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The use of complexation with alkanolamines to facilitate skin permeation of mefenamic acid

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Abstract

The preparation of mefenamic acid (MH)-alkanolamine [monoethanolamine, diethanolamine, triethanolamine and propanolamine] complexes was attempted to increase the transdermal flux of MH. A lipophilic enhancer system consisting of isopropyl myristate (IPM) and ethanol (9:1; EI system) produced a marked enhancement of MH flux from the alkanolamine complexes through hairless rat skin membrane. Among the alkanolamines examined, the propanolamine complex had the greatest enhancing effect on the permeation of MH. The observed permeation enhancement of MH–alkanolamine complexes by the EI system was explained by an analysis based on a two-layer diffusion model. The stratum corneum immersed in IPM forms a continuous phase of vehicle and stratum corneum and, from the phase, ethanol transport the MH–alkanolamine complexes to the epidermis and dermis, and the complexes, which are more water soluble than MH, exhibit increased partition into the epidermis and dermis, as the flux increases.

Keywords: Mefenamic acid; Alkanolamine; Complex; Percutaneous absorption

1. Introduction

Mefenamic acid (MH) is a non-steroidal anti-inflammatory drug (NSAID), one of the most widely used groups of therapeutic agents in clinical practice at present (Brooks and Day, 1991). MH is available worldwide in the form of tablets, capsules and a pediatric suspension. However, since MH is administered orally, gastrointestinal disorders become an issue as far as side effects are concerned (Smolinske et al., 1990). For this reason, percutaneous administration of MH has been studied as a way to minimize these. Unfortunately, MH has a number of unfavorable physicochemical properties, such as its poor solubility in water and octanol (Loth, 1991; TenHoor et al., 1991). Therefore, alternative strategies to overcome the problems arising from poor skin permeability need to be developed. To achieve this goal, various strategies including the use of a penetration enhancer (Naito et al., 1985) and a prodrug approach (Schwenker and Chen, 1991) have been used. However, none of these methods has been able to achieve a high skin permeation rate. A recent study in our laboratory involving MH transport through hairless rat skin using a lipophilic multicomponent system, consisting of a alkanolamine, ethanol and isopropyl myristate (IPM; amine-EI system), demonstrated that this system significantly enhances the permeation of MH. The formation of an ion pair between MH and alkanolamines may be responsible for the enhanced skin

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permeation of MH (Fang et al., 2002). More recently, we attempted the preparation of MH–alkanolamine complexes to develop a transdermal drug delivery system for MH. DSC, FT-IR and X-ray crystallographic studies confirmed that MH and alkanolmines form complexes (Fang et al., 2003).

The purpose of the present study is to investigate the enhancing effect of MH–alkanolamine complexes. In this paper we analyzed the observed skin permeation data for MH complexes with alkanolamines across in vitro hairless rat skin from the EI (IPM:ethanol = 9:1) system using a two-layer diffusion model.

2. Theoretical

We have proposed that a two-layer skin model with polar and non-polar routes in the stratum corneum (SC) could comprehensively account for the in vitro skin permeation of drugs with different lipophilicities and effect of the enhancers on this permeation (Kobayashi et al., 1994). To analyze the effect of the amine-EI system, the skin barrier to drug permeation was evaluated using a two-layer model with a heterogeneous SC, consisting of lipid and pore pathways with porosity ε, and viable epidermis and dermis (ED).

The permeability of a membrane for a diffusing substance is defined by its resistance.

$$R_{FT} = R_{SC} + R_{ED} \tag{1}$$

$$\frac{1}{P_{FT}} = \frac{1}{P_{SC}} + \frac{1}{P_{ED}} \tag{2}$$

where R_{FT}, R_{SC} and R_{ED} are the resistance of full-thickness skin, SC and ED; P_{FT}, P_{SC} and P_{ED} are the permeability coefficients through full-thickness skin, SC and ED, respectively. P_{SC} can be expressed using permeability coefficients through lipid and pore pathways, P_L and P_P, and the area ratio of the pore/lipid pathway, which can be substituted for the porosity in the SC, ε. Using a linear free energy relationship (Leo and Hansch, 1971; Hansch and Dunn, 1972; Anderson et al., 1988), P_{SC} is represented as

$$P_{SC} = (1-\varepsilon)P_L + \varepsilon P_P = (1-\varepsilon)A(K_{O/W})^B \frac{D_L}{L_{SC}} + \varepsilon\alpha\left(\frac{1}{1/K_{O/W}}\right)^\beta \frac{D_P}{L_{SC}} \tag{3}$$

where $K_{O/W}$ is the *n*-octanol/water partition coefficient, A, B, α and β are coefficients depending on vehicle and SC characteristics, D_L and D_P are diffusion coefficients of the lipid and pore pathways in the SC, and L_{SC} is the thickness of the SC. The partition coefficient between pore pathway and vehicle can be assumed to be unity, when using water as a vehicle, assuming that the pore is filled with water (pore route). On the other hand, when IPM is used as vehicle, the IPM/pore partition coefficient is a function of the reciprocal of the *n*-octanol/water partition coefficient.

A similar rule is applied to the SC–ED partitioning of drugs, because the ED is a porous hydrogel filled with receiver fluid.

$$P_{ED} = \gamma\left(\frac{1}{K_{O/W}}\right)^\delta \frac{D_{ED}}{L_{ED}} \tag{4}$$

where γ and δ are coefficients describing the vehicle characteristics, D_{ED} is the diffusion coefficient in ED, and L_{SC} is the thickness of the ED.

Following substitution in Eqs. (3) and (4) with the P_{SC} and P_{ED} in Eq. (2), rearrangement give

$$P_{FT} = \frac{[(1-\varepsilon)A(K_{O/W})^B D_L + \varepsilon\alpha(1/K_{O/W})^\beta D_P]\gamma(1/K_{O/W})^\delta D_{ED}}{L_{ED}[(1-\varepsilon)A(K_{O/W})^B D_L + \varepsilon\alpha(1/K_{O/W})^\beta D_P] + L_{SC}\gamma(1/K_{O/W})^\delta D_{ED}} \tag{5}$$

3. Materials and methods

3.1. Materials

MH, monoethanolamine (M), diethanolamine (D), triethanolamine (T), propanolamine (P), aminopyrine, aspirin, salicylic acid, naproxen and flufenamic acid were purchased from Wako Pure Chemical Ind., Ltd. (Osaka, Japan). Bufexamac, flurbiprofen, ketoprofen, IPM, and dehydrated ethanol (JP grade) were supplied by Sigma Chemical Co. (Louis, USA), Toko Yakuhin Ind. Co. (Tokyo, Japan), Nissan Chemical Ind., Ltd. (Tokyo, Japan), Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan), Imazu Yakuhin Kogyo K.K. (Tokyo, Japan), respectively. Diclofenac sodium was obtained from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan) and diclofenac acid was prepared as previously reported

(Fang et al., 2002). All other chemicals and solvents were of reagent grade.

3.2. Preparation of MH complex with alkanolamines

Equimolar amounts of MH and alkanolamine (M, D, T, P) were dissolved in ethanol by mixing, and the ethanol was removed in vacuo after treatment with ultrasound for 1 h. The residues were dried at 60 °C for 4 h to give the complexes and their melting points were determined by DSC. These complexes are referred to as MH–M, MH–D, MH–T and MH–P, respectively.

3.3. Solubility measurements

The solubilities of drugs in water, IPM, ethanol and the EI system were determined at 32 °C. An excess of each drug was dispersed into 2 ml solutions in a glass vial. Each vial was shaken for 24 h in a water bath and its contents filtered through a 0.45 μm membrane before assaying the drugs by HPLC. Each experiment was performed in triplicate.

3.4. Determination of n-octanol/water partition coefficient

To determine the *n*-octanol/water partition coefficient of MH and its complex, equal volumes (5 ml) of distilled water and *n*-octanol were added to 10 mg of each drug in a glass-stoppered tube and agitated for 24 h in a thermostated bath at 32 °C. After centrifuging (3000 × *g* for 5 min) to ensure separation of the phases, the drug in the water layer was analyzed by HPLC and the drug in the *n*-octanol layer was diluted with acetonitrile before assaying it by HPLC.

3.5. In vitro permeation procedure

Male hairless rats (WBN/ILA-Ht) weighing 180–220 g (6–8 weeks old) used in all experiments were supplied by Life Science Research Center of Josai University (Saitama, Japan). The experiments were performed in accordance with the guidelines for animal use in the Life Science Research Center of Josai University. The full-thickness skin was prepared as described in a previous publication (Fang et al., 2002), and the stripped skin was prepared by the tape (Nichiban Co., Tokyo, Japan) stripping technique as described in a previous report (Flynn et al., 1981). The skin permeation experiment was carried out as previously reported (Fang et al., 2002).

3.6. Intact and stripped skin uptake experiments

A procedure similar to that used for the in vitro permeation experiment was used for the determination of MH and its complexes in the skin. Isolated full-thickness skin or tape-stripped skin was mounted in side-by-side glass diffusion cells and connected to a water bath at 32 °C. The dermis side was filled with distilled water to equilibrate the skin for 2 h, then this was removed, with the dermal side in contact with a sheet of aluminum foil. The SC side was subsequently filled with 2.5 ml 0.01 μmol/ml MH or its complexes in the EI system. After exposure to the drug solution for 8 h, the excess drug on the skin surface was gently wiped off with alcohol swabs. The treated skin site (0.95 cm^2) was punched out, then, the skin was cut, homogenized in ethanol solution containing internal standard under ice-cooling and, after centrifugation at 9000 × *g* for 5 min, the supernatant was subjected to analysis by HPLC. The concentration of drug in the skin was calculated as the amount of drug in the skin divided by amount of skin. The recovery of drug added to homogenate was 97.3 ± 5.6%.

3.7. Analytical method

MH and its complexes were determined by HPLC as described in a previous publication (Fang et al., 2002). Analysis was performed on a 5 μm LiChrospher® 100 RP-18e reversed-phase column (250 mm × 4.6 mm i.d., Cica-MERCK, Darmstadt, Germany), operated at 40 °C. The mobile phase was 10 mM phosphate solution—acetonitrile (4:6, pH 2.65) at a flow-rate of 1 ml/min, the detector was set at 230 nm, and indomethacin was used as internal standard. Aminopyrine (Hatanaka et al., 1990), bufexamac (Kamata and Akiyama, 1986) and salicylic acid (Hosoya et al., 1998) were measured under conditions previously described. Other drugs used in this study were determined by the method published by Hirai et al. (1997).

The amount of ethanol in receptor fluids was determined by gas chromatography as described in a previous publication (Fang et al., 2002).

3.8. Data analysis

The amount of each drug permeating through the skin during a sampling interval was calculated based on the measured receptor-phase concentration and volume. The cumulative amount of drug permeating per unit area versus time was plotted. The flux was calculated from the slope of the linear portion of the plot. The permeability coefficient was obtained by dividing the flux by the initial drug concentration in the donor phase.

4. Results and discussion

4.1. Relationship between lipophilicity and skin permeability of NSAIDs from IPM

Although there is an enormous amount of information available about the effect of hydrophilic vehicles on drug delivery, very little systematic information has been published on the effect of lipophilic vehicles on transdermal drug delivery (Wenkers and Lippold, 1999). To analyze the effect of the amine-EI system, we evaluated the effect of IPM, a lipophilic vehicle, on the skin permeation of NSAIDs having a wide range of lipophilicity as indicated by the *n*-octanol/water partition coefficient $K_{O/W}$ ($\log K_{O/W}$, 0.5–4.88). The permeation coefficient of each NSAID, $\log K_{O/W}$ values from the literature, the experimental solubilities in IPM and molecular weights (MW) are listed in Table 1. The permeability coefficient is equal to the product of the partition coefficient and the diffusivity of the drug in the membrane divided by the thickness of the membrane (assumed to be relatively constant). The diffusivity of drugs should depend inversely on the cube root of their molar volumes so that the permeability coefficient should not change much because of changes in diffusivity of the drugs since their molar volumes (for many compounds, MW is often a reasonable approximation of the molecular volume) remain largely unchanged (Table 1). The effect of IPM on the skin permeation of drugs with different lipophilicities was evaluated using a two-layer model. Fig. 1 illustrates the experimentally observed data points and a set of simulated curves based on Eqs. (4) and (5) using the obtained parameters (Table 2). The permeation coefficients of other drugs from water

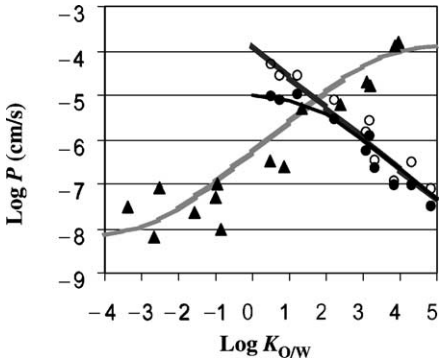

Fig. 1. Relationship between the permeability ($\log P$) of drugs from the IPM and water through hairless rat skin and the *n*-octanol/water partition coefficient ($\log K_{O/W}$) of drugs. Each data point represents the mean of three permeation experiments. Key: (●, ▬), intact skin (from IPM); (○, ▬), stripped skin (from IPM); and (△, ▬), intact skin (from water). Solid lines represent the simulated curves based on Eqs. (4) and (5) using the parameters listed in Table 2. The permeation coefficient of drugs from water relied on previously published data (Morimoto et al., 1992; Kobayashi et al., 1994).

relied on previously published data (Morimoto et al., 1992; Kobayashi et al., 1994). In the case of IPM, the experimentally determined permeabilities generally decrease with increasing NSAID lipophilicity, expressed as $K_{O/W}$, and the results agree well with a previous study (Uchida et al., 1993). For example, aminopyrine and bufexamac, the two drugs with the highest permeabilities, have the lowest $\log K_{O/W}$. Conversely, diclofenac acid and flufenamic acid, the two drugs with the lowest permeabilities, have rather high $\log K_{O/W}$ values. As $\log K_{O/W}$ increases, the drug becomes more like the vehicle (the drug should become more soluble in IPM) and the log experimental P values decrease to give an inverse relationship between log experimental P and $\log K_{O/W}$. On the other hand, in the case of water, as the $\log K_{O/W}$ increases, the drug becomes less like the vehicle and the log experimental P value increases. For drugs with a low $\log K_{O/W}$, the SC/hydrophilic vehicle (water) partition coefficient will probably be lower than the SC/lipophilic vehicle (IPM) partition coefficient because water has a greater affinity than IPM. The reverse is true for drugs with a high $\log K_{O/W}$, IPM has a greater affinity than water for drugs and therefore the SC/IPM partition coefficient of drugs will be less than the corresponding SC/water partition coefficient. Drugs of similar size and high lipophilicity have high

Table 1
Permeability coefficient and octanol/water partition coefficient for various NSAIDs across hairless rat intact and stripped skin from IPM

Drug	$P \times 10^{-6}$ (cm/s)[a]	Solubility (mM)	$\log K_{O/W}$[b]	MW
Amiopyrine	90.6 (550.6)[c]	103.8	0.50[d]	231.29
Bufexamac	75.4 (278.8)	0.448	0.77[e]	223.30
Aspirin	97.1 (272.8)	39.02	1.23[e]	180.16
Salicylic acid	29.2 (79.4)	181.0	2.25[e]	138.12
Ketoprofen	5.18 (9.38)	64.89	3.11[d]	254.28
Naproxen	11.8 (24.9)	19.67	3.18[e]	230.26
MH	2.14 (3.36)	8.786	3.31	241.29
Flurbiprofen	0.92 (1.06)	162.1	3.86[d]	244.26
Diclofenac acid	0.89 (2.81)	15.89	4.31[e]	295.14
Flufenamic acid	0.30 (0.72)	169.6	4.88[e]	281.23

[a] P, permeability coefficient.
[b] $K_{O/W}$, n-octanol/water partition coefficient.
[c] Values in parentheses represent permeability coefficient of drugs across the stripped skin.
[d] Morimoto et al. (1992).
[e] Yano et al. (1986).

permeabilities from aqueous solution. In contrast, the permeabilities of lipophilic drugs out of lipophilic vehicles should be low. The results of our current study support the findings of previous work showing that the percutaneous absorption of a compound can be influenced by the vehicle which is in contact with the skin (Hilton et al., 1994). The experimentally observed higher skin permeability of hydrophilic drugs from IPM was somewhat surprising, since it is generally accepted that hydrophilic drugs normally exhibit very poor penetration of the lipophilic SC. In an effort to understand the mechanism governing the permeation enhancement of hydrophilic drugs caused by the IPM, further permeation experiments were performed using stripped skin. The pertinent skin permeation data obtained with NSAIDs across intact and stripped hairless rat skin are presented in Table 1 and Fig. 1. The results clearly demonstrate that when the drugs were delivered from the IPM, the permeability of a drug across stripped skin was essentially similar to that across intact skin. These results strongly suggest that IPM markedly reduces or completely abolishes the barrier function of the SC as far as drug permeation is concerned. When using the lipophilic vehicle IPM, the SC does not seem to offer any significant resistance to the skin penetration of NSAIDs. The ED seems to be the decisive barrier to the skin penetration of NSAIDs from the lipophilic vehicle IPM. The above results can be expressed as a change in the parameter AD_L (A shows the degree of the transfer of the vehicle in the skin and D_L is diffusion coefficient of the drug in the lipid pathway of the SC, hence, parameter AD_L shows the mobility of the drug in the skin): the result was due to a 20-fold increase in AD_L relative to water, implying that the IPM enhanced diffusivity in the lipophilic pathway by soaking into the pathway (Pitt et al., 1988; Table 2). The present results are supported by previous published observations. Leopold and Lippold have studied the mechanism governing the penetration enhancing effect of lipophilic vehicles through human cadaver skin by differential scanning calorimetry and reported that IPM, which causes both a reduction in enthalpy and a decrease in phase-transition temperature, appears to fluidize the lamellar-gel phase of SC lipids (Leopold and Lippold, 1995). Suh and Jun have also investigated the effectiveness and mode of action of IPM as an enhancer for

Table 2
Approximate magnification of parameter to water and IPM

Parameter	Water	IPM
L_{SC} (cm)	1.54×10^{-3}	1.54×10^{-3}
L_{ED} (cm)	7.20×10^{-2}	7.20×10^{-2}
ε	1.00×10^{-2}	1.00×10^{-2}
AD_L (cm^2/s)	8.00×10^{-14}	1.60×10^{-12}
αD_P (cm^2/s)	1.00×10^{-9}	1.00×10^{-9}
γD_{ED} (cm^2/s)	1.00×10^{-5}	1.00×10^{-5}
B	7.00×10^{-1}	0
β	0	7.00×10^{-1}
δ	0	7.00×10^{-1}

the permeation of naproxen through shed snake skin and concluded that IPM exerted its enhancing action on the permeation of naproxen through the snake skin primarily by greatly increasing the diffusion coefficient rather than the partition coefficient of drug in the membrane (Suh and Jun, 1996). The accumulated evidence to date, including that from the present investigation, supports the following mechanism of action for IPM. IPM partition into the relatively highly ordered region of the lipid bilayer induces disorder and increases the fluidity in this region. The disorder that is induced in this region leads to an increased effective free volume and increased effective diffusivity in this region. This result suggests that the two-layer diffusion model could be extended to assess and predict the effect of lipophilic enhancers on transdermal drug transport.

4.2. Physicochemical properties and solubility of MH and its complexes

The physicochemical properties of MH and its alkanolamine complexes are summarized in Table 3. The melting point of MH was greatly reduced by complexation with alkanolamines. As expected, the aqueous solubilities of MH complexes were significantly higher than MH in water, and the solubilities of MH–M and MH–P were higher than MH in ethanol. In contrast, the solubilities of the MH complexes in IPM were lower than those in polar solvents, suggesting that the complexes were polar in nature. The *n*-octanol/water partition coefficient ($K_{O/W}$) of the complexes was significantly lower than that of MH.

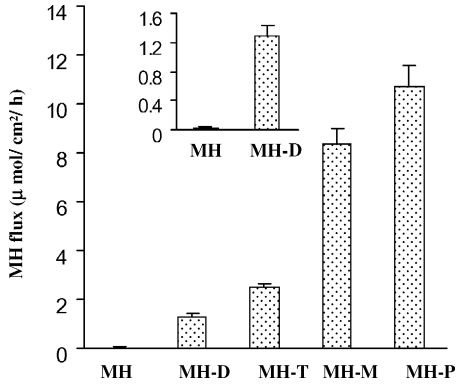

Fig. 2. Fluxes of MH and its complexes through hairless rat skin from the EI system. The inset presents the fluxes of MH and MH–D on an expanded scale. Each column represents the average ± S.E. of five permeation experiments.

4.3. MH flux and partition coefficient

The flux and permeability coefficient of MH and its complexes and the ethanol flux are presented in Table 4. The permeation data in Fig. 2 clearly indicate that the EI system produced a marked enhancement of MH flux when the alkanolamine complexes were used as permeants. The MH flux was in following order: MH–P > MH–M > MH–T > MH–D > MH. This higher permeability of salt through the skin has been also reported for benztropine free base and its mesylate salt through hairless mouse and human cadaver skin with a lipophlic vehicle consisting of an alkanol and IPM. The benztropine salt exhibited a higher skin permeability than that of the benztropine free base (Gorukanti et al., 1999).

Table 3
Physicochemical properties of MH and its complexes

Parameter	MH	MH–M	MH–D	MH–T	MH–P
Melting point (°C)	231.7	131.8	168.7	110.0	110.1
Solubility (mM) at 32 °C					
Water	0.25	118	15.7	9.32	1063
Ethanol	58.6	278	28.3	59.3	808
IPM	12.3	8.70	0.04	2.49	4.02
EI system	47.2	23.2	4.14	15.3	42.7
$K_{O/W}$[a] at 32 °C	2057	6.14	5.48	98.5	4.53

[a] $K_{O/W}$ is *n*-octanol/water partition coefficient.

Table 4
Flux and permeability coefficient of drugs and ethanol flux through hairless rat skin from the EI system and skin concentration of MH after exposed to drug solution for 8 h

Drug	Drug flux and permeability		Ethanol flux (mg/cm^2/h)	Skin concentration (μmol/g)	
	Flux (μmol/cm^2/h)	$P \times 10^{-6}$ (cm/s)		Intact skin	Stripped skin
MH	0.03 ± 0.002	1.76 ± 0.12	19.1 ± 0.46	3.90 ± 0.08	2.61 ± 0.08
MH–M	8.37 ± 0.65	1002 ± 77.8	22.4 ± 2.59	99.2 ± 3.11	119 ± 2.57
MH–D	1.45 ± 0.16	972.8 ± 107.2	27.3 ± 2.80	41.2 ± 4.89	42.4 ± 2.61
MH–T	2.53 ± 0.01	459.4 ± 1.82	18.1 ± 1.99	39.0 ± 2.20	38.1 ± 2.52
MH–P	10.7 ± 0.90	696 ± 58.6	31.1 ± 2.67	89.0 ± 4.72	165 ± 2.90

Each data represents the mean ± S.E. of three or five experiments.

The relatively lower permeability coefficient obtained with MH can be explained by the difference in the partition behavior of MH and its complexes. Waranis and Sloan examined the relationship between the solubility parameter of prodrugs of 6-mercaptopurine and the permeability coefficient through excised skin with three vehicles and found that the increase in the solubility parameter (the decrease in lipophilicity) of the prodrug was associated with an increase in the permeability coefficient in a lipophilic vehicle (IPM; Waranis and Sloan, 1987). In the present study, the *n*-octanol/water partition coefficients determined with MH, MH–M, MH–D, MH–T and MH–P at 32 °C were 2057 ($\log K_{O/W} = 3.31$), 6.14 ($\log K_{O/W} = 0.79$), 5.48 ($\log K_{O/W} = 0.74$), 98.5 ($\log K_{O/W} = 1.99$), 4.53 ($\log K_{O/W} = 0.64$), respectively. It is, therefore, conceivable that MH with a $\log K_{O/W} = 3.31$ was sufficiently non-polar for its permeation rate to be controlled primarily by the aqueous strata of the ED layer in skin with disrupted SC (Flynn, 1983). On the other hand, the complexes of MH having a $\log K_{O/W} = 0.64$–1.99 were slightly too polar to preferentially pass through the ED after the drug molecules diffused through the SC of the skin, following disruption by the EI system (Flynn and Stewart, 1988). Therefore, one may conclude that the lipophilicity of a drug is the main factor predicting the skin permeability of a drug from the EI system, a lipophilic binary vehicle, which more effectively enhances the skin permeation of hydrophilic drugs.

Fig. 3 shows the relationship between the *n*-octanol/water partition coefficient and the permeability coefficient from the EI system through hairless rat skin with the fitted curves based on Eq. (5). Fig. 3 shows a trend towards an increased permeability coefficient as the lipophilicity of the drug decreased. The experimentally observed permeability coefficients agree with the predicted values based on Eq. (5) (the residual sum of squares the $\log P$ is 6.455), suggesting that the two-layer skin diffusion model enables us to elucidate the mechanism governing the skin permeation of MH complexes and the action of the EI system from a physicochemical standpoint.

4.4. MH and ethanol fluxes

The flux of ethanol through hairless rat skin from a drug suspension in the EI system was found to range from 18.1 to 31.1 mg/cm^2/h (Table 4). A linear

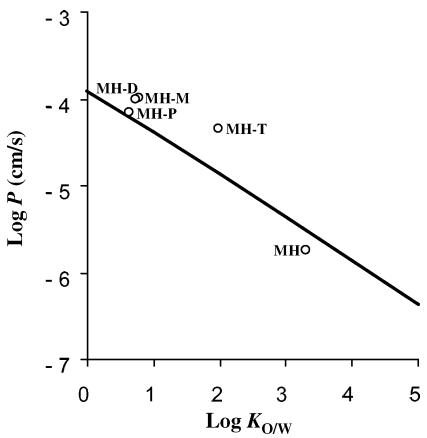

Fig. 3. Relationship between the permeability ($\log P$) of MH and its complexes from the EI system through hairless rat skin and the *n*-octanol/water partition coefficient ($\log K_{O/W}$). Solid lines represent the fitted curves based on Eq. (5). Each data point represents the mean of five permeation experiments.

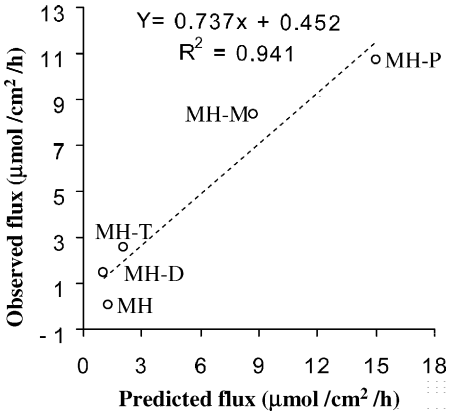

Fig. 4. Relationship between the observed MH flux in the EI system and the predicted MH fluxes calculated from the equation below. Predicted MH flux (μmol/cm^2/h) = [ethanol flux (g/cm^2/h)/specific gravity (g/cm^3)] × solubility in ethanol (μmol/cm^3). Each data point represents the mean of three or five permeation experiments.

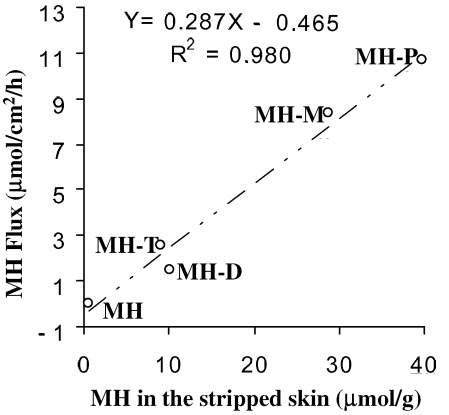

Fig. 5. Correlation of the uptake of MH into stripped skin with its permeation rate through intact skin following application of the EI system containing MH and its complex with alkanolamine for 8 h. Each data points represent the average of three experiments.

correlation of drug and ethanol fluxes has been observed in permeant/enhancer situations such as nitroglycerine/ethanol (Berner et al., 1989), levonorgestrel/ethyl acetate–ethanol (Catz and Friend, 1990), and estradiol/ethanol (Liu et al., 1991). In the present study, a nearly linear correlation was observed for the MH flux through hairless rat skin in the EI system with the predicted MH flux calculated by multiplying the ethanol flux and the solubility of MH–alkanolamine complexes in ethanol, indicating that the solubility of the complex in ethanol and the ethanol flux from the EI system are significant determinants of the MH flux (Fig. 4). Consequently, the solvent drag effect of ethanol might partly contribute to the enhanced skin permeation of MH, indicating that other factors such as partitioning into the skin from the EI system are involved.

4.5. MH flux and skin uptake

As can be seen from the data in columns 5 and 6 of Table 4, there was greatly increased uptake of MH into both intact and stripped skin from the EI system following complexation with alkanolamines. In the case of MH, the uptake of MH into stripped skin was reduced compared with that of intact skin. The rank order for the uptake of MH into stripped skin is MH–P > MH–M > MH–D > MH–T > MH. This is nearly in accordance with the rank order of the flux of MH and its complexes.

It was previously reported that full-thickness skin represents an artificially high barrier towards the percutaneous absorption of hydrophobic drugs. This is because drugs with very low water solubility do not partition freely from the SC into the aqueous environment of the ED (Bronaugh and Stewart, 1984, 1986). This has been attributed to the dermal tissues which, being essentially an aqueous barrier, inhibit the partitioning of hydrophobic substance from the lipophilic SC. Wenkers et al. reported that the viable epidermis, not the SC, is the rate-limiting barrier for the transport of NSAIDs out of a lipophilic vehicle (Wenkers and Lippold, 1999). In addition, Harada et al. reported that the penetration of emedastine with ethanol:IPM (37:63) and ethanol:IPM (73:27) was almost as great as that across tape-stripped skin, suggesting that the ED is the rate-limiting step in skin penetration rather than the SC (Harada et al., 2000). Therefore, it is probable that the epidermis is the barrier for the transport of MH from the EI system. On the other hand, for very lipophilic permeants, there could be a problem with poor solubility in the aqueous environment of the ED. In the present study we obtained a good linear correlation of the MH flux through hairless rat skin from the EI system with the uptake of MH into stripped skin from the EI system (Fig. 5). The flux of MH permeating through the skin appears to be related directly

to the amount of drug in the stripped skin. This result strongly suggests that the increasing effect of the partition of MH into the ED following complexation with alkanolamine is the main factor involved in the enhanced permeation of MH.

5. Conclusions

Based on the results of this investigation, we can conclude that temporary masking of the carboxylic group of MH by complexation with alkanolamine, is a useful means of modifying the lipophilicty of parent molecules to optimize partitioning into the skin and to maximize percutaneous penetration. The observed permeation enhancement of MH–alkanolamine complexes by the EI system follows from an analysis based on a two-layer diffusion model. The SC immersed in IPM represents a continuous phase of vehicle and SC, ethanol transport the MH–alkanolamine complexes to the ED, and the complexes, which were more water soluble than MH, exhibit increased partition into the ED as the flux increases.

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