Permeability of Pure Enantiomers of Ketorolac through Human Cadaver Skin

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Abstract □ The permeability of pure enantiomers of ketorolac acid, a potent non-narcotic analgesic, through human cadaver skin was evaluated. The melting temperature of each enantiomer was 20 °C higher than that of the racemic compound. As expected, the solubility of the racemic compound in water and isopropyl alcohol/water/isopropyl myristate (IPA/water/IPM, 50:50:1.5) was roughly 2 times higher than that of the enantiomers. The permeability of the enantiomers through poly(ethylenevinyl acetate) (EVA) synthetic membrane and human cadaver skin was determined with a side-by-side diffusion cell. The skin flux of the racemic compound was about 1.5 times higher than those of the enantiomers. On the other hand, no significant differences in the intrinsic permeability coefficient of the racemic compound and the enantiomers in the EVA membrane and human cadaver skin was observed. An excellent agreement between the predicted and experimental flux ratio of the racemic compound and enantiomer in the EVA membrane and cadaver skin was observed. The IPA/water/IPM (50:50:1.5) provided the highest in vitro skin flux of the *S* enantiomer among the three vehicle formulations studied. The skin flux of the active pure *S* enantiomer was ca. 34% higher than that of the impure *S* enantiomer in the racemic mixture. Furthermore, about 14% intersubject variability in the in vitro skin flux of the *S* enantiomer was observed. The required skin flux of the *S* enantiomer as calculated from the pharmacokinetic parameters was about 32 μg/cm^2/h from a 25 cm^2 transdermal patch, which was readily achievable from the IPA/water/IPM (50:50:1.5) ternary vehicle system.

Introduction

Ketorolac is a nonsteroidal agent with potent analgesic and moderate anti-inflammatory activities.[1,2] Ketorolac is a chiral drug and exists as an equal mixture of *S* and *R* enantiomers in racemate mixture. Guzman et al. (1986) reported that essentially all of the pharmacological activity resides in the *S* enantiomer, which is approximately twice as potent as the racemate in animal models.[3] Caldwell et al. (1988) also reported that the use of the *S* enantiomer should provide safer and more effective use of this class of drugs.[4] Ketorolac tromethamine, as a racemic mixture, is currently administered intramuscularly (im) and orally (conventional tablet) for postoperative pain management.[5] Because the biological half-life of racemic ketorolac is reported to be 4−6 h, frequent dosing is necessary to maintain the therapeutic effect of the drug to alleviate pain in postoperative patients.

An alternative route of administration, transdermal delivery, of a racemic mixture of ketorolac was reported for sustained delivery of this drug to overcome frequent dosing regimens as encountered with intramuscular and oral routes.[6−8] Roy et al. (1994) reported a low to mild skin irritation upon application of a ketorolac transdermal patch that might be associated with the high skin flux of ketorolac acid through human skin in vivo needed to achieve a desirable therapeutic effect of the drug.[8] Because the *S* enantiomer was reported to be twice as potent as the racemic mixture, theoretically, half of the total racemate dose would be required to induce analgesia in humans provided both the enantiomers had similar total body clearance. Therefore, we evaluated the transdermal delivery of single enantiomer of ketorolac through human cadaver skin.

The principal objectives of this report are to assess the physicochemical properties and membrane transport characteristics of enantiomers, and to optimize transdermal formulation with respect to vehicle compositions to enhance skin flux.

Experimental Section

Materials—The racemic compound (*SR*) and pure *R* and *S* enantiomers of ketorolac free acid were obtained from the Institute of Organic Chemistry at Syntex (Palo Alto, CA). Isopropyl alcohol (IPA), isopropyl myristate (IPM), and 95% ethanol (EtOH) were purchased from Sigma (St. Louis, MO) and Aldrich Chemicals (Milwaukee, WI). Capmul (glyceryl mono- and dicaprylate; monoctanoin) was purchased from Capitol City Products (Columbus, OH). Poly(ethylenevinyl acetate) (EVA, 28% vinyl acetate) synthetic membrane was obtained from 3M (St. Paul, MN). A stereospecific chiral HPLC column (Chiral-AGP, 100 × 4.0 mm; 5 μm particle size) was purchased from ChromTech. All other chemicals were of reagent grade and were used as such without further purification.

Membrane Partition Coefficients Determination—The EVA membrane/water partition coefficients ($K_{EVA/water}$) of *SR*, *S*, and *R* enantiomers were determined by the drug uptake method. Briefly, EVA membrane pieces of known dimension were cut and placed in a small vial containing 25 mL of the saturated drug solution at 25 °C. The solution was gently stirred to reach equilibrium. The uptake of the drug from the bulk solution was monitored until no more drug depletion was noticed. The $K_{EVA/water}$ was determined as follows:

$$K_{EVA/water} = V_b(C_i - C_f)/V_pC_f \quad (1)$$

where V_b is the volume of bulk solution, C_i is the initial drug concentration, C_f is the final drug concentration, and V_p is the volume of the EVA membrane.

Permeation Studies—Human cadaver skin was used for the permeation studies. Samples of split-thickness skin were removed from the abdomen of human cadavers within 48 h postmortem with a dermatome set at 300 μm. The skin was cut into circular patches and checked immediately for any leaks prior to the application of the drug solution. The skin or EVA membrane was then mounted carefully between the two halves of the side-by-side diffusion cells. The receiver compartments (22 mL) were filled with an isotonic phosphate buffer of pH 7.4 (containing 0.002% gentamicin as an antibacterial agent) to maintain perfect sink conditions throughout the diffusion experiments. The whole side-by-side diffusion cell assembly was then placed in a water bath maintained at 25 °C for the EVA membrane or at 32 °C for the skin. The effective diffusion area was 7.1 cm^2. The donor solution and receiver fluid were stirred throughout the experiment to ensure a suitable mixing of solutions. The EVA membrane and skin were allowed to equilibrate with the buffer solution for about 30 min before charging the donor solution. The blank receiver samples were subjected to HPLC assay to ensure the absence of any interfering peaks that might have leached out from the synthetic membrane or skin into the receiver fluid. The donor compartment (22 mL) was then charged with a saturated aqueous solution of ketorolac acid and covered immediately with a lid to

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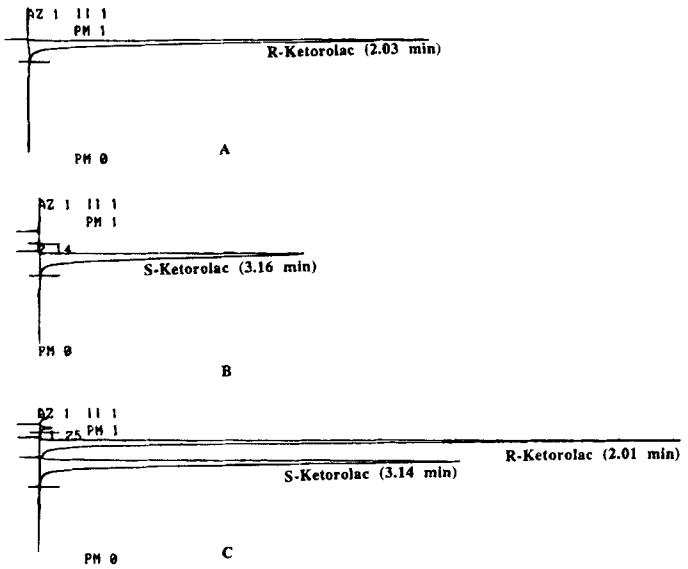

Figure 1—Chromatographic resolution of enantiomers of ketorolac using a Chiral-AGP column: (A) pure *R* enantiomer; (B) pure *S* enantiomer, and (C) racemic mixture.

prevent evaporation of solution. At predetermined time intervals, 1 mL of receiver fluid was withdrawn and replaced with an equal amount of fresh buffer solution. The duration of the skin diffusion experiments was at least 30 h, while the EVA membrane experiment was conducted for 6 h. Ketorolac acid concentration in the receiver fluid sample was determined by a stereoselective HPLC assay. The drug concentration in the donor compartment was also monitored to ensure lack of chiral conversion of an enantiomer during the course of the diffusion experiments.

The modified Franz diffusion cells were used for evaluation of vehicle formulations using cadaver skin. The active diffusion area of the cells was 2.0 cm^2. The skin permeation procedures were essentially the same as described in the previous report from this laboratory.[8] The donor compartment was charged with 2 mL of saturated ketorolac acid solution and covered immediately with a plastic film (Saran Wrap) to prevent any significant loss of volatile components from the transdermal solution. At predetermined time intervals, 1 mL of receiver fluid was withdrawn and replaced with an equal amount of fresh buffer solution. The duration of the skin diffusion experiments was 28 h. The drug concentration in the receiver fluid was determined by a stereoselective HPLC assay.

Drug Assay—A chiral HPLC analytical column was used for the stereospecific assay with UV detection. The mobile phase consisted of 60 mM phosphate buffer of pH 7.0. The flow rate was 1.3 mL/min and the peak height was integrated by a Chrom-Jet Integrator (Spectra Physics). A typical chromatographic resolution of *R* and *S* enantiomers of ketorolac acid using a chiral column is shown in Figure 1. The relative retention times were 2.0 and 3.2 min for *R* and *S* enantiomers, respectively. A base line resolution was obtained for these two enantiomers. Various concentrations of an enantiomer of ketorolac acid in methanol were used to construct a calibration curve. Calibration curves were obtained by plotting the peak height of the authentic sample as a function of ketorolac free acid concentrations. The racemic drug concentration was determined by a similar procedure as reported.[7]

Data Analysis—The steady-state flux was determined as

$$J = V/A(dC/dt) \qquad (2)$$

where J is the steady-state flux through the EVA membrane or cadaver skin ($\mu g/cm^2/h$), V is the receptor volume (mL), A is the active diffusion area (cm^2), C is the receptor concentration ($\mu g/mL$), and t is the time (h). The steady-state flux was determined from the slope of the linear portion of the cumulative amount–time plot. The lag time (T_{lag}) was determined by extrapolating the linear portion of the curve to the abscissa.

Table 1—Physicochemical Properties of *S*, *R*, and Racemic (*SR*) Ketorolac

Property	*S*	*R*	*SR*
Purity (%)	>99	>99	50:50
Melting temperature (°C)	176	176	156
Solubility (mg/mL)			
(i) 0.01N HCl (25 °C)	0.028	0.028	0.050
(ii) 0.01N HCl (32 °C)	0.033	0.035	0.065
(ii) IPA/water/IPM (50:50:1.5) pH = 5.0 (32 °C)	24.2	23.5	45.8
$K_{EVA/water}$ (pH = 2.1)	192	146	184

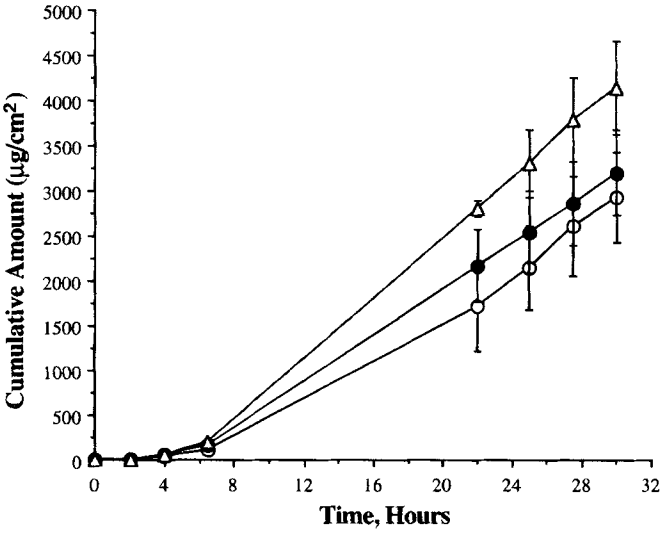

Figure 2—Representative permeation profiles of racemic compound and enantiomers of ketorolac through human cadaver skin from IPA/water/IPM (50:50:1.5) vehicle mixture at 32 °C. Key: *S* enantiomer (open circle); *R* enantiomer (closed circle); and racemic compound, *SR* (open triangle).

Results and Discussion

Physicochemical Properties—The physicochemical properties of *S*, *R*, and *SR* ketorolac acid are presented in Table 1. The optical purity as determined by a recently developed stereoselective HPLC assay was greater than 99% for each enantiomer. The melting temperature of each enantiomer was 20 °C higher than that of the racemic compound. As expected, the lower melting racemic mixture exhibited roughly a 2 times higher solubility in 0.01 N HCl (pH = 2.1) and IPA/water/IPM ternary vehicle than that of an individual enantiomer, while *S* and *R* had identical solubilities in these vehicles. Interestingly, no significant chiral conversion of the enantiomers in these vehicles as measured by a stereoselective assay was noticed (data not shown). The $K_{EVA/water}$ (pH 2.1) values were virtually the same for the racemic compound and the enantiomers of ketorolac within the limit of experimental error. The p*K*a of ketorolac acid in water was reported to be 3.5.[9] It should be mentioned that the pK_a of ketorolac acid had a tendency to shift upward as the volume fraction of IPA or ethanol in water is increased. For example, the apparent pK_a of ketorolac in 35% IPA in water was reported to be 4.95, about 1.5 units higher than that of the pK_a in pure water.[10]

Permeability of Pure Enantiomers through EVA Membrane and Human Cadaver Skin—The IPA/water/IPM ternary vehicle mixture was selected on the basis of our previous experiences with this vehicle composition as a skin penetration enhancer.[8] Typical cumulative amount–time profiles of *S*, *R*, and *SR* of ketorolac through human cadaver skin from the IPA/water/IPM vehicle mixture are shown in Figure 2. In all cases, a steady-state skin flux was attained

Table 2—Permeation Parameters of *S*, *R*, and *SR* Ketorolac through EVA Membrane and Human Cadaver Skin

Donor	Specie	J (μg/cm^2/h)	T_{lag} (h)	$P \times 10^3$ (cm/h)
		28% EVA (25 °C)		
Aqueous[a]	*S*	1.8 ± 0.2	*b*	52 ± 7
	R	1.9 ± 0.2	*b*	61 ± 6
	SR	2.7 ± 0.2	0.3 ± 0.1	52 ± 4
		Skin (32 °C)		
Aqueous[a]	*S*	0.4 ± 0.1	14.7 ± 3.9	12 ± 1
	R	0.5 ± 0.1	17.0 ± 1.5	14 ± 2
	SR	1.3 ± 0.4	12.2 ± 4.4	20 ± 6
IPA/water/IPM[c]	*S*	114 ± 24	6.0 ± 1.0	4.8 ± 1.0
	R	128 ± 21	5.2 ± 0.3	5.5 ± 0.9
	SR	170 ± 20	6.0 ± 1.0	3.7 ± 0.9

[a] pH = 2.1. [b] T_{lag} for enantiomers in EVA membrane could not be determined accurately because of relatively short lag time. [c] IPM/water/IPM (50:50:1.5), pH = 4.9; the skin permeability of this particular skin donor was unusually higher than those of previously published data from this lab (Ref. 8) and in the current Table 3. Each value is the mean ± SD of 3–4 diffusion experiments.

within 5–6 h after application of the drug solution and was maintained throughout the entire duration of the diffusion experiment. Again, no significant chiral conversion of each enantiomer to antipode during its diffusion through split-thickness cadaver skin or EVA membrane was observed. The permeation parameters of *S*, *R*, and *SR* ketorolac in the EVA membrane and cadaver skin from a saturated aqueous solution (pH = 2.1) and IPA/water/IPM (50:50:1.5) vehicle are summarized in Table 2. The permeability coefficient was determined from the ratio of the skin flux and the drug solubility in a given vehicle. As expected, there was no significant difference in the permeability coefficient of *S* and *R* enantiomer in cadaver skin and EVA membrane. Regardless of membranes, no statistically significant differences in permeability coefficient and T_{lag} of racemic compound and enantiomers from an aqueous saturated drug solution were observed. This result implies that the membrane partition coefficient and diffusion coefficient (D is inversely proportional to T_{lag}) were virtually the same for the racemic compound and the two enantiomers. Indeed, the $K_{EVA/water}$ that closely mimicked the stratum corneum/water partition coefficient was essentially the same for the racemic compound and enantiomers of ketorolac (see Table 1).

The ratio of skin flux of racemic compound (r) and enantiomer (e) from a saturated drug solution can be estimated from a thermodynamic equation as follows:[11, 12]

$$J_r/J_e = C_r^*/C_e^* = e^{-A(T_{mr} - T_{me})/T} \quad (3)$$

where J_r and J_e are the steady-state flux of racemic compound and enantiomer, C_r^* and C_e^* are the aqueous solubility of racemic compound and enantiomer, T_{mr} and T_{me} are the melting temperatures, T is the experimental temperature, and A is a constant. Based on melting temperature values (in K) and aqueous solubility values for the racemic mixture and the enantiomer (Table 1), the value for A was estimated to be 8.6 for the EVA membrane. A theoretical flux ratio of 1.8 was estimated for the EVA membrane by inserting into eq 3 the melting temperature values and the value for A as calculated above. The experimental J_r/J_e ratio for the EVA membrane was 1.5, in close agreement with the calculated theoretical value of 1.8. Similarly, a theoretical skin flux ratio of 1.9 was calculated for the water and IPA/water/IPM vehicles. The experimental values were 3.3 and 1.4 for water and IPA/water/IPM, respectively. The experimental value for water was slightly higher than the predicted value, which was possibly because of a relatively high margin of error in determining

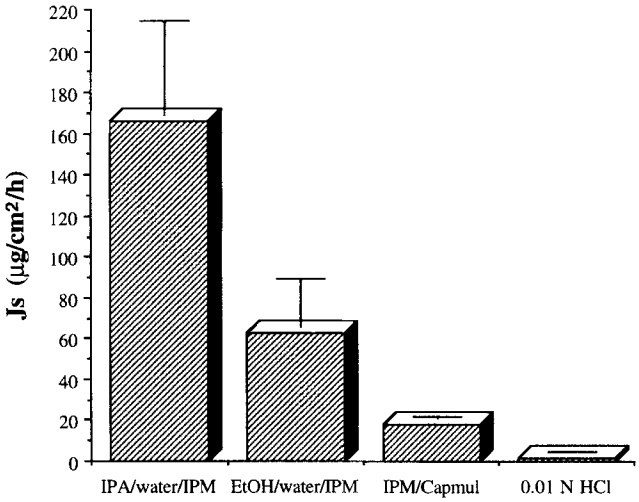

Figure 3—Bar plot showing a mean steady-state skin flux of *S* enantiomer of ketorolac acid through cadaver skin from various saturated drug solutions at 32 °C. Key: IPA/water/IPM (50:50:1.5); EtOH/water/IPM (47.5:52.5:0.8), IPM/Capmul (4:1), 0.01 N HCl (pH = 2.1).

such a low intrinsic skin flux from pure water. In contrast, the predicted and experimental flux ratio (J_r/J_e) value for the IPA/water/IPM ternary vehicle mixture was in close agreement with the calculated theoretical value. These data clearly suggested that the flux ratio of the racemic compound and the single enantiomer of ketorolac acid could be readily predicted from the thermodynamic eq 3. It should be emphasized that the skin flux of the pure *S* enantiomer from the IPA/water/IPM ternary vehicle was about 34% higher than that of the impure *S* enantiomer in the racemic mixture. The reason for such a high flux of pure *S* enantiomer is not clear. Obviously, further studies are needed to explain such a high skin flux of the pure enantiomer.

Effect of Vehicle Composition on Skin Flux of *S* Enantiomer—In order to enhance the skin flux of the pharmacologically active *S* enantiomer of ketorolac acid through human cadaver skin, various skin penetration enhancers in combination were used. The relative skin fluxes of the *S* enantiomer from IPA/water/IPM, ETOH/water/IPM, and IPM/Capmul vehicles saturated with *S* enantiomer of ketorolac acid are shown in Figure 3. The IPA/water/IPM ternary vehicle mixture provided the highest skin flux among the three transdermal formulations studied. The enhancement factor as determined from the ratio of skin flux from a given vehicle mixture and from 0.01 N HCl aqueous solution was 128, 48, and 14 for IPA/water/IPM, EtOH/water/IPM, and IPM/Capmul, respectively. These data clearly suggested that these vehicles had the ability to modify the permeability of the stratum corneum, leading to an enhanced skin flux of the *S* enantiomer. It was speculated that fluidization of the lipid of the stratum corneum was primarily responsible for such an enhancement.[8]

The intersubject variability (five skin donors) in the skin flux and lag time of the *S* enantiomer are summarized in Table 3. The skin flux values ranged from 48 to 66 μg/cm^2/h, with a mean value of 57 ± 8 μg/cm^2/h. The lag time ranged from 1.3 to 5 h, with a mean value of 3.5 ± 1.5. The observed 14% variability in the skin flux of the *S* enantiomers was rather normal for a transdermal drug delivery system. Moreover, the intersubject variability in the in vitro skin flux noticed in this study was somewhat similar to previously reported data from this lab.[8] It was suspected that such intersubject differences in the skin flux of the *S* enantiomer were possible because of the inherent variability in the lipid

Table 3—Intersubject Variability in the Skin Flux (J_s) of *S* Enantiomer of Ketorolac through Human Cadaver Skin at 32 °C[a]

Skin Donor	J_s (μg/cm^2/h)	T_{lag} (h)	$P \times 10^3$ (cm/h)
1	59 ± 3	4.6 ± 0.3	2.7 ± 0.1
2	48 ± 6	5.0 ± 0.3	2.2 ± 0.3
3	63 ± 5	4.0 ± 0.2	2.8 ± 0.2
4	66 ± 8	2.6 ± 0.7	3.0 ± 0.4
5	51 ± 3	1.3 ± 0.1	2.5 ± 0.1
Mean	57	3.5	2.6
SD	8	1.5	0.3

[a] The donor phase was a saturated *S* enantiomer solution in IPA/water/IPM (50:50:1.4) vehicle system at pH 5.0. Each value is the mean ± SD of 3 or 4 diffusion experiments.

Table 4—Prediction of Delivery Rate and Skin Flux of *S* Enantiomer from Pharmacokinetic Parameters

Compound	Cl_0[a] (L/h)	$T_{1/2}$[a] (h)	C_{ss} (μg/mL)	K_0 (mg/h)	Patch Size (cm^2)	J_s (μg/cm^2/h)
Racemic (*SR*)	1.6	4.2	0.50	0.82	25	33
S enantiomer	3.2	2.5	0.25	0.80	25	32

[a] Reference 14; Cl_0 values are based on 70 kg body weight. $K_0 = Cl_0 \times C_{ss}$. $J_s = K_0$/patch size.

content of the stratum corneum, which acts as a primary diffusional barrier to ketorolac acid transport across human skin.

The in vivo delivery rate (K_0, in mg/h) of the *S* enantiomer was predicted from the pharmacokinetic parameters following the intramuscular administration of racemic ketorolac tromethamine.[13,14] Table 4 shows the pharmacokinetic parameters and the predicted drug delivery rates of the racemic compound and the *S* enantiomer. The terminal biological half-life ($T_{1/2}$) of the *S* enantiomer was roughly 2 times shorter than that of the racemic compound. Similarly, the total body clearance (Cl_0, for 70 kg body weight) of the *S* enantiomer was about 2 times higher than that of the racemic compound. These results strongly suggested that stereoselective metabolism of the *S* enantiomer and the in vivo chiral conversion of a small fraction of the *S* enantiomer to the *R* antipode were primarily responsible for such a high clearance rate of the *S* enantiomer.[13] The minimum effective concentration (C_{ss}) to induce analgesia for the racemic compound was reported to be about 0.5 μg/mL,[2] and because the *S* enantiomer was twice as potent as the racemic compound,[3] roughly a 0.25 μg/mL steady-state blood level of the *S* enantiomer would be required for analgesia. On the basis of this assumption, the delivery rate, K_0, was estimated to be 0.82 and 0.80 mg/h for the racemic compound and the *S* enantiomer, respectively. Thus, even though the *S* enantiomer is 2-times more potent than the racemic compound, the steady-state K_0 was essentially the same, because of the high metabolic clearance of the *S* enantiomer. The steady-state skin flux (J_s) of the *S* enantiomer required to maintain therapeutic effective blood levels was estimated to be 32 μg/cm^2/h from a 25 cm^2 transdermal patch. This required skin flux was readily achievable from the IPA/water/IPM (50:50:1.4) vehicle system saturated with the *S* enantiomer, which provided a mean in vitro skin flux of 57 μg/cm^2/h (see Table 3).

Conclusions

In summary, we assessed the physicochemical properties and membrane permeability characteristics of the racemic compound and the enantiomers of ketorolac. As expected, the solubility of the racemic compound in water and IPA/water/IPM (50:50:1.5) was about 2 times higher than that of the enantiomers, while the EVA membrane partition coefficients were virtually the same. The permeability coefficient of the racemic compound in the EVA membrane and human cadaver skin was 1.5 times greater permeable than that of the enantiomers. An excellent agreement between the predicted and experimental flux ratio (J_r/J_e) values was obtained in the EVA membrane and cadaver skin. The skin flux of the active pure *S* enantiomer was about 34% higher than that of the impure *S* enantiomer in racemic mixture. The required skin flux of pure *S* enantiomer as calculated from the pharmacokinetic parameters was about 32 μg/cm^2/h from a 25 cm^2 transdermal patch, which was readily achievable from the IPA/water/IPM (50:50:1.4) ternary vehicle system.

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