5)$$

Flynn *et al.*[15] proposed that the diffusion coefficient of a drug in an isotropic polymer (D) could be described as a function of molecular weight ($M.W.$) as follows:

$$\log D = -s \log M.W. + k \quad (6)$$

where s and k are constants. The relationship may be extrapolated to heterogeneous membranes such as skin.

When a drug-suspended solution is used, the activity of dissolving the drug is generally the same as that of the solid drug. If the solid drug is the same as the neat crystalline drug, the activity of the drug would be given by Eq. 1.

Pore Theory Fick's law can not be directly applied to the porous membranes, where the diffusion of a drug takes place through the membrane pores (Fig. 2):

$$dQ/dt = D_v K' \varepsilon \Delta C/\tau L \quad (7)$$

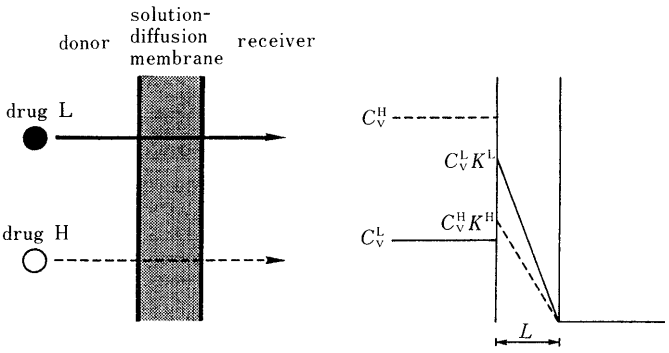

Fig. 1. Permeation Model of Lipophilic (●) and Hydrophilic (○) Drugs through the Solution-Diffusion Membrane

where D_v is the diffusion coefficient of the drug in the vehicle (solvent) that fills in the membrane pore and K' is the partition coefficient of the drug between the bulk solvent and the solvent in the membrane pore. The apparent partition coefficient between the membrane and bulk solvent is modified by porosity (ε), reflecting the volume fraction of pores in the membrane. The membrane thickness (L) is also modified by tortuosity (τ), reflecting a geometrically averaged path length in nonlinear pores. If the composition of bulk solvents is the same as that in the membrane pore, K' can be assumed to be 1. Under the assumptions that the drug is suspended in the donor vehicle and a sink condition on the receiver side is maintained, Eq. 7 is transformed to:

$$dQ/dt = D_v \varepsilon C_v / \tau L \quad (8)$$

Equation 8 is also expressed as follows:

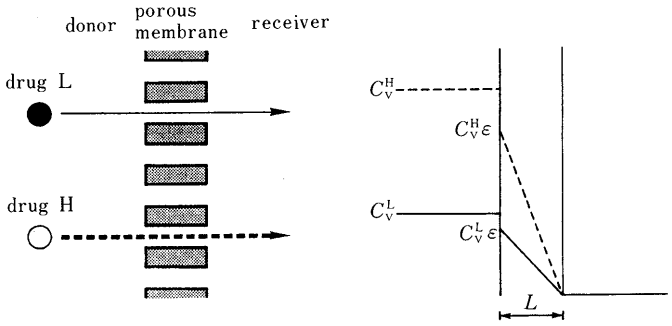

Fig. 2. Permeation Model of Lipophilic (●) and Hydrophilic (○) Drugs through the Porous Membrane

$$dQ/dt = D_v \varepsilon a_v / \tau L \gamma_v \quad (9)$$

where γ_v is the activity coefficient of the drug in the vehicle. The permeability coefficient is given by:

$$P = D_v \varepsilon / \tau L \quad (10)$$

Results

Table II shows the molecular weight (*M.W.*), melting point (T_m) and logarithm of the octanol/water partition coefficient (K_{ow}) of the drugs used in the present study. There were about 3- and 4.5-fold differences in *M.W.* and T_m among the drugs, respectively, whereas the difference in K_{ow} was about 6×10^7 times, suggesting that the polarity of drugs varied markedly compared with *M.W.* and T_m.

Silicone Membrane Permeation Figure 3 shows the cumulative amount of several drugs which permeated across the silicone membrane from their aqueous suspensions. As can be seen from this figure, a steady state permeation was achieved immediately after a short lag time for all drugs, but the slope of the linear portion, namely the steady state permeation rate (dQ/dt), markedly varied among the drugs. In the case of DPH, dQ/dt was determined as the average permeation rate by the data between 40 to 70 h, because the cumulative amount of DPH permeated up until 35 h was under the detection limit (0.1 μg/ml). This variation in membrane permeability seems

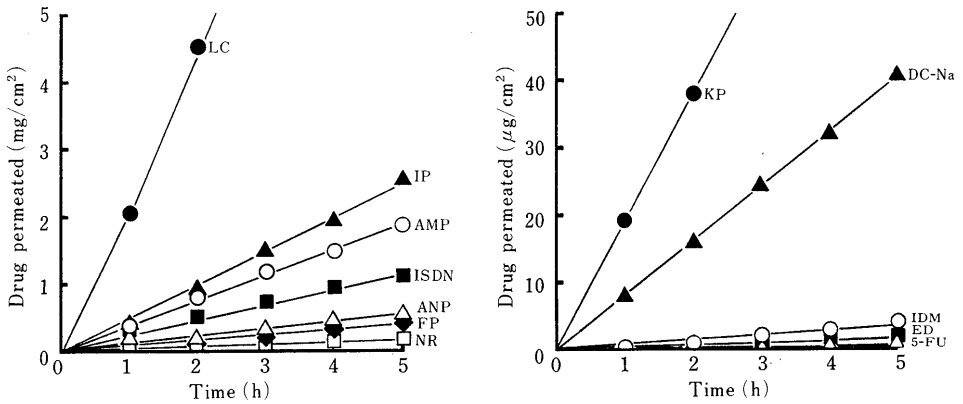

Fig. 3. Permeation Profiles of Lipophilic (●) and Hydrophilic (○) Drugs through the Silicone Membrane

Each value represents the mean of 3 experiments. Each S.E. is contained in each symbol.

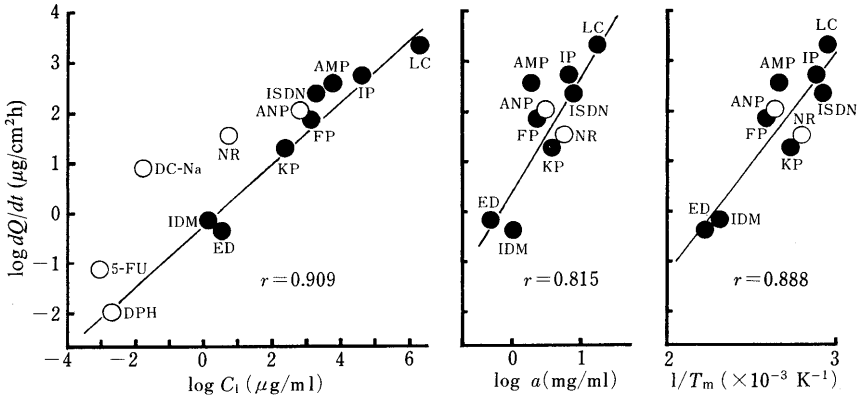

Fig. 4. Relationship between the Steady State Permeation Rate through the Silicone Membrane and Activity of Lipophilic (●) and Hydrophilic (○) Drugs

Each value represents the mean of 3 experiments. Each S.E. is contained in each symbol.

to be caused by the difference in physicochemical properties of both the drugs and membranes, such as the diffusion coefficient of drugs in the membrane (D_m), membrane/donor vehicle partition coefficient of drugs (K), solubility of drugs in the donor vehicle (C_v) and membrane thickness (L), which are shown in Eq. 3. Due to the constant L of the silicone membrane used in this experiment (0.015 cm), only C_v, D_m and K are the practical factors influencing membrane permeability. Although C_v could be estimated as solubility in water (C_w), in this case, it was difficult to determine D_m and K. Thus, *M.W.* was used as an indicator of D_m according to Eq. 6. K_{ow}, a general indicator of the polarity of drugs, was also used instead of K. Although low correlations were found between dQ/dt and the factors, dQ/dt had a tendency to relate to the product of K_{ow} and C_w, which becomes the solubility in octanol ($r=0.787$).

From a thermodynamic point of view, the influence of the thermodynamic activity of drugs on dQ/dt was investigated based on Eq. 4. Although it is difficult to measure the thermodynamic activity of drugs in the donor vehicles (a_v), Rytting *et al.* have proposed that the infinitely dilute solution of drugs in an alkane solvent such as isooctane, hexane and cyclohexane could serve as a reference state.[16] Moreover, the activity of drugs in a crystalline state (a) is given by Eq. 1. Therefore, the solubility of drugs in isooctane (C_i) and a were used as indicators for a_v. The difference in molar heat of fusion among the drugs tested was so small (about 1.7-fold) that the reciprocal of the melting temperature ($1/T_m$) was also used as an indicator. As clearly shown in Fig. 4, a linear relationship existed between dQ/dt and each of these indicators (C_i, a and $1/T_m$) for activity ($r=0.909$, 0.815 and 0.888, respectively).

In order to obtain a better understanding of silicone

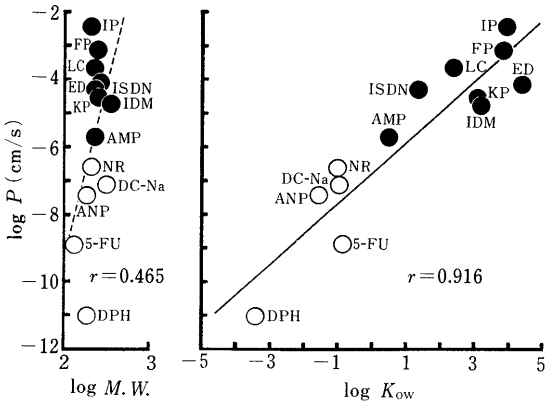

Fig. 5. Relationship between the Permeability Coefficient of Lipophilic (●) and Hydrophilic (○) Drugs through the Silicone Membrane and Several Parameters Influencing Their Permeabilities

Each value represents the mean of 3 experiments. Each S.E. is contained in each symbol.

TABLE II. Physicochemical Parameters of Drugs Used in This Experiment

	β-Estradiol (ED)	Ibuprofen (IP)	Flurbiprofen (FP)	Indomethacin (IDM)	Ketoprofen (KP)	Lidocaine (LC)	Isosorbide dinitrate (ISDN)	Cyclobarbital (CB)	Aminopyrine (AMP)
M.W.[a]	272.37	206.27	244.27	357.81	254.29	234.33	236.14	236.26	231.29
T_m (°C)[b]	175.5	74.0	113.0	158.5	93.0	65.0	69.0	171.0	102.5
log K_{ow}[c]	4.40	3.94	3.86	3.19	3.11	2.37	1.34	0.873	0.497

	5-Fluorouracil (5-FU)	Diclofenac sodium (DC-Na)	Nicorandil (NR)	Antipyrine (ANP)	Morphine hydrochloride (MPH)	Isoproterenol hydrochloride (IPH)	Dopamine hydrochloride (DPH)	Levodopa (L-DP)
M.W.	130.08	318.13	211.17	188.23	375.85	247.70	189.64	197.00
T_m (°C)	282.6[d]	284.0[d]	85.0	105.3	200.0[d]	165.7	243.6[d]	294.0[d]
log K_{ow}	−0.860	−0.962	−1.02	−1.55	−2.53	−2.69	−3.40	−4.70

a) Molecular weight. *b*) Melting temperature measured by DSC. *c*) Logarithm of octanol/water partition coefficient at 37 °C. Each value represents the mean of 3 experiments. *d*) Decomposition temperature.

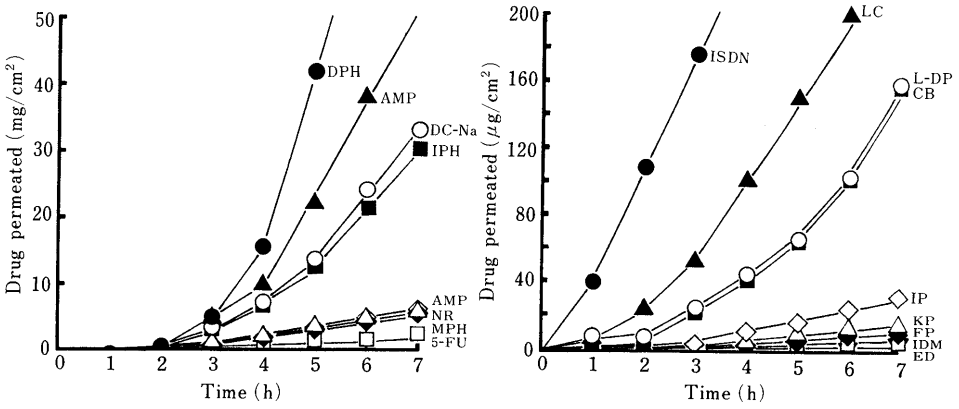

Fig. 6. Permeation Profiles of Lipophilic (●) and Hydrophilic (○) Drugs through the pHEMA Membrane

Each value represents the mean of 3 experiments. Each S.E. is contained in each symbol.

membrane permeation, the relationship between the permeability coefficient (P) and the physicochemical parameters of the drugs was investigated (Fig. 5). As a result, P was found not to be influenced by $M.W.$ ($r=0.465$), but it did increase with increasing K_{ow} ($r=0.916$).

pHEMA Membrane Permeation The permeation profiles of drugs through the pHEMA membrane are shown in Fig. 6. The lag time was 2 to 3 h for every drug, while the dQ/dt for hydrophilic drugs was higher than that for lipophilic drugs. As proven using Eq. 8, dQ/dt is controlled by C_v, the diffusion coefficient of the drug in vehicles (D_v), L, and porosity and tortuosity of membrane (ε and τ). Since the same pHEMA membrane was used in all experiments, ε, τ and L should be the same for each experiment. In practice, D_v and C_v became influencing factors of dQ/dt. However, dQ/dt did not correlate with $M.W.$ ($r=-0.323$), but it correlated positively with C_w ($r=0.967$).

The permeation rate of drugs through the porous membrane is proportional to a_v (Eq. 9) similar to the solution-diffusion membrane. However, the correlations between dQ/dt and the indicators of a_v (C_i, a and $1/T_m$) were very low ($r=-0.372$, 0.404 and 0.449, respectively).

Moreover, the relationship between P and the physicochemical parameters of the drugs was investigated based on Eq. 10. As shown in Fig. 7, P was almost constant (about 1.5×10^{-5} cm/s), independent of $M.W.$ and K_{ow}.

Skin Permeation After reviewing the artificial membrane permeation of drugs using silicone and pHEMA membranes, we then focused on the skin permeation of drugs. Figure 8 shows the time course of the cumulative amount of several drugs which permeated excised hairless rat skin. The permeation rate varied about 3×10^3-fold from 163 μg/cm^2/h of ED for the minimum, to 480 mg/cm^2/h of DPH for the maximum. In order to evaluate the contribution of the physicochemical parameters of the drugs to skin permeability, dQ/dt is plotted against $M.W.$, C_w and K_{ow} as shown in Fig. 9. $M.W.$ had little effect on

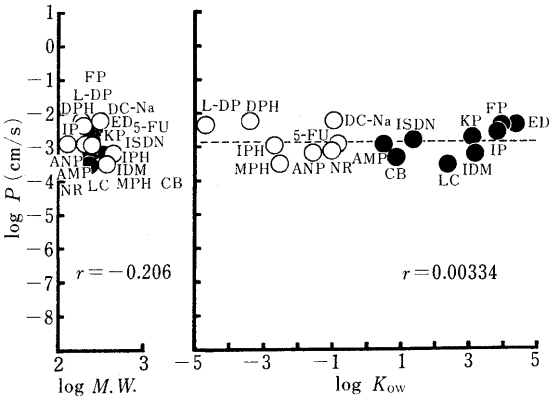

Fig. 7. Relationship between the Permeability Coefficient of Lipophilic (●) and Hydrophilic (○) Drugs through the pHEMA Membrane and Several Parameters Influencing Their Permeabilities

Each value represents the mean of 3 experiments. Each S.E. is contained in each symbol.

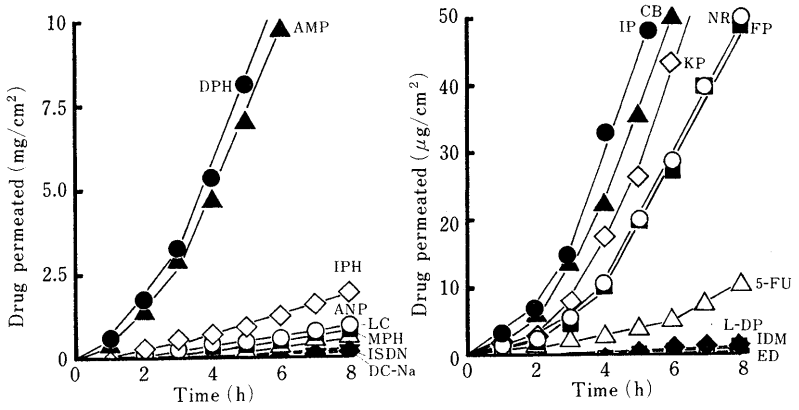

Fig. 8. Permeation Profiles of Lipophilic (●) and Hydrophilic (○) Drugs through Excised Hairless Rat Skin

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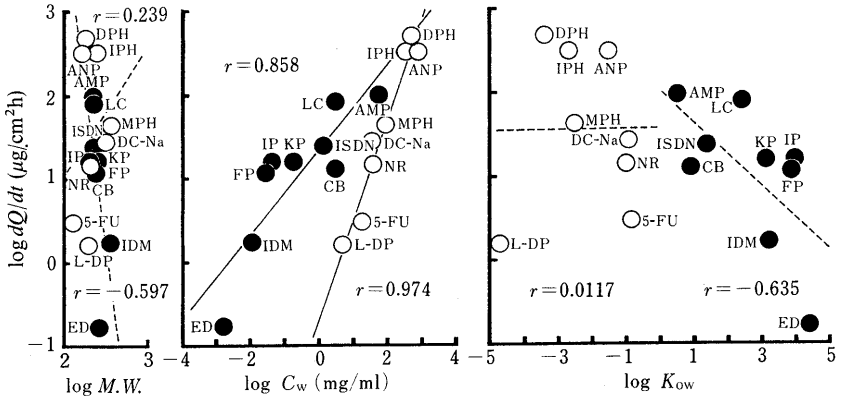

Fig. 9. Relationship between the Steady State Permeation Rate of Lipophilic (●) and Hydrophilic (○) Drugs through Excised Hairless Rat Skin and Several Parameters Influencing Their Permeabilities

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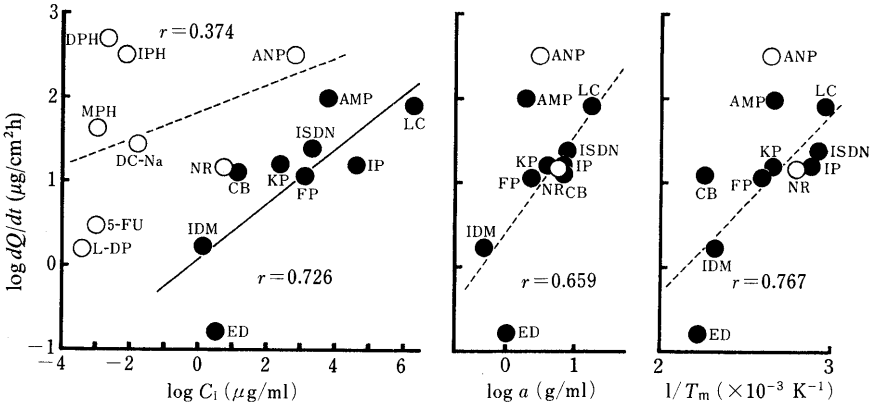

Fig. 10. Relationship between the Steady State Permeation Rate through Excised Hairless Rat Skin and Activity of Lipophilic (●) and Hydrophilic (○) Drugs

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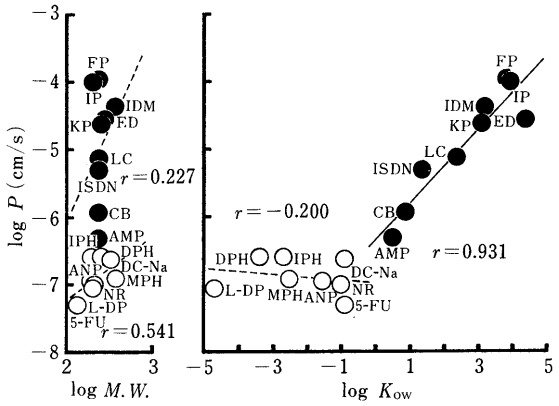

Fig. 11. Relationship between the Permeability Coefficient of Lipophilic (●) and Hydrophilic (○) Drugs through Excised Hairless Rat Skin and Several Parameters Influencing Their Permeabilities

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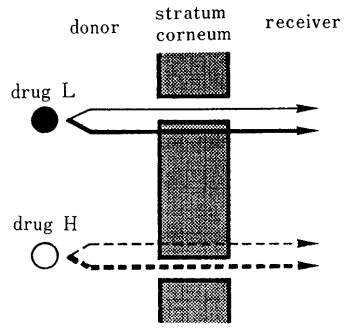

Fig. 12. Permeation Model of Lipophilic (●) and Hydrophilic (○) Drugs through Excised Hairless Rat Skin

dQ/dt for both lipophilic ($K_{ow} \geqq 1$) and hydrophilic ($K_{ow} < 1$) drugs ($r = -0.594$ and 0.239, respectively). The correlation between dQ/dt and K_{ow} was also low. In contrast, dQ/dt correlated well with C_w. A high correlation coefficient ($r = 0.974$) was obtained for hydrophilic drugs, similar to the case of the pHEMA membrane.

From a thermodynamic point of view, the relationship between dQ/dt and a_v was examined. Figure 10 shows the results. In the case of lipophilic drugs, although the correlation between dQ/dt and a was somewhat low ($r = 0.659$), linear relations were found between the permeation rate and the other two parameters ($r = 0.777$ in the case of C_i, $r = 0.767$ in the case of $1/T_m$), which are similar to those obtained for the silicone membrane. By contrast, the dQ/dt of hydrophilic drugs was independent of C_i ($r = 0.374$).

Figure 11 shows the relationships between P and $M.W.$ and between P and K_{ow}. P was independent of $M.W.$ for both lipophilic and hydrophilic drugs ($r = 0.227$ and 0.541, respectively). On the other hand, the relationship between P and K_{ow} was linear for the lipophilic drugs ($r = 0.931$) similar to the case of silicone membrane, whereas P of the hydrophilic drugs was almost constant (about 1.0×10^{-7} cm/s), independent of K_{ow}, similar to the case of pHEMA membrane.

Prediction of Skin Permeability The preceding results suggest the existence of at least two routes with different permeation mechanisms in the skin barrier, stratum corneum: one is the so-called lipid pathway, the main route for skin permeation of lipophilic drugs, and the other is the pore pathway, the main route for hydrophilic drugs. The lipid and pore pathways may be described by the solution-diffusion theory and pore theory, respectively. Based on this concept, the stratum corneum can be described as a membrane having two parallel domains as shown in Fig. 12. Combining the contributions of both domains to dQ/dt and P, Eqs. 11 and 12 can be derived:

$$dQ/dt_T = dQ/dt_L + dQ/dt_P \tag{11}$$

$$P_T = P_L + P_P \tag{12}$$

where subscripts T, L and P mean total, lipid and pore, respectively. Equations 11 and 12 are transformed based on Eqs. 3 and 8 as follows:

$$\begin{aligned} dQ/dt_T &= (1-\varepsilon)C_v D_L K_{LV}/\tau_L L + C_v D_v \varepsilon/\tau_p L \\ &= (1-\varepsilon)D_L a_v/\gamma_L \tau_L L + D_v \varepsilon a_v/\gamma_v \tau_p L \end{aligned} \tag{13}$$

$$P_T = (1-\varepsilon)D_L K_{LV}/\tau_L L + D_v \varepsilon/\tau_p L \tag{14}$$

where K_{LV} is the lipid domain/vehicle partition coefficient of the drug. Assuming that the L, ε, τ_L and τ_P are almost constant among skin samples and that D_L and D_v are almost constant among drugs, Eq. 14 can be reduced to Eq. 15:

$$P_T = XK_{LV} + Y \tag{15}$$

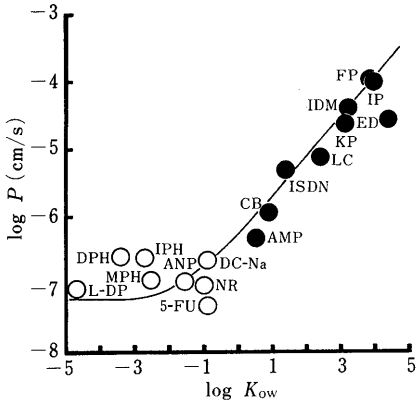

Fig. 13. Nomogram for Estimating Skin Permeability of Lipophilic (●) and Hydrophilic (○) Drugs

Table III. Estimation of Skin Permeability of Pentazocine and Eptazocine Hydrochloride

	K_{ow}	P_{obs} (cm/s)[a]	P_{cal} (cm/s)[b]
Pentazocine	2.42	8.81×10^{-6}	12.8×10^{-6}
Eptazocine HBr	−1.97	1.32×10^{-7}	1.16×10^{-7}

a) Observed permeability coefficient. b) Calculated permeability coefficient.

where X and Y are constants. K_{LV} may be related to K_{ow} by a linear free energy relationship as described by Leo and Hansch[17]:

$$K_{LV}=\alpha K_{ow}^{\beta} \tag{16}$$

where α and β are constants. Finally, P_T is given by Eq. 17.

$$P_T=AK_{ow}^{\beta}+C \tag{17}$$

where $A=\alpha X$. A, β and C were calculated from the data in Fig. 11. The final equation becomes:

$$P=4.78\times10^{-7}K_{ow}^{0.589}+8.33\times10^{-8} \tag{18}$$

Figure 13 indicates that the relationship between P for hairless rat skin and K_{ow} can be adequately described by Eq. 18, and that P can be predicted from K_{ow} based on Eq. 18. In order to confirm the advantage of this predictive method, the calculated permeability coefficient (P_{cal}) was compared with the observed one (P_{obs}) for pentazocine as a model lipophilic drug and eptazocine hydrobromide as a model hydrophilic drug (Table III). The P_{cal} was close to P_{obs}, suggesting that this method is indeed useful in predicting the skin permeability of drugs.

Discussion

Establishment of criteria to predict the skin permeability of drugs has been one of the main purposes of pharmaceutical researches of transdermal drug delivery for many years. Some attempts to establish the criteria were made by utilizing such physicochemical properties of drugs as the organic solvent/water partition coefficient, solubility in the stratum corneum, molecular weight, thermodynamic activity, solubility parameter and so on.[3-6,18-20] However, these methods could not be used to predict relatively high permeability of hydrophilic drugs such as tetraethylammonium bromide and glucose, because the stratum corneum was treated as a homogeneous solution-diffusion membrane in those methods. As an alternative, several lipoidal membranes were utilized instead of skin.[21,22] However, these lipoidal membranes, as homogeneous solution-diffusion membranes, could predict only the skin permeability of lipophilic drugs.

In the present study, the permeability of a number of drugs with a variety of physicochemical properties through hairless rat skin was compared with that through the silicone and pHEMA membranes to clarify the skin permeation mechanism of drugs. The silicone membrane has been used as a typical solution-diffusion membrane by many investigators. A steady state permeation rate of drugs through the silicone membrane which correlated with both the solubility in the membrane and thermodynamic activity of drugs was obtained with progesterone derivatives by Chien *et al.*[9,10] The molecular weight of the drugs did not affect silicone membrane permeability. This might be due to the fact that the diffusion coefficient of permeants in polymer with low viscosity, such as silicone rubber, do not vary much with the molecular weight.[23]

Also, a pHEMA membrane was used as a typical porous membrane. Generally, it has been recognized that hydrogels such as pHEMA have two distinct diffusion mechanisms, solution-diffusion and porous.[24,25] However, Miyajima *et al.* reported that solutes without interaction with a polymer matrix primarily permeated through water-filled pores in the pHEMA membrane according to the free volume theory.[11] The pore theory may be assumed in the present experiment for the pHEMA membrane, since the permeability coefficient of drugs was almost constant independent of the polarity of drugs (Fig. 7). No linear relationship between the permeation rate and thermodynamic activity-related parameters of drugs was obtained. It is well known that solute molecules interact with solvent molecules in aqueous solutions, for example through hydrogen bonding. In particular, some drugs are able to hydrate in aqueous solutions.[26] Therefore, the thermodynamic activity of dissolving a drug in water, a diffusion medium of pHEMA membrane in this case, may be different from that of a neat crystalline drug.

It is significantly interesting to discover that the relationships between skin permeability and lipophilicity of drugs can be approximately classified into 2 types, those for lipophilic drugs and those for hydrophilic drugs. These results suggest that at least two permeation pathways, lipid and pore pathways, exist in the stratum corneum. The existence of parallel lipid and pore pathways was also pointed out by Ackermann *et al.*[7] They indicated that no general pattern emerged when the permeability coefficient of hydrocortisone 21-*n*-alkyl esters, alkanols and hydrophilic compounds through nude mouse skin was taken as a function of their ether/water partition coefficient; hence, they concluded that the skin could not be regarded as a simple lipoidal barrier. Ghanem *et al.* used the pore model to explain the effect of ethanol on β-estradiol permeation,[6] too.

Recently, evidence for the existence of parallel pathways has been given not only by the drug permeability-physicochemical properties relationship but also by the morphology of the stratum corneum. A concept that lipid and protein domains lie in morphologically distinguishable regions of the stratum corneum has become dominant

ever since a mathematical model of the stratum corneum as a two-phase protein-lipid heterogeneous membrane was proposed by Michaels and his co-workers.[27] This concept was supported by a histological study by Elias.[8] He described the stratum corneum as a mosaic of cornified cells containing cross-linked keratin filaments and intercellular lipid-containing regions. Based on this view, Barry estimated that the transcellular route through the protein-filled cell provided the main pathway for polar drugs and the intercellular route, lipid-rich regions, became significant pathways for non-polar penetrants.[28] However, our data indicated that the permeability coefficient of hydrophilic drugs was not affected by their partition coefficients, suggesting that the diffusion medium for hydrophilic drugs was water penetrated from the donor solution, rather than conified cells themselves. Recently, Raykar *et al.* proposed a sponge domain in addition to lipid and protein domains in the stratum corneum.[29] This domain was defined to be composed of water of hydration and to have the properties of bulk water. Moreover, they indicated that the protein domain did not contribute to the permeation of drugs.[30] The lipid and pore pathways in our model of stratum corneum may correspond to the lipid and sponge domain proposed by Raykar *et al.*

We used this concept for the structure of skin and the permeation mechanism in the prediction of skin permeability of drugs. Our method not only has highly theoretical validity but also high precision at prediction of skin permeability of drugs (with only 5 discrepancies). And, it is a simple method applicable to a wide variety of drugs. Further studies would be required to extend the applicability, for example, to cases of high molecular drugs, other solvents and permeation enhancers.

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