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Effect of pH on skin permeation enhancement of acidic drugs by l-menthol-ethanol system

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Abstract

The effect of pH on the skin permeation enhancement of three acidic drugs by the l-menthol-ethanol system was investigated. The total flux of acidic drugs from the system remarkably varied over the pH range 3.0–8.0, and the permeation enhancement factor depended on the system pH and drug. A skin permeation model, which consists of two permeant (unionized and ionized) species, two system (oily and aqueous) phases, and two permeation (lipid and pore) pathways, was developed. The assumptions were made that only the unionized species can distribute to the oily phase and transport via the lipid pathway. The model explained the relationship between the concentration of drug in the aqueous phase and system pH. The skin permeability data were also described by the model and permeability coefficients corresponding to the physicochemical properties of permeant were calculated for the lipid and pore pathways. The model simulation showed that the permeation of acidic drugs occurred from the aqueous phase and the oily phase acted as a reservoir. Whether the total flux increased with increase of pH was dependent on the lipophilicity of drug. These results suggest that the pH of l-menthol-ethanol system should be given attention to elicit the maximum permeation enhancement.

Keywords: l-Menthol; Ethanol; Skin permeation; Permeation enhancement; pH; acidic drug

1. Introduction

Cooper (1984) reported that the combination of propylene glycol and oleic acid more markedly increased skin permeation of salicylic acid than the individual components used alone. Since then, various combinations of a simple solvent with a lipophilic compound have been tested as skin permeation enhancer systems (Møllgaard, 1993). The l-menthol-ethanol enhancer system is one of most attractive of these, because the two components act synergistically in permeation enhancement (Obata et al., 1991; Katayama et al., 1992) and are commonly used in topical pharmaceutical products, and as such, their toxicity is documented (Barry, 1983; Eccles, 1994).

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To elicit the maximum synergistic effect of l-menthol and ethanol, optimization of the system composition has been attempted by many researchers (Wada et al., 1993; Levison et al., 1994). Interactions of the system or each component with drug, e.g. change in the thermodynamic activity, or skin, e.g. modification of skin permeation pathways, have also been well investigated (Kobayashi et al., 1994; Kaplun-Frischoff and Touitou, 1997). However, the effect of pH on permeation enhancement has received scant attention, although a buffer or water was contained in most systems studied, and various weakly electrolytic compounds were frequently used as drug candidates or model permeants.

In our previous study, an l-menthol-ethanol system facilitated skin permeation of indomethacin by 100 times at pH 7.5 and 5.0, whereas little effect was observed at pH 3.0 (Katayama et al., 1992). Such pH-dependency in the permeation enhancement may result from a different effect of the system on the lipid pathway, the main route for skin permeation of unionized species of drug, and the pore pathway, the main route of ionized species, similar to the effect of ethanol (Kurihara-Bergstrom et al., 1990). Because there were two immiscible liquid phases in our system as in other typical l-menthol-ethanol systems, another explanation could be a reservoir effect of oily phase on unionized drugs, which is often found in heterogeneous topical formulations such as microemulsions (Gallarate et al., 1993). Our previous experimental results led us to minutely evaluate the effect of pH on skin permeation enhancement of weak electrolytes by the l-menthol-ethanol system.

In the present study, skin permeabilities of acidic drugs from the l-menthol-ethanol system were measured at various pH values and compared with the corresponding data of nonelectrolytes. Three nonsteroidal antiinflammatory drugs, flufenamic acid, indomethacin and ketoprofen, were used as model acidic drugs, and cortisone and D-mannitol were used as model permeants for hydrophobic and hydrophilic nonelectrolytes, respectively. Drug concentration in the aqueous phase of the system was also measured. The permeation and concentration data were analyzed based on a skin permeation model consisting of biphasic vehicle and two permeation pathways. The role of l-menthol in permeation enhancement is discussed in comparison with data for l-menthol-free ethanol system.

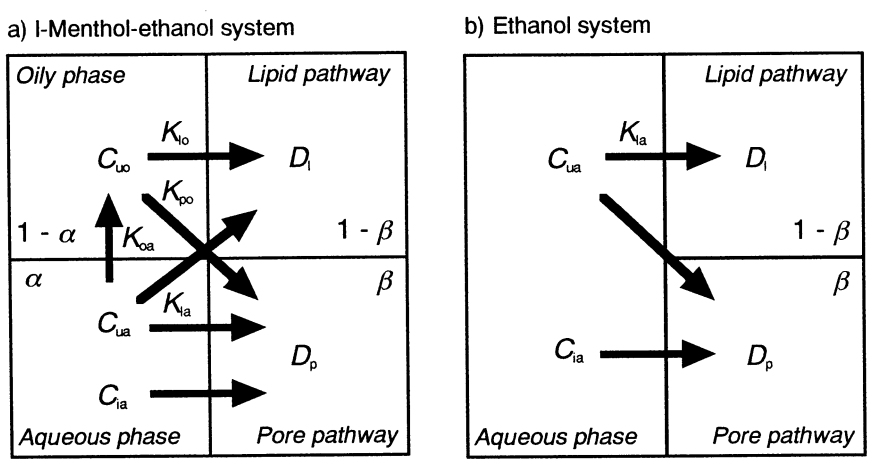

Fig. 1. Skin permeation model for the l-menthol-ethanol (a) and ethanol (b) systems. C, concentration; D, diffusion coefficient; K, partition coefficient; α, volume fraction of aqueous phase; β, porosity of skin; u, unionized species; i, ionized species; o, oily phase; a, aqueous phase; l, lipid pathway; p, pore pathway.

2. Theoretical

Fig. 1 shows the skin permeation models for l-menthol-ethanol and l-menthol-free ethanol systems. In these models, the skin is considered to have two permeation pathways: the so-called lipid pathway, where the drug is transported according to a partitioning theory, and the pore pathway, where the permeation occurs by a porous mechanism (Hatanaka et al., 1998). The assumptions are made that the l-menthol-ethanol system forms two liquid phases, oily (l-menthol-rich) and aqueous (water-rich) phases and that the ethanol system is a homogeneous aqueous liquid. A well-stirred infinite-dose condition in the donor solution and a perfect sink condition in the receiver solution were also assumed.

Based on the pH-partition theory, only the unionized species of acidic permeants can distribute to the oily phase of l-menthol-ethanol system and permeate across skin via the lipid pathway. Therefore, the total flux (J_{tot}) is the sum of five fluxes relating to different combinations of permeant species, system phases and permeation pathways. If the diffusivities of unionized and ionized species in the pore pathway are identical, J_{tot} is mathematically expressed as follows:

$$J_{tot} = \frac{(1-\alpha)(1-\beta)D,K_{lo}}{h} C_{uo} + \frac{\alpha(1-\beta)D_l K_{la}}{h} C_{ua} + \frac{(1-\alpha)\beta D_p K_{po}}{h} C_{uo} + \frac{\alpha\beta D_p}{h} C_{ua} + \frac{\alpha\beta D_p}{h} C_{ia} \quad (1)$$

where the C, D and K terms denote the concentrations, diffusion coefficients and partition coefficients, α, β and h are the volume fraction of aqueous phase in the system, porosity and thickness of skin, the subscripts u and i refer to unionized and ionized species, the subscripts o and a correspond to oily and aqueous phases, and the subscripts l and p imply liquid and pore pathways, respectively. From the relationships, $K_{lo} = K_{la}/K_{oa}$, $K_{po} = 1/K_{oa}$ and $K_{oa} = C_{uo}/C_{ua}$, Eq. (1) is reduced to:

$$J_{tot} = (P_l + P_p)C_{ua} + \alpha P_p C_{ia} \quad (2)$$

where the P terms are the permeability coefficients and

$$P_l = \frac{(1-\beta)D_l K_{la}}{h} \quad (3)$$

$$P_p = \frac{\beta D_p}{h} \quad (4)$$

When the apparent permeability coefficient (P_{app}) is defined as the total flux divided by the concentration of permeant in the aqueous phase, the following equation is obtained:

$$P_{app} = (P_l + P_p)f_{ua} + \alpha P_p(1 - f_{ua}) \quad (5)$$

where f_{ua} is the fraction of unionized species of acidic drug in the aqueous phase and then

$$f_{ua} = \frac{1}{1 + 10^{pH - pk_a}} \quad (6)$$

Eq. (5) shows that the permeability coefficient via the lipid and pore pathways can be distinguished and estimated from skin permeation data at various pH values.

On the other hand, the total flux of anionic drug from the homogeneous ethanol system consists of three flux terms, flux of unionized species via the lipid and pore pathways and that of ionized species via the pore pathway:

$$J_{tot} = \frac{(1-\beta)D_l K/_{1a}}{h} C_{ua} + \frac{\beta D_p}{h} C_{ua} + \frac{\beta D_p}{h} C_{ia} \quad (7)$$

Dividing Eq. (7) by the donor concentration, the total permeability coefficient (P_{tot}) is:

$$P_{tot} = P_l f_{ua} + P_p \quad (8)$$

Similar to P_{app} for l-menthol-ethanol system, P_{tot} for ethanol system is a function of P_l, P_p and pH. Comparison of P_l and P_p values obtained from the two enhancer systems gives us information about the role of l-menthol in skin permeation enhancement.

Because $C_{ia} = 0$ in Eq. (1) and Eq. (7) for lipophilic nonelectrolytes such as cortisone, P_{app} and P_{tot} become simpler as:

$$P_{app} = P_{tot} = P_l + P_p \quad (9)$$

It can further be seen that $C_{uo} = 0$ and $K_{la} = 0$ for hydrophilic nonelectrolytes such as D-mannitol, so that P_{app} and P_{tot} are:

$$P_{app} = \alpha P_p \tag{10}$$

$$P_{tot} = P_p \tag{11}$$

Regardless of pH, the P_{app} and P_{tot} of hydrophilic nonelectrolytes reflect change in the pore pathway.

3. Materials and methods

3.1. Materials

l-Menthol, ethanol, cortisone and *D*-mannitol were obtained from Nacalai Tesque, Inc. (Kyoto, Japan), indomethacin and ketoprofen were from Sigma Chemical Co. (St. Louis, MO), and flufenamic acid was from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). D-[1-^{3}H(N)]Mannitol (specific activity of 274 MBq/mg) was purchased from NEN Research Products (Boston, MA). All other chemicals and solvents were at least reagent grade and were obtained commercially.

3.2. Preparation of donor solutions

The l-menthol-ethanol enhancer systems were prepared by adding 1% l-menthol to 20% v/v ethanol in isotonic phosphate buffer saline (pH 2.0–8.0). All systems consisted of two phases, oily and aqueous phases, and the volume fraction of the aqueous phase was 0.988. Fifty milligrams of each drug was dissolved in 50 ml of each system at 37 °C, making the apparent drug concentration (C_{app}) of 0.1%. Radiolabelled D-mannitol was also dissolved in the systems containing nonlabeled D-mannitol at a concentration of 1.3 μCi/ml. The drug concentrations in the aqueous phase of systems ($C_{ua} + C_{ia}$) were measured at various pH values and the partition coefficient between oily and aqueous phases (K_{oa}) and pK_a of acidic drugs were estimated by the data-fitting to the following equation:

$$C_{ua} + C_{ia} = \frac{C_{app}}{(1-\alpha)K_{oa}f_{ua} + \alpha} \tag{12}$$

For nonelectrolytic drugs, the K_{oa} value was averaged values calculated from Eq. (12) substituting $f_{ua} = 1$ for all pHs.

Using 20% v/v ethanol in isotonic phosphate buffer saline (pH 2.0–8.0) as the l-menthol-free ethanol systems, 0.1% drug solutions were prepared at 37 °C. Because flufenamic acid and indomethacin were suspended in the ethanol systems at acidic pH values (pH 3.0–6.0 for the former and pH 3.0–5.0 for the latter), the solubilities were measured and viewed as the donor concentrations for skin permeation study. The pK_a values of acidic drugs in the systems were determined by a potentiometric titration (Kushla and Zatz, 1991).

3.3. Skin permeation study

The skin permeation study was performed according to the method of Hatanaka et al. (1995) with a minor modification. In brief, skin permeability of a drug was measured at 37 °C using side-by-side cell and abdominal skin samples excised from 6 week old male Wistar rats (Japan SLC Inc., Hamamatsu, Japan) and then fully hydrated with the same isotonic phosphate buffer saline used in the donor and receiver solutions. The receiver solution was pH 7.4 phosphate buffer saline and donor solution was the 0.1% drug solution described above. The drug concentrations in the receiver solution were determined and cumulative amounts of drug permeated across the skin were calculated every hour until 10 h after drug application. The total flux was estimated by fitting the cumulative amount vs. time data to previously reported Laplace transformed equation (Katayama et al., 1992):

$$\bar{q} = \frac{J_{tot}(6LT)^{1/2}}{s^{1/2}\sinh(6LTs)^{1/2}} \tag{13}$$

where $\bar{q}$ is the Laplace transform of cumulative amount of drug permeated across a unit area of skin, s is the Laplace variable with respect to time, and LT is the lag time.

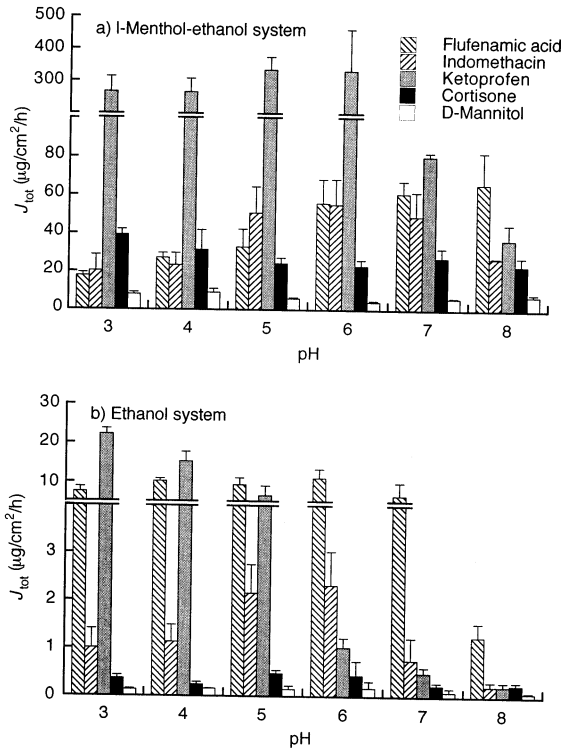

Fig. 2. Total flux of various drugs from the l-menthol-ethanol (a) and ethanol (b) systems at various pH values. Each value represents the mean ± S.D. of three experiments. J_{tot}, total flux.

3.4. Analytical method

Flufenamic acid and ketoprofen were assayed by HPLC. The HPLC system consisted of a pump (LC-6A, Shimadzu, Kyoto), a 4.6 × 150 mm stainless steel column packed with Nucleosil 100–5C18 (Machery Nagel, Düren, Germany) in a column oven (CTO-6A, Shimadzu) set at 40 °C, an ultraviolet detector (SPD-6A, Shimadzu) and an integrator (C-R6A, Shimadzu). The mobile phases were acetonitrile/0.1 M sodium dihydrogen phosphate (45:55) for flufenamic acid and methanol/0.1% phosphoric acid (70:30) for ketoprofen, and the flow rates were 1.0 ml/min. The internal standards were oxyphenbutazone and indomethacin, and the detector wavelengths were set at 280 and 255 nm for flufenamic acid and ketoprofen, respectively. Indomethacin and cortisone were also assayed by HPLC and D-mannitol concentration was measured by counting the radioactivity as reported previously (Katayama et al., 1992).

3.5. Data analysis

Data analysis was carried out by a nonlinear least squares regression program, MULTI (Yamaoka et al., 1981) or that based on a fast inverse Laplace transform algorithm, MULTI(FILT) (Yano et al., 1989).

4. Results and discussion

4.1. Effect of pH on skin permeation of acidic drugs from l-menthol-ethanol system

Skin permeabilities of various drugs from the l-menthol-ethanol and ethanol systems were measured over the pH range 3.0–8.0, and the data were summarized as the total flux in Fig. 2. The total flux of nonelectrolytes from the two systems was independent of system pH, and the permeability of cortisone and D-mannitol was enhanced up to 90 and 50 times by adding l-menthol to the ethanol system. In contrast to nonelectrolytes, the skin permeation of acidic drugs was drastically affected by pH of the systems, and the pH-dependency differed among drugs and systems. As a result, the enhancement factor of l-menthol (l-menthol-ethanol/ethanol ratio of total flux) varied between twice for flufenamic acid at pH 3.0 and 300 times for ketoprofen at pH 6.0.

4.2. Effect of pH on distribution of acidic drugs in l-menthol-ethanol system

To clarify the causes for pH-dependent skin permeation enhancement of acidic drugs by the l-menthol-ethanol system, the manner in which a drug presents in the system was firstly investigated. Fig. 3 shows the drug concentration in the aqueous phase of l-menthol-ethanol and ethanol systems at various pHs. Flufenamic acid and indomethacin were not completely dissolved in the ethanol systems at acidic pHs. The solubilities were lowest at pH 3.0, increased with increase of

pH, and exceeded 1000 μg/ml at pH 7.0 and 6.0, respectively (Fig. 3a and b). Other drugs were completely dissolved in all ethanol systems. Although the pK_a values of acidic drugs in the ethanol systems, which were determined by a potentiometric titration, were slightly higher than those in water, which were taken from the literature (Table 1), the drugs were confirmed to be dissociated depending on pH in the system as they are in water.

The concentration of D-mannitol in the aqueous phase of l-menthol-ethanol systems was around 1000 μg/ml regardless of pH, suggesting that the drug is substantially in the phase (Fig. 3e). Cortisone also showed a constant concentration, but the value was lower than that of D-mannitol and then 30% of the drug distributed in the oily phase (Fig. 3d). On the other hand, the concentration of acidic drugs evidently depended on pH and the relationship of concentration with pH seemed to correspond to increase in ionized fraction with increase of pH (Fig. 3a–c). The data were then fitted to Eq. (12), which was derived assuming that only unionized drug is distributed to the oily phase. The concentration-pH relationship could be well described by the equation (Fig. 3a–c), the partition coefficient between oily and aqueous phases (K_{oa}) similar to octanol/water partition coefficient (K_{ow}) was obtained, and pK_a in the aqueous phase was estimated to be slightly higher than that in water (Table 1).

Assuming regular solution behavior, the partition coefficient is a function of solubility parameters (δ) of solute and holding phases (Srebrenik and Cohen, 1976). The solubility parameters of solutes here calculated by the group contribution method (Fedors, 1974) are 12.08, 13.03. 11.95 and 12.67 for flufenamic acid, indomethacin, ketoprofen and cortisone, respectively. On the other hand, the solubility parameter of l-menthol is 9.49

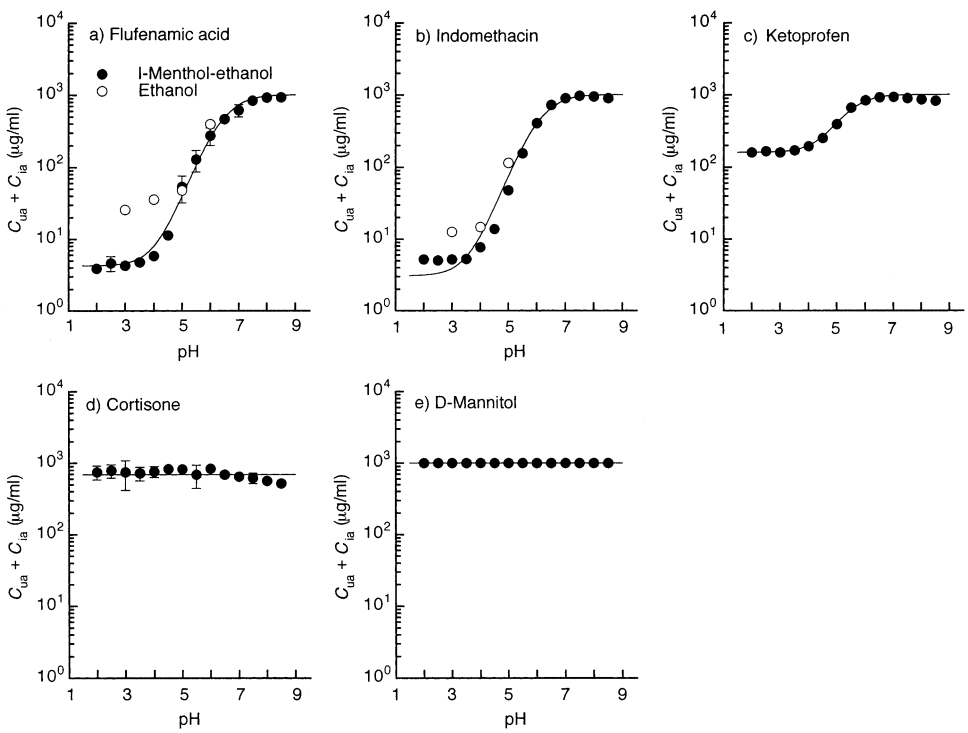

Fig. 3. Concentration of various drugs in the aqueous phase of l-menthol-ethanol and ethanol systems at various pH values. Each value represents the mean ± S.D. of 3 experiments. $C_{ua} + C_{ia}$, sum of concentrations of unionized and ionized drugs in aqueous phase.

Table 1
Physicochemi cal parameters of drugs used in this study

	MW	log K_{ow}	pK_a	log K_{oa}	pK_a	
					l-Menthol-ethanol system	Ethanol system
Flufenamic acid	281.2	4.88[b]	3.90[c]	4.29	4.16	4.66
Indomethacin	357.8	4.30[d]	4.30[d]	4.43	3.69	4.77
Ketoprofen	254.3	2.94[e]	4.45[f]	2.64	4.62	4.77
Cortisone	360.5	1 47[g]	–	1.58	–	–
D-Mannitol	182.2	−3.10[g]	–	–	–	–

The values of log K_{oa} and pK_a in I-menthol-ethanol system were obtained by computer-fitting of concentration data in aqueous phase to Eq. (12). The values of pK_a in ethanol system were determined by a potentiometric titration (Kushla and Zatz, 1991). *MW*, molecular weight; log K_{ow}, logarithm of partition coefficient between n-octanol and water; log K_{oa}, logarithm of partition coefficient between oily and aqueous phases.

[b] Dunn (1973).
[c] McDougall et al. (1988).
[d] Inagi et al. (1981).
[e] Yano et al. (1986).
[f] Fini et al. (1973)
[g] Leo et al. (1971).

and lower than that of octanol ($\delta = 10.3$), indicating that the former is more hydrophobic than the latter. The oily phase in the l-menthol-ethanol system may not be pure l-menthol but may contain a small amount of more polar ethanol ($\delta = 13.0$). The aqueous phase also consists of ethanol and aqueous buffer solutions. Therefore, the difference in the polarity between oily and aqueous phases must be smaller than that between l-menthol and water. The mixing of solvents might accidentally produce K_{oa} values similar to K_{ow} values.

The pK_a value of acids generally rise in a solvent having low dielectric constant (ε) to above that in water (Benet and Goyan, 1967). The ε values of aqueous phases in the l-menthol-ethanol and ethanol systems may be lower than that of water ($\varepsilon = 78.5$) because of ethanol ($\varepsilon = 24.3$). Unfortunately, the measurement of pH in semi-aqueous solvents such as the aqueous phases here reflect the thermodynamic activity of hydrogen ion in the solvents and thus are not directly comparable to aqueous pH (Bates et al., 1963). However, the delta values, a quantity for the change of solvation energy in transferring the hydrogen ion from water to another solvent and a correcting factor from apparent pK_a values to the true one, are expected to be positive values for the aqueous phases due to their low polarity compared to water (Bates et al., 1963). The lower dielectric constant and polarity might push up the pK_a values of acidic drugs.

The pH-dependent concentration in the aqueous phase of l-menthol-ethanol system could be explained using Eq. (12) and the obtained K_{oa} and pK_a values were valid as described above. It is reliable to assume that only unionized species of acidic drugs present in the oily phase of the system. The distribution of ionized species to the phase can be ignored. Thus, the distribution to the oily phase is higher with higher system pH and lipophilicity of drug.

4.3. Effect of pH on skin permeation pathways

It is well known that corrosive chemicals and protein denaturants such as acids and alkalies injure the barrier of skin permeation (Flynn, 1979). There is a possibility that the pH-dependency in skin permeation enhancement by the l-menthol-ethanol system may result from different level of skin damage. Next, the apparent permeability coefficient (P_{app}) of drugs from the system was calculated by dividing the total flux

(Fig. 2) by the concentration in the aqueous phase (Fig. 3) and plotted against pH together with total permeability coefficient (P_{tot}) from the ethanol system in Fig. 4. The P_{app} and P_{tot} values of nonelectrolytes remained constant over the pH range tested (Fig. 4d and e). Because D-mannitol is believed to permeate across skin via the pore pathway, the constant permeability means no change in the barrier properties of pathway. For lipophilic cortisone, the permeability coefficient via the lipid pathway (P_l) may be remarkably higher than that via the pore pathway (P_p) and thus both P_{app} and P_{tot} values can be regarded as the P_l values. However, the P_l value does not always reflect the change of lipid pathway but also that of thermodynamic activity of permeant in the vehicle based on the partitioning transport theory (Hatanaka et al., 1995). One cannot judge whether the barrier function of the lipid pathway is modified only from such data.

The P_{app} and P_{tot} values of acidic drugs were high at acidic pHs and decreased as pH increased (Fig. 4a–c). A similar phenomenon has been reported for many weak acids applied to skin as aqueous buffer solutions, and documented to be caused by change in the contribution of unionized and ionized species having distinguishable permeabilities to total permeation (Swarbrick et al., 1984; Hadgraft and Valenta, 2000). Then, the P_{app} and P_{tot} data were analyzed based on the skin permeation models, where it is assumed that the pH of system does not influence the barrier function of permeation pathways but the dissociation of drugs. The data were well explained by the models as shown in Fig. 4a-c, and the pK_a, P_l and P_p values listed in Table 2 were obtained.

The obtained pK_a values (Table 2) did not completely agree with those previously estimated by a potentiometric titration or from the concentration data in the aqueous phase (Table 1). The

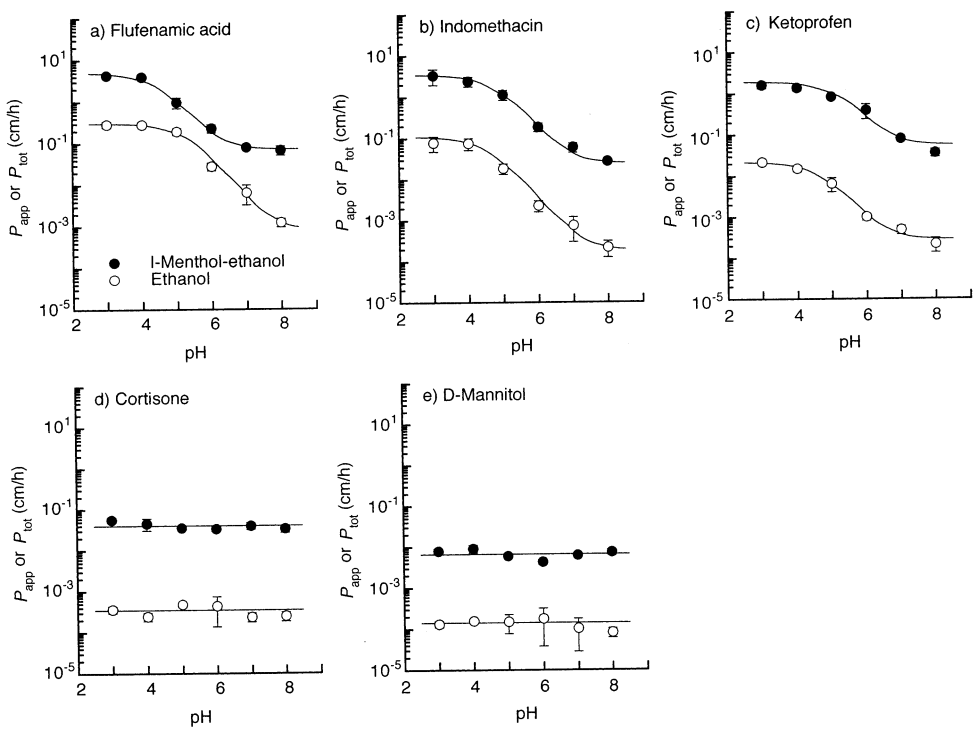

Fig. 4. Apparent permeability coefficient of various drugs from the l-menthol-ethanol system and total permeability coefficient from ethanol system. Each value represents the mean ± S.D. of three experiments. P_{app}, apparent permeability coefficient; P_{tot}, total permeability coefficient.

Table 2
Skin permeation parameters calculated in model analysis

	I-Menthol-ethanol system			Ethanol sysetm		
	$p\mathrm{K_a}$	P_l (cm/h)	P_p (cm/h)	$p\mathrm{K_a}$	P_l (cm/h)	P_p (cm/h)
Flufenamic acid	4.30	4.87	7.23×10^{-2}	5.13	3.03×10^{-1}	8.28×10^{-4}
	±0.26	±0.99	$\pm0.86\times10^{-2}$	±0.09	$\pm0.18\times10^{-1}$	$\pm1.42\times10^{-3}$
Indomethacin	4.64	3.46	2.50×10^{-2}	4.42	1.10×10^{-1}	1.90×10^{-4}
	±0.63	±0.16	$\pm1.25\times10^{-2}$	±0.19	$\pm0.17\times10^{-1}$	$\pm7.04\times10^{-4}$
Ketoprofen	5.05	1.86	5.74×10^{-2}	4.56	2.15×10^{-2}	2.84×10^{-4}
	±0.20	±0.22	$\pm3.41\times10^{-2}$	±0.11	$\pm0.17\times10^{-2}$	$\pm1.48\times10^{-4}$
Cortisone	–	4.00×10^{-2}[b]		3.50×10^{-4}[b]		
D-Mannitol	–	–	6.66×10^{-3}	–	–	1.42×10^{-4}
			$\pm1.89\times10^{-3}$			$\pm0.71\times10^{-4}$

The values were obtained by computer-fitting of skin penneation data to Eq. (5) and (Eq. (8))–(Eq. (11)). Each value represents the mean $\pm$ computer-calculated S.D. P_l, permeability coefficient via lipid pathway; P_p, permeability coefficient via pore pathway.
[b] The value represents the sum of P_l and P_p.

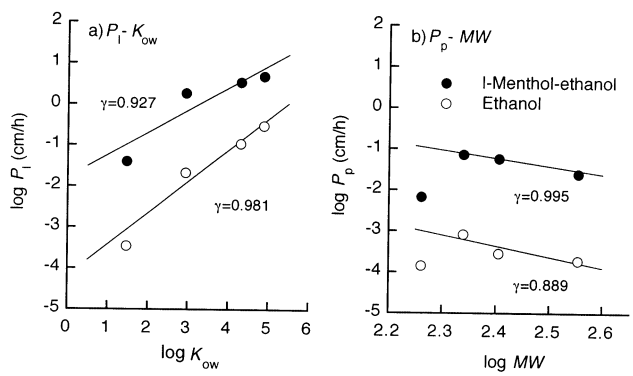

Fig. 5. Relationships between permeability coefficient of various drugs via the lipid (a) and pore (b) pathways and their physicochemical parameters. Each value represents the mean of three experiments. P_l, permeability coefficient via the lipid pathway; P_p, permeability coefficient via the pore pathway; K_{ow}, n-octanol/water partition coefficient; MW, molecular weight.

pH value of skin in the permeation study might not completely equal that in the systems due to a pH-gradient across skin. Fig. 5 shows the relationship of P_l and P_p values with physicochemical properties of drugs. A positive linear relationship existed between P_l and K_{ow} of cortisone and acidic drugs for each system, whereas P_p of acidic drugs was related negatively to the molecular weight (MW). These results are consistent with a partitioning transport via the lipid pathway and a porous transport via the pore pathway (Hatanaka et al., 1998). The P_l and P_p values of l-menthol-ethanol systems were always higher than the corresponding ethanol systems. It has been reported that the addition of l-menthol to 40% ethanolic aqueous solution increases the diffusion coefficient of permeants in the lipid and pore pathways (Kobayashi et al., 1994). The possibility that l-menthol affects the partitioning of permeants to the lipid pathway and contribution of two pathways to total permeation (β) cannot be ignored because the system composition here is different from that in the previous report. The P_p value of acidic drugs was higher than that of *D*-mannitol (Fig. 5b). Because ionized species of acidic drugs have a large hydrophobic nucleus linked to a

carboxylic ion, the permeants themselves might affect the permeation barrier in a similar way to anionic surfactants (Ashton et al., 1992).

Taking the model analysis results of acidic drugs together with permeation data of nonelectrolytes, the pH change in the l-menthol-ethanol systems is believed not to affect the two permeation pathways. The pH-dependent skin permeation enhancement does not result from different skin damage.

4.4. Contribution of each flux to total flux of acidic drugs from l-menthol-ethanol system at various pHs

Although there was no effect of pH change of l-menthol-ethanol system on the skin permeation pathways, the distribution of acidic drugs in the system was pH-dependent. The total flux of acidic drugs is the sum of five fluxes relating with different combinations of drug species, system phases and permeation pathways. Finally, the contribution of the five fluxes to the total flux was simulated. Each of the five was calculated by multiplying the permeability coefficient and concentration in the system using parameter values in Tables 1 and 2 and plotted as a function of system pH in Fig. 6. For all acidic drugs, the total flux was mainly attributed to two fluxes, that of unionized species via the lipid pathway and that of ionized species via the pore pathway from the aqueous phase of the system. In spite of a large amount of unionized drug in the oily phase especially at acidic pHs, the drug scarcely permeated across the skin from the phase because of low partitioning to the lipid and pore pathways. This means that the oily phase acts as a reservoir of acidic drugs. Relatively low concentration and permeability coefficient caused permeation of unionized species from the aqueous phase via the pore pathway to be scanty.

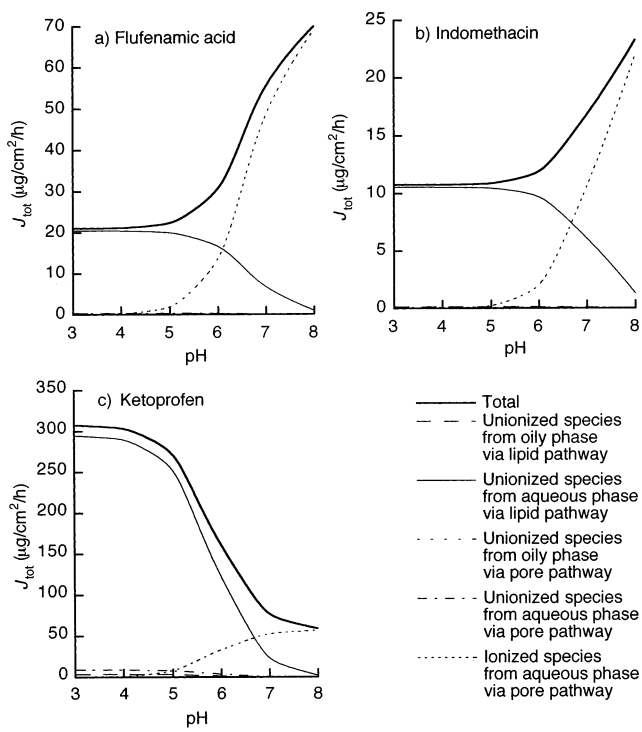

Fig. 6. Contribution of five fluxes on the total flux of acidic drugs from the l-menthol-ethanol system at various pH values. Each curve represents simulation result using parameter values in Tables 1 and 2.

At acidic pHs, acidic drugs were primarily transported across skin as the unionized species via the lipid pathway from the aqueous phase of l-menthol-ethanol system due to remarkably high permeability coefficient and higher concentration than that of ionized species. As pH increased, the concentration of unionized species decreased and that of ionized species increased. When the concentration ratio of ionized species to unionized species exceeded the lipid pathway/pore pathway ratio of permeability coefficient, the permeation of ionized species via the pore pathway from the aqueous phase became the main permeation. Whether the total flux increased or decreased with increase of pH depended on the hydrophobicity of the drug. For highly lipophilic acidic drugs such as flufenamic acid and indomethacin, the high distribution of unionized species to the oily phase at acidic pHs remained the concentration in the aqueous phase and thus total flux at a low level. The exponential rise in the concentration of ionized species with increase of pH resulted in higher total fluxes at higher pHs. In contrast, the total flux of less lipophilic ketoprofen was very high at acidic pHs because of higher drug concentration in the aqueous phase than that of other acidic drugs. The high total flux could not be overcome by the increased concentration of ionized species. However, the total flux vs. pH profile of ketoprofen is expected to be the opposite when the volume fraction of oily phase is 10 times higher. The pH-dependency in skin permeation enhancement by l-menthol-ethanol is affected by system composition as well as lipophilicity and pK_a of acidic drugs.

5. Conclusion

Skin permeability of acidic drugs from the l-menthol-ethanol systems varied depending on the system pH. The phenomenon was not a result from different effects on skin among pHs but was caused by a reservoir effect of oily phase in the system on unionized drugs. The pH-dependency was affected by lipophilicity and pK_a of permeant, and system composition. To elicit the maximum permeation enhancement of l-menthol-ethanol system for electrolytic drugs, one should be aware of the system pH.

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