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Effect of fatty acid Esters on permeation of ketoprofen through hairless rat skin

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Abstract

Twelve medium to long chain fatty acid Esters (Esters), the total number of carbon atoms of which ranged from 17 to 34, were used to study the effect of the vehicle on the permeation of ketoprofen, and the effect was compared with the case of indomethacin. The solubility of ketoprofen was higher in Esters with a smaller number of carbon atoms. The permeation rate of ketoprofen from the Ester suspension through excised hairless rat skin was proportional to its solubility in the suspension, which was the same in the case of indomethacin. The diffusion constant and partition coefficient were calculated using the computer program MULTI(FILT). The diffusion constant decreased with increasing number of carbon atoms, and the partition coefficient was increased with increasing number of carbon atoms, in both cases of ketoprofen and indomethacin. Esters also penetrated the skin with the concentration of about 10 mg/g, independent of the number of carbon atoms. The Esters in the skin increase the diffusion rate of the drugs, especially in the case of Esters with a small number of carbon atoms. Also the drug solubility in the skin was improved, although the effect was similar for the range of Esters investigated in the present study. Then the permeation rate of ketoprofen and indomethacin increased.

Keywords: Fatty-acid ester; Skin permeation; Ketoprofen; Indomethacin; Diffusion constant; Partition coefficient

1. Introduction

It is well known that the vehicle of transdermal formulations affects the permeation rate of drugs. Fatty acid ester (Ester) is one such ingredient. It has been reported that isopropyl myristate (IPM) and some other Esters increase drug permeation (Ozawa et al., 1988; Sato et al., 1988; Kumar et al., 1992; Harada et al., 1993). However, only a few reports are available to clarify the effect of Ester systematically. Catz and Friend (1989) reported the enhancement effect of a series of short chain Esters. However, short chain Esters cannot be used as vehicles because they tend to irritate the skin.

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We reported previously that a series of medium to long chain Esters, the total number of carbon atoms of which ranged from 17 (IPM) to 34 (isocetyl stearate), improved the permeation of indomethacin (Fujii et al., 1996). Medium to long chain Esters are widely used as ingredients of cosmetics, as they are safer than short chain ones. Indomethacin, which hardly permeates from water or liquid paraffin suspension, permeates from the Ester suspension at a rate of 0.7–2.8 μg/cm^2/h. The permeation of indomethacin is correlated with its solubility in Esters, because of the higher skin concentration of indomethacin with higher solubility Esters.

In this study, we used ketoprofen as a model drug and compared it with the case of indomethacin. Ketoprofen has almost the same partition coefficient as indomethacin (log *P* octanol/water = 3); however, its molecular weight and melting point are lower and its solubility is higher than those of indomethacin. Twelve Esters were selected according to the total number of carbon atoms and the variety of structure.

2. Materials and methods

2.1. Materials

Ketoprofen was purchased from Nippon Bulk Yakuhin Co., Ltd. (Osaka). The Esters used in this experiment are shown in Table 1. All Esters except ICIS were gifts from Kokyu Alcohol Kogyou Co., Ltd. (Chiba). Nikko Chemicals Co., Ltd. (Tokyo) provided ICIS and liquid paraffin. These Esters were of Japanese Standard of Cosmetic Ingredients grade or Japanese Cosmetic Ingredients Codex grade.

2.2. Solubility of ketoprofen in Esters

An excess amount of ketoprofen (about 5%) was suspended in Esters and incubated at 37°C overnight. After centrifugation, 0.5 g of the supernatant was extracted with 25 ml of pH 7.1 phosphate buffer solution (PBS) at 37°C. The concentration of ketoprofen in PBS was determined by HPLC, and solubility in Esters was calculated.

2.3. Permeation studies

The skin permeation rate was measured in a modified Franz-type diffusion cell apparatus. The effective area available for permeation was 1.1 cm^2. The receptor compartment was filled with 16 ml of isotonic phosphate buffer solution (pH 7.1) maintained at 37°C, and mixed with a star-head magnet at 600 rpm. A piece of suitably sized abdominal skin from a hairless male rat (5–6

Table 1
Fatty acid esters used in this experiment[1]

Name	Abbr.	Number of carbon atoms			Structure	
		R1	R2	Total	R1	R2
Octyl Isononanoate	IOIN	9	8	17	iso	iso
Isononyl Isononanoate	ININ	9	9	18	iso	iso
Isodecyl Isononanoate	IDIN	9	10	19	iso	iso
Isotridecyl Isononanoate	ITIN	9	13	22	iso	iso
Isocetyl Octanoate	ICIO	8	16	24	iso	nor
Cetyl Octanoate	CIO	8	16	24	iso	nor
Octyl Isopalmitate	IOIP	16	8	24	iso	iso
Octyl Palmitate	IOP	16	8	24	nor	iso
Isocetyl Myristate	ICM	14	16	30	nor	iso
Isocetyl Palmitate	ICP	16	16	32	nor	iso
Isocetyl Isostearate	ICIS	18	16	34	iso	iso
Isocetyl Stearate	ICS	18	16	34	nor	iso

[1] R1, fatty acid moiety; R2, alcohol moiety; iso, with side chains; nor, without side chains.

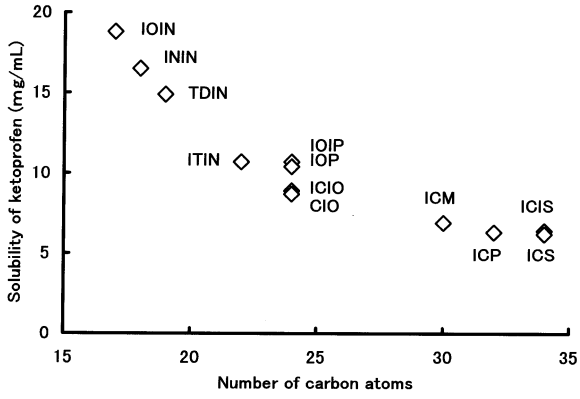

Fig. 1. Relationship between total number of carbon atoms and solubility of ketoprofen in Esters.

weeks old, Saitama Laboratory Animals, Saitama) was excised immediately before skin permeation experiments. The piece of skin was mounted on the cell and approximately 0.1 g of suspension was poured on it. At appropriate times, 200 μl aliquots were withdrawn from the receptor compartment. The same volume of fresh solution was added to the receptor compartment after withdrawal to keep the volume constant.

2.4. Ketoprofen concentration in skin

After the skin permeation studies, ketoprofen concentration in the skin was determined 24 h after application. Sample-applied skin was wiped with paper moistened with liquid paraffin and cut off from the margin to set to the cell. Then, the skin was homogenized with a methanol–water mixture and centrifuged at 3000 rpm. Ketoprofen concentration in the supernatant was measured by HPLC.

2.5. Analysis of ketoprofen concentration

Ketoprofen concentrations were determined using an HPLC system (Shimadzu, Kyoto). The analytical system consisted of a pump (LC 6A), a UV detector (SPD 6A) operated at 264 nm and an integrator (CPR 4A). The sample was injected by an autoinjector equipped with a system controller (SIL 9A, SCL 6B). The column (TSK-GEL ODS-120T, 150 × 4.6 mm i.d., Tosoh, Tokyo) was eluted at ambient temperature with 0.1% phosphoric acid solution: methanol (35:65) as the mobile phase, at a flow rate of 1 mL/min.

2.6. Ester concentration in skin

The skin concentrations of IOIN, IOP and ICS after 24 h application were determined by GC. Skin was homogenized in propanol according to the same procedure as that for ketoprofen concentration in skin. The supernatant was filtered through a 0.20 μm membrane filter (Advantec TOYO, Tokyo). The system for analysis was GC-14B with a FID detector (Shimadzu) under the following conditions: column, wide bore column HR-1 (0.53 × 15 mm, Shimadzu); carrier gas, nitrogen gas (70 kPa); column temperature 120–165°C for IOIN, 180–250°C for IOP, 220–300° for ICS.

2.7. Data analysis

The nonlinear least square program MULTI(-FILT) (Yano et al., 1989) was used for calculation of the diffusion constant and partition coefficient from the accumulated permeation amount–time data (Hashida et al., 1988).

3. Results

3.1. Solubility of ketoprofen in Esters

The solubilities of ketoprofen in Esters are shown in Fig. 1 as a function of the total number of carbon atoms. The solubility of ketoprofen in Ester with smaller number of carbon atoms is higher, and the solubility in IOIN is about three times that in ICIS. There is no evident effect of the structure of Ester on the solubility of ketoprofen. Ketoprofen solubility in water and liquid paraffin was 0.24 and 0.18 mg/mL, respectively. The solubilities of ketoprofen in Esters are markedly higher than those in water or liquid paraffin by 30–100-fold.

3.2. Permeation rate of ketoprofen from suspension in Esters

Fig. 2 shows typical examples of the permeation profiles of ketoprofen from suspension in Esters. The highest permeation rate was obtained from IOIN suspension, and the lowest, from ICIS; the order was almost the same as that of solubility. The steady-state permeation rates were calculated from the linear part of the profiles and plotted against solubility (Fig. 3). Good correlation was obtained ($r = 0.970$), and the y-intercept was almost the same as that for the permeation rate from the liquid paraffin suspension. In contrast, the skin concentrations of ketoprofen after 24 h application showed no significant difference among each other (Fig. 4), but higher than those after application of water or liquid paraffin suspension.

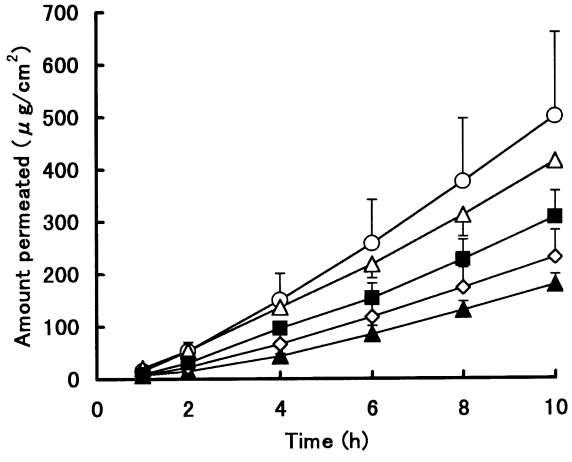

Fig. 2. Permeation profiles of ketoprofen from suspension through excised hairless rat skin. ○, IOIN; Δ, ININ; ■, ITIN; ◇, CIO; ▲, ICS. Each point represents the mean ± SD of at least three experiments.

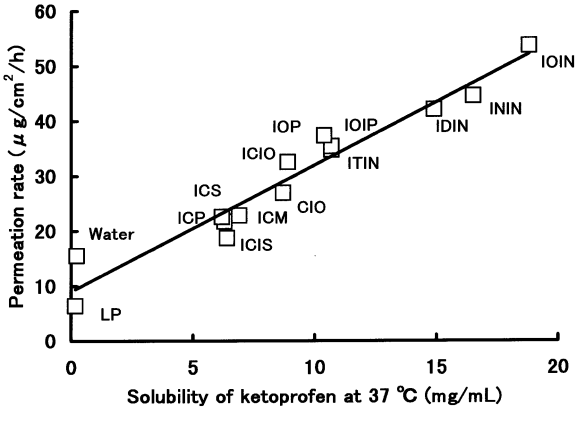

Fig. 3. Relationship between ketoprofen solubility in Ester and permeation rate from suspension.

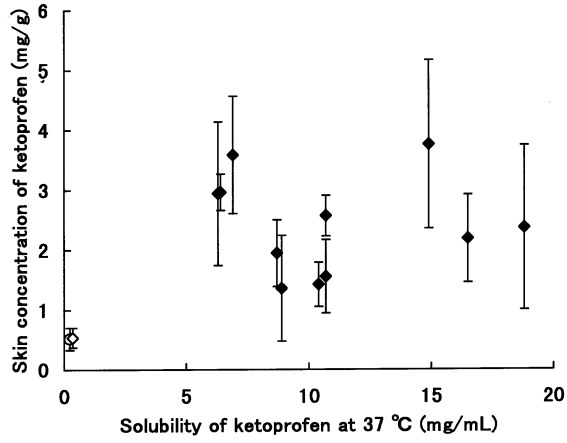

Fig. 4. Relationship between ketoprofen solubility and observed concentration in skin. ◆, Esters; ◇, water; ○, liquid paraffin.

3.3. Effect of Esters on diffusion and partition of ketoprofen

The permeation rate is expressed as CKD/L (C: concentration in vehicle; K: partition coefficient between vehicle and skin; D: diffusion constant in skin; L: diffusion length), i.e. it depends on the diffusion constant and the partition coefficient between the vehicle and skin. To clarify the contribution of both factors, permeation data were analyzed by MULTI(FILT), and the diffusion factor, $D' = D/L^2$ and the partition factor, $K' = KL$, were calculated. Then, $L = 0.1$ cm, which is the thickness of hairless rat skin, was substituted into the above equations, D and K were estimated, and results are shown in Table 2.

The diffusion constant D of ketoprofen decreased with increasing number of carbon atoms ($r = -0.914$). The diffusion constants applied as liquid paraffin and water suspension were 0.883 and 2.09×10^{-3} cm^2/h, respectively, i.e. Esters with a large number of carbon atoms showed

diffusion constants similar to liquid paraffin, while those with a small number of carbon atoms showed diffusion constants similar to water. The partition coefficient K increased with increasing number of carbon atoms ($r = 0.915$). Thus, the calculated skin concentration (the product of C and K), remained constant regardless of the number of carbon atoms of Esters. In contrast, the calculated skin concentration for liquid paraffin and water was about 0.7 mg/cm^3; therefore, the skin concentration of ketoprofen increased when Esters were used, but there was no difference in the skin concentration among the kinds of Esters used.

3.4. Skin concentration of ester

The skin concentrations of IOIN, IOP and ICS, which have the smallest, intermediate and largest number of carbon atoms in this study, were determined. They were found to exist at extremely high concentrations in the skin, i.e. 16 ± 4, 8 ± 4 and 10 ± 2 mg/g, respectively, there were no significant differences among them.

4. Discussion

Ketoprofen solubility in Esters was higher than that in water or liquid paraffin. The solubility parameters of Esters were estimated according to the method reported by Fedors, (1974). The values were around 8.5 and almost the same as that of liquid paraffin (Table 3). The solubility of ketoprofen, of which the solubility parameter was calculated to be 13, was estimated to be 0.2 mg/mL. This value is similar to the solubility of ketoprofen in liquid paraffin, but it cannot explain the high solubility in Esters. There must be some kind of interaction, such a hydrogen bond formation, between ketoprofen and Esters. Table 3 also shows the three-dimensional solubility parameters (Hansen and Beerbower, 1985). The solubility parameter of the hydrogen bond (σ_H) and polar (σ_P) contribution showed a high correlation with solubility ($r = 0.900$). Thus, the solubility of ketoprofen in Ester depends on the hydrogen bond formation.

There is a linear relationship between the solubility of ketoprofen in Ester and its permeation

Table 2
Diffusion constant and partition coefficient for skin permeation of ketoprofen calculated by MULTI(FILT)

	C[a] (mg/mL)	D[b] (10^{-3} cm^2/h)	K[c]	CK[d] (mg/cm^3)
IOIN	18.8	1.630	0.175	3.3
ININ	16.5	1.849	0.146	2.4
IDIN	14.9	1.641	0.172	2.6
TDIN	10.7	1.249	0.260	2.8
IOIP	10.7	1.502	0.220	2.4
IOP	10.4	1.527	0.235	2.4
ICIO	8.9	1.239	0.295	2.6
CIO	8.7	1.094	0.283	2.5
ICM	6.9	0.759	0.435	3.0
ICP	6.3	0.800	0.430	2.7
ICIS	6.4	0.856	0.341	2.2
ICS	6.2	0.769	0.473	2.9
LP	0.18	0.883	4.000	0.77
Water	0.24	2.090	3.090	0.74

[a] C: solubility in Ester;
[b] D: diffusion constant in skin;
[c] K: partition coefficient between Ester and skin;
[d] CK: calculated skin concentration.

Table 3
Solubility parameters of Esters and solubility of ketoprofen

	C[a] (mg/mL)	$-\log X_2$[b]	σ[c] $(cal/cm^3)^{1/2}$	σ_D[d] $(cal/cm^3)^{1/2}$	σ_P[d] $(cal/cm^3)^{1/2}$	σ_H[d] $(cal/cm^3)^{1/2}$
IOIN	18.8	1.64	8.6	7.8	0.85	3.6
ININ	16.5	1.67	8.5	7.7	0.83	3.5
IDIN	14.9	1.69	8.6	7.8	0.81	3.4
TDIN	10.7	1.78	8.6	7.9	0.76	3.2
IOIP	10.7	1.75	8.7	8.1	0.73	3.1
IOP	10.4	1.76	8.8	8.2	0.73	3.1
ICIO	8.9	1.82	8.7	8.1	0.73	3.1
CIO	8.7	1.83	8.8	8.2	0.73	3.1
ICM	6.9	1.85	8.7	8.3	0.66	2.8
ICP	6.3	1.86	8.7	8.3	0.64	2.7
ICIS	6.4	1.83	8.7	8.2	0.62	2.6
ICS	6.2	1.84	8.7	8.3	0.62	2.6
LP	0.18	3.51	8.5	8.5	0.00	0.0
Water	0.24	4.77	23	7.6	7.8	21

[a] C: solubility in Ester;
[b] X_2: mole fraction of ketoprofen;
[c] σ:solubility parameter;
[d] σ_D, σ_P, σ_H: three-dimensional solubility parameter of dispersion, polar and hydrogen bond contribution, respectively.

rate from the Ester suspension. It is well known that the permeation rate from suspension is the same because of the same activity (Higuchi, 1960). The difference in permeation rate indicates some effect of Esters on the skin. The results of MULTI(FILT) calculation show low partition to the skin of ketoprofen from an Ester suspension in which it is highly soluble, and the constant skin concentration regardless of the Ester used, which were supported by experimental data. It seems to follow the Higuchi's law. However, the skin concentrations of ketoprofen after application of Ester suspensions were higher than when the liquid paraffin or a water suspension was applied. Sloan et al., (1986) reported that for a vehicle of which the solubility parameter was similar to that of skin, solubility of the vehicle was high in the skin, and thus, the skin function was changed as a result. Leopold and Lippold, 1995 suggested that alteration of the lamellar structure of the stratum corneum lipid by fluidizing action or by dissolution or extraction of the lipids with some kind of vehicle increases the drug diffusivity and changes the solubility in the barrier. In our case, Esters partitioned to the skin at relatively high concentrations, about 10 mg/g. If Esters were to act simply by carrying the dissolved ketoprofen, the increase concentration in the skin would only be $60 \sim 200$ μg/g, which would be less than 1/10 of the experimental skin concentration. Thus, the partitioning of Esters to the skin changed the skin function and changed the partition and diffusion of ketoprofen. The effect of an Ester on the partition of ketoprofen to the skin was independent on kind of Ester used, although the diffusion constant depended on it. The reason is not clear, but molecular weight σ_H or σ_P may have an effect on it.

In the case of indomethacin (Fujii et al., 1996), its solubility was also correlated with σ_H and σ_P ($r = 0.957$) and a linear relationship was obtained between indomethacin solubility in Ester and its permeation rate ($r = 0.957$). The skin concentration of indomethacin and the solubility of indomethacin in Ester showed a linear relationship, in contrast with the case of ketoprofen. The diffusion constant and partition coefficient of indomethacin were calculated using the same

Table 4
Diffusion constant and partition coefficient for skin permeation of indomethacin calculated using MULTI(FILT) with the assumption of infinite and finite conditions

	Infinite				Finite		
	C^a (mg/mL)	D^b (10^{-3} cm^2/h)	K^c	CK^d (μg/cm^3)	D^b(10^{-3} cm^2/h)	K^c	CK^d (μg/cm^3)
IPM*	2.30	0.663	0.223	514	0.626	0.273	201
IOIN	2.03	0.672	0.188	382	0.613	0.242	166
ININ	1.68	0.795	0.155	261	0.720	0.198	115
IDIN	1.53	0.649	0.215	330	0.585	0.287	141
IPIS*	1.48	0.596	0.227	336	0.546	0.293	142
TDIN	1.14	0.586	0.267	304	0.522	0.374	128
IOIP	1.09	0.511	0.237	259	0.470	0.308	114
IOP	1.04	0.530	0.235	245	0.486	0.307	107
ICIO	0.79	0.510	0.290	229	0.460	0.404	97
CIO	0.89	0.404	0.390	347	0.363	0.576	146
CC*	1.12	0.600	0.262	293	0.539	0.356	121
SC*	1.16	0.616	0.252	292	0.554	0.340	121
ITM*	0.72	0.516	0.275	198	0.472	0.365	83
ICM	0.65	0.325	0.426	277	0.298	0.605	118
ICP	0.59	0.371	0.514	303	0.324	0.865	122
ICIS	0.55	0.263	0.494	272	0.247	0.675	113
ICS	0.57	0.283	0.386	220	0.264	0.519	100

[a] C, solubility in Ester;
[b] D, diffusion constant in skin;
[c] K, partition coefficient between Ester and skin;
[d] CK, calculated skin concentration at 24 h after application.
* IPM, isopropyl myristate; IPIS, isopropyl isostearate; CC, cetyl caprylate; SC, stearyl caprylate; ITM, isotridecyl myristate

procedure as that for ketoprofen (infinite condition) and the results are shown in Table 4. The diffusion constant D decreased with increasing number of carbon atoms ($r = -0.942$), and the partition coefficient K increased with increasing number of carbon atoms ($r = 0.896$), which is similar to the case of ketoprofen. However, the calculated skin concentration did not show a linear relationship with solubility, which did not fit with observed skin concentration (Fig. 5). In cases using a suspension, it was presumed that the dissolution rate of the drug is high and the concentration of the drug in the suspension is kept constant (infinite condition). The donor phase was not stirred, so the low dissolution rate of indomethacin may sometimes cause problems, for example, indomethacin did not permeate within 10 h from liquid paraffin suspension (Henmi et al., 1994), although 4 μg/cm^2 permeated from a water suspension (Fujii et al., 1997). Thus, D and K were estimated using MULTI(FILT) under the assumption that indomethacin did not dissolve in the donor phase even if its concentration decreased due to partition in the skin (finite condi-

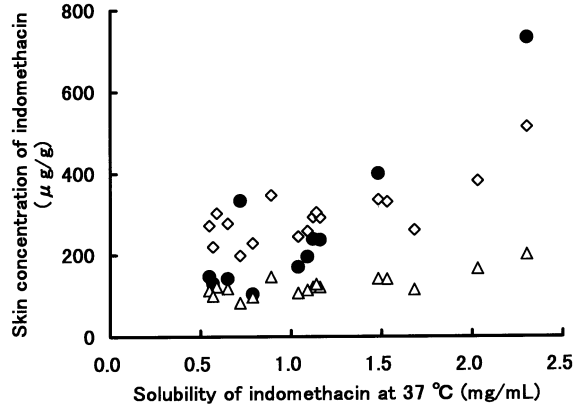

Fig. 5. Relationship between solubility of indomethacin and skin concentration of indomethacin. ●, observed; ◇, calculated under infinite condition; Δ, calculated under finite condition.

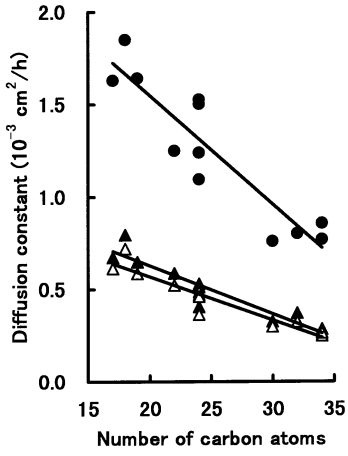

Fig. 6. Relationships between diffusion constant and the number of carbon atoms of Esters. ●, ketoprofen; ▲, indomethacin (infinite condition); Δ, indomethacin (finite condition).

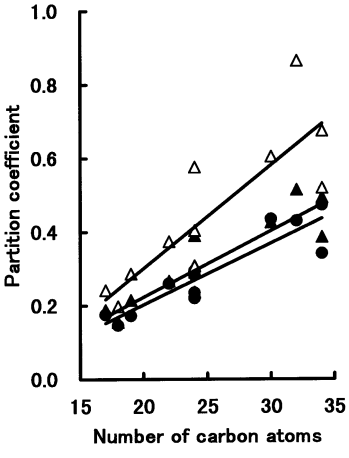

Fig. 7. Relationships between partition coefficient and the number of carbon atoms of Esters. ●, ketoprofen; ▲, indomethacin (infinite condition); Δ, indomethacin (finite condition).

tion), and the skin concentration after 24 h application was calculated with those D and K (Table 4). The diffusion constant D under the finite condition was little lower and the partition coefficient K was slightly higher than those under the infinite condition, which also showed a linear relationship with the number of carbon atoms (D, $r = -0.942$; K, $r = 0.913$) (Fig. 6 and Fig. 7). The skin concentration calculated under the finite condition also did not show a linear relationship with the solubility (Fig. 5). The observed skin concentration after application of the suspension low in indomethacin solubility Esters were close to those calculated under the finite condition, and after application of the suspension high in indomethacin solubility Esters were close to those results under the infinite condition. There is a possibility that the dissolution rate of indomethacin was low in the low solubility Esters and the skin concentration became low, and consequently, a linear relationship was observed between the solubility and observed skin concentration.

5. Conclusion

The Esters were partitioned at considerably high concentrations to the skin, which led to an increase in the diffusion rate of the drugs, especially in the case of Esters with a small number of carbon atoms. The Esters also affected drug solubility in the skin, although the effect was similar for the range of Esters investigated in the present study. Consequently, the permeation rate of ketoprofen and indomethacin increased due to the high partition to the skin and the increase in the diffusion constant.

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