Transdermal Delivery of Ketorolac Tromethamine: Permeation Enhancement, Device Design, and Pharmacokinetics in Healthy Humans

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Abstract □ Transdermal delivery of ketorolac tromethamine, a potent non-narcotic analgesic, through human skin in vitro and in vivo was investigated. In order to enhance and sustain the flux of ketorolac through human skin, various compositions of isopropyl alcohol (IPA), water, and isopropyl myristate (IPM) were evaluated. The solubility of ketorolac acid in an IPA/water binary vehicle mixture increased as the volume fraction of IPA increased from 0 to 90%. The solubility of ketorolac acid in an IPA/water/IPM (saturated) ternary vehicle mixture was practically the same as in the IPA/water binary vehicle mixture. The permeation of ketorolac acid through cadaver skin was evaluated using modified Franz diffusion cells. The skin flux increased as the IPA volume fraction was increased from 0 to 50% and then leveled off beyond 80% IPA loading. When IPM was added to the IPA/water binary vehicle mixture, a significant increase in the skin flux of ketorolac was observed. The skin flux decreased exponentially as the donor solution pH was raised from 3.5 to 7.0. The permeability of ketorolac through various membranes such as a microporous membrane and pressure-sensitive adhesive was evaluated. While a microporous membrane offered practically no diffusion resistance, the in vitro flux of ketorolac through cadaver skin decreased substantially upon lamination of pressure-sensitive adhesive onto a microporous membrane. Three liquid-reservoir type transdermal devices were fabricated using 6.5% ketorolac tromethamine gel, a microporous membrane, an adhesive membrane, and polyester backing film: TD-A (microporous membrane/acrylic adhesive), TD-B (microporous membrane/silicone adhesive), and TD-C (microporous membrane). The pharmacokinetics of ketorolac in 10 healthy humans following application of a transdermal device for 24 h was evaluated. The maximum plasma concentrations (C_{max}) were 0.20, 0.18, and 0.82 μg/mL for TD-A, TD-B, and TD-C, respectively. The total AUC values for the concentration–time curves were TD-C > TD-A > TD-B, and the terminal half-life ranged from 6.6 to 9.7 h.

Introduction

Ketorolac tromethamine is a nonsteroidal agent with potent analgesic and moderate anti-inflammatory activity.[1-3] This drug is currently administered intramuscularly and orally in a divided multiple dose for short-term management of postoperative pain. Intramuscular injection is the preferred route of administration (30 mg q.i.d.) for moderate to severe pain management, even though patient compliances are rather low for this mode of drug delivery.[4] The drug is also administered via the oral route as a conventional tablet (10 mg q.i.d.) for management of mild to moderate pain.[5] Oral bioavailability of ketorolac tromethamine is reported to be 90% with a very low first-pass metabolism. Regardless of the route of administration, the biological half-life of ketorolac ranges from 4 to 6 h.[3] Because of such a short half-life, frequent dosing is required to alleviate pain in postoperative patients. To avoid an invasive drug delivery technique (i.e., intramuscular injection) and to eliminate frequent dosing regimens, there is a need for an alternative noninvasive mode of delivery of ketorolac tromethamine. Transdermal delivery (i.e., through the skin) of ketorolac certainly appears to be an attractive route of administration as a noninvasive mode of delivery and to maintain the drug blood levels for an extended period of time.

Transdermal delivery of ketorolac acid through human skin was previously reported.[6,7] In a pilot clinical trial, we reported transdermal feasibility of ketorolac acid from a saturated drug solution.[7] The isopropyl alcohol (IPA)/water/isopropyl myristate (IPM) ternary vehicle system provided the highest ketorolac plasma levels during a 24 h application of the prototype transdermal device among the three vehicle systems tested.[7] Moreover, the chemical stability of ketorolac in the IPA/water/IPM ternary vehicle system was relatively higher among the three transdermal formulations tested and had only a very mild skin irritation reaction. Although IPA/water/IPM vehicle systems provided the highest C_{max} (maximum plasma concentration), the decline in blood levels 8 h after application was rather rapid.[7] These preliminary results led us to investigate further the transdermal delivery of ketorolac tromethamine from IPA/water/IPM vehicle system to sustain drug plasma levels for a longer period of time to avoid frequent dosing regimens.

The principal objectives of the present study were 3-fold: (1) to optimize an IPA/water/IPM ternary vehicle formulation with respect to in vitro skin flux and stability of ketorolac, (2) to design and characterize a liquid-reservoir transdermal delivery system (TDS), and (3) to evaluate the pharmacokinetics of ketorolac tromethamine in healthy humans following application of the TDS.

Experimental Section

Materials—Ketorolac free acid and ketorolac tromethamine were obtained from the Institute of Organic Chemistry at Syntex (Palo Alto, CA). IPA and IPM were purchased from Sigma (St. Louis, MO) and Aldrich Chemicals (Milwaukee, WI). Hydroxypropyl cellulose (Klucel, HP) was purchased from Aqualon Co. (Wilmington, DE). Acrylic and silicone pressure-sensitive adhesives (PSA) were supplied by Monsanto (Minneapolis, MN) and Dow Chemicals Co. (Midland, MI), respectively. The backing film membrane was purchased from Schübach AG (Burgdorf, Switzerland). The polyester release liner and microporous membrane (3M-CoTran) were obtained from 3M (St. Paul, MN). All other chemicals used in the study were of analytical reagent grade and were used as such without any further purification.

Solubility Determinations—The solubility of ketorolac free acid in various compositions of IPA, IPM, and purified water vehicle mixtures was determined by equilibrating the excess of solute with the vehicle for at least 24 h. The temperature of the solution was maintained at 25 °C using a circulating water bath. The sample was filtered and appropriately diluted before assaying the ketorolac by HPLC.[6]

Transdermal Device Design and Patch Fabrication—The composition of ketorolac tromethamine gel formulation (w/w) was as follows: 6.5% ketorolac tromethamine, 45.5% IPA, 45.5% water, 1.4% IPM, and 1.1% Klucel. Klucel was used as a thickening agent,

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Table 1—Ketorolac Transdermal Device Components

Components	Transdermal Device		
	TD-A	TD-B	TD-C
Ketorolac gel (g/patch)	1.5	1.5	0.86
Backing film	Schübach	Schübach	Schübach
Microporous membrane	3M CoTran	3M CoTran	3M CoTran
Contact adhesive (PSA)	Acrylate	Silicone	None
Protective release liner	Polyester liner	Polyester liner	Polyester liner
Patch size (cm^2)	20	20	22
Active diffusion area (cm^2)	20	20	7.5

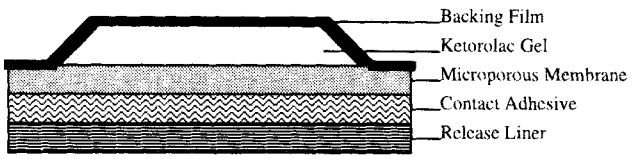

Figure 1—Schematic diagram of a ketorolac liquid-reservoir transdermal device.

enabling ease of fabrication of the patch. Briefly, ketorolac tromethanamine was completely dissolved in water at room temperature, followed by the sequential addition of IPA and IPM vehicles. The solution was mixed for 10 min in a closed container to prevent any significant loss of the volatile component IPA. The pH of the solution was adjusted to 5.0 ± 0.2 with 0.1 N HCl. Hydroxylpropyl cellulose was then added to the solution and mixed overnight to allow gel formation. The gel was stored at room temperature and used later for patch fabrication.

Table 1 shows the various components of the three transdermal devices. Two types of pressure-sensitive adhesives (PSA) were used for membrane fabrication: acrylic copolymer (TD-A) and silicone PSA (TD-B). The adhesive was laminated onto the release side of a polyester release liner and dried in an oven at about 50 °C for 20 min to drive off the volatile organic solvents. The dried adhesive film was then laminated onto the microporous membrane. The pressure-sensitive adhesive provided two major functions for the transdermal device: (1) to provide a good contact between the skin and the device during entire wearing period of the patch, and (2) to act as a rate-controlling membrane that would modulate the delivery of the drug and vehicles from the gel. The adhesive/microporous membrane and backing polyester film were used for the liquid-reservoir patch fabrication. Briefly, a known amount (1.5 g) of ketorolac gel was dispensed onto the microporous-membrane side of the adhesive membrane and immediately heat-sealed with a backing film. A schematic diagram of the transdermal device is shown in Figure 1. The active (diffusion) area of the patch was 20 cm^2. The patches were pouched in aluminum-type foil to prevent photodegradation of the drug.

The third transdermal device (TD-C) had a microporous membrane with a peripheral contact adhesive (supplied by TheraTech, Inc., Salt Lake Cit, UT). The release mechanism of the drug and vehicles from the TD-C patch was strictly through the pores of the microporous membrane. The non-rate-controlling patch was fabricated in a similar fashion as described for adhesive membrane devices. The drug loading was 0.86 g/patch and the active diffusion area was 7.5 cm^2. The patches were pouched in aluminum-type foil.

In Vitro Skin Permeation—Human cadaver skin (ca. 300 μm thickness) was used for the skin permeation studies using a modified Franz static diffusion cell. The split-thickness skin was mounted carefully on a modified Franz diffusion cell and fastened with an O-ring. The active diffusion area was 2.01 cm^2. The receiver compartment was then filled with 22.0 mL of isotonic phosphate buffer of pH = 7.4, containing 0.002% gentamicin as an antibacterial agent. The diffusion cells were placed in a water bath and the temperature was maintained at 32 °C using a circulating water bath (Haake, Buckler Instrument). The receiver fluid was stirred for the duration of the experiment. The skin samples were allowed to equilibrate with the buffer solution for 30 min. The receiver fluid (1 mL) was withdrawn and injected into the HPLC before charging with the donor solution to ensure the absence of any interfering peaks from the skin tissues. The donor compartment was then charged with 2.0 mL of ketorolac solution and immediately closed with a rubber stopper to prvent loss of volatile components from the solution. At specific intervals, 1 mL of receiver fluid wwas withdrawn from the receiver compartment and replaced with fresh receiver fluid. The drug concentrations in the receiver fluid samples were assayed by HPLC.

In the case of the microporous/adhesive membrane and transdermal device, the system was applied with slight pressure onto the stratum corneum of split-thickness skin. The patch/skin unit was then mounted on a diffusion cell to determine the flux of ketorolac through the cadaver skin.

In Vitro Dissolution—The in vitro release profiles to ketorolac from a transdermal device were also determined. A reciprocating disk apparatus with an automated sampler (Hansen Research) was used for the dissolution studies. The protective release liner was removed from the transdermal device, mounted on the bottom of a stainless steel disk, and immersed immediately in the dissolution media. A phosphate buffer of pH = 7.4 was used as the dissolution media, and the temperature of the media was maintained at 32 °C using a circulating water bath. The mixing of the dissolution media was performed by a reciprocating movement of the disk. After each agitation cycle or time point, the disk was transferred to another glass jar containing fresh receptor fluid. At predetermined intervals and at each cycle of agitation, a sample aliquot (1.5 mL) was taken for each glass cylinder and transferred automatically into an HPLC vial. This continued until all the cycles were completed. The samples were assayed for ketorolac by the HPLC method.

Study Design in Humans—The absorption of transdermally delivered ketorolac from the three transdermal devices was evaluated in 10 healthy subjects in a three-way randomized fashion. The protective release liner was removed from the transdermal device and applied immediately to the chest of each subject. The patches were held in place on the skin for 20 s and then left on occluded for 24 h. The patch was then removed and, following a washout period of approximately 1 week, all the subjects received the next formulation. Each subjected received two TD-C patches, but only one patch each of TD-A and TD-B.

Blood samples (7 mL each) were collected in heparinized tubes immediately prior to application of the transdermal devices and at the following times thereafter: 0.5, 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, and 48 h. The plasma was separated from the whole blood by centrifugation at 3000 rpm for 10 min and the plasma was transferred into polypropylene tubes. The plasma was stored at −20 °C for later HPLC assay.

Assay Procedure—The ketorolac sample was assayed by HPLC (SP 8800 precision isocratic pump, Spectra Physics) using UV detection at 314 nm. A Spherisorb ODS I column (5 μm, 25 cm × 4.5 mm, Alltech) and acetonitrile/water/acetic acid (44:58:1; pH 3.0) as a mobile phase were used for chromatographic resolution. The flow rate was 1 mL/min and the peak height was integrated by a Chrom-Jet Integrator (Spectra Physics). Various concentrations of ketorolac tromethamine 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 concentrations. Ketorolac concentrations in plasma samples were determined by a similar HPLC procedure.[8]

Data Analysis—The in vitro skin flux was determined from Fick's law of diffusion:

$$J_s = 1/A(dM/dt) \quad (1)$$

$$P_e = J_s/\Delta C \quad (2)$$

where J_s is the skin flux (μg/cm^2/h), dM/dt is the amount of drug permeated per unit time, A is the diffusion area (cm^2), P_e is the effective permeability coefficient (cm/h), and ΔC is the concentration gradient across the skin. In most cases, ΔC was assumed to be the donor concentration provided the drug concentration in the receiver compartment never exceeded 10% of the donor concentration. The steady-state skin flux was determined from the slope of the linear portion of a cumulative amount−time plot (6−24 h). The lag time (T_{lag}) was determined by extrapolating the linear portion of the cumulative amount−time curve to the abscissa.

The following pharmacokinetic parameters in healthy humans were computed for each formulation: (1) time to maximum concentration (T_{max}), (2) peak plasma concentration (C_{max}), (3) plasma half-life ($T_{1/2}$), and (4) the area under the concentration−time curve from 0 to 24 h (AUC_{0-24}) and from 0 to infinity ($AUC_{0-\infty}$) determined by using the

Table 2—In Vitro Permeation of Ketorolac Through Cadaver Skin from Various Compositions of IPA/Water and IPA/Water/IPM Vehicle Mixtures at 32 °C[a]

IPA/water (w/w)	C_d (mg/mL)	J_s (μg/cm^2/h)	T_{lag} (h)	IPA/water/IPM (w/w)	C_d (mg/mL)	J_s (μg/cm^2/h)	T_{lag} (h)
0:100	0.14	0.8 ± 0.4	4.6 ± 0.7				
20:80	1.1	9.0 ± 2.0	2.8 ± 0.3	20:80:0.1	0.95	19.5 ± 0.1	1.7 ± 0.5
30:70	5.6	17.9 ± 2.8	2.5 ± 1.0	30:70:0.2	5.7	41.4 ± 5.1	NA
40:60	16.8	23.5 ± 4.7	2.5 ± 1.0	40:60:0.3	17.9	74.9 ± 6.4	1.0 ± 0.5
50:50	32.5	26.1 ± 5.1	3.1 ± 0.7	50:50:1.5	36.4	123.4 ± 12.6	0.8 ± 0.7
60:40	49.5	31.8 ± 8.9	NA	60:40:2.0	53.8	151.4 ± 34.2	2.5 ± 0.7
80:20	84.9	26.6 ± 10.9	3.3 ± 0.7				
100:0	50.0	6.3 ± 4.3	2.7 ± 0.1				

[a] Each value is the mean ± SD of three or four diffusion experiments. All the data were obtained on a single skin donor to avoid interindividual variations in skin permeability. NA = not available.

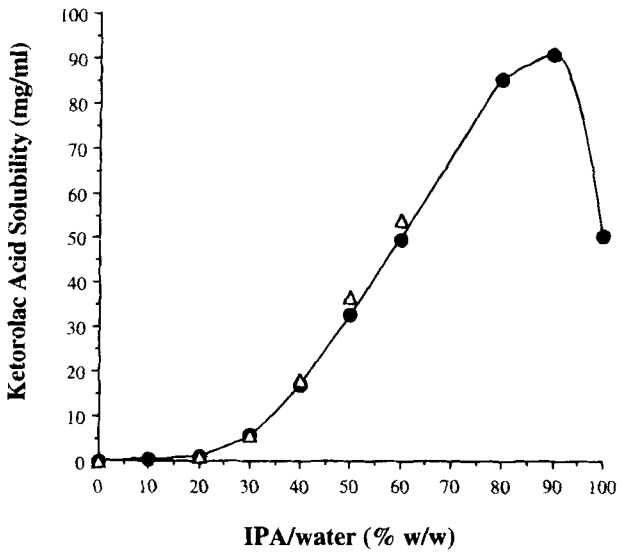

Figure 2—Solubility of ketorolac acid in vehicles at 25 °C. Key: IPA/water (closed circle), IPA/water/IPM (open triangle).

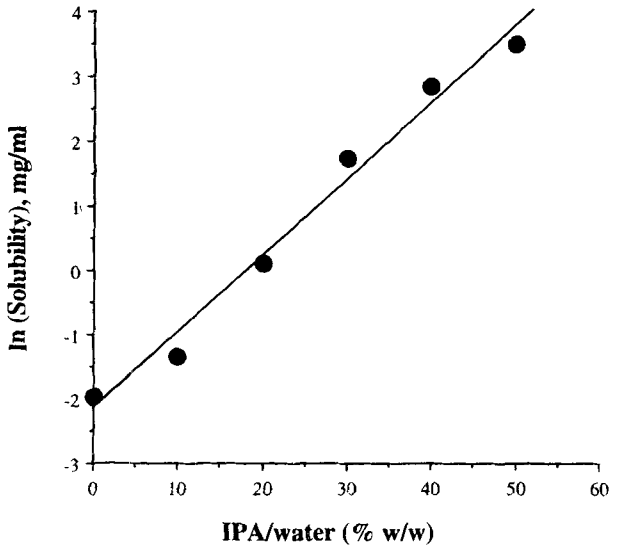

Figure 3—Plot showing a log linear relationship between the solubility of ketorolac and the percent weight fraction of IPA in water, with a correlation coefficient of 0.991.

linear trapezoidal rule. Statistical analysis was performed using analysis of variances (ANOVA).

Results and Discussion

Solubility of Ketorolac Acid—The solubility of ketorolac acid in the IPA/water binary vehicle mixture at 25 °C is shown in Figure 2. The solubility of ketorolac acid increased as the IPA volume fraction in water increased up to 90%. The solubility of ketorolac acid, however, dropped significantly in the neat IPA. The solubility of a solute in a mixed solvent system may be described by the log linear equation as described by Yalkowsky *et al.*:[9]

$$\ln C_v = \ln C_w + f\sigma \qquad (3)$$

where C_v is the drug solubility in the vehicle consisting of f volume fractions of cosolvent in water, C_w is the water solubility, and σ is a parameter representing the solubilizing power of the cosolvent for the drug. Figure 3 shows the plot of ln C_v versus f. A log-linear relationship between ln C_v and f ($r = 0.991$) was observed when the IPA volume fraction was less than or equal to 50%, with an estimate of $\sigma = 0.118$ and C_w (water solubility) = 0.12 mg/mL at 25 °C. The experimental value for saturated aqueous solubility was 0.14 mg/mL, which is in close agreement with the value estimated from eq 3. As the IPA volume fraction exceeded 50%, an obvious deviation from the linearity was observed. In fact, roughly a 50% drop in the solubility of ketorolac acid was observed as the IPA volume fraction increased from 90% to 100%.

The solubility of ketorolac acid in the IPA/water/IPM ternary vehicle mixtures is also shown in Figure 2. It should be pointed out that the amount of IPM added to the IPA/water cosolvent system was sufficient enough to yield one phase system without any obvious phase separation. Interestingly, the solubilities of ketorolac acid in various compositions of IPA/water/IPM ternary vehicle mixtures were practically the same as in the IPA/water binary vehicle mixture. Thus, adding a small fraction of IPM to an IPA/water mixture had very litle effect on the solubility of ketorolac acid.

Effect of Vehicle Compositions and Donor pH on In Vitro Skin Flux—The steady-state skin flux of ketorolac acid through human cadaver skin from various compositions of IPA/water and IPA/water/IPM vehicle systems is summarized in Table 2. The skin flux increased as the weight fraction of IPA in water increased from 0 to 50% and remained relatively unchanged as the IPA fraction was raised from 50% to 80%. Even though the drug solubility in the 80% IPA was about 2.5 times higher than that of the 50% IPA, no significant difference in the skin flux of ketorolac acid was observed. However, the skin flux dropped dramatically in the neat IPA. The lag time of ketorolac acid in the IPA/water binary vehicle mixtures ranged from 2.5 to 3.3 h, which was about 1.5 h shorter than that in the purified water (T_{lag} = 4.6 h).

The skin flux of ketorolac acid from various compositions of IPA/water/IPM ternary vehicle mixtures is also summarized in Table 2. The skin fluxes of ketorolac acid increased exponentially as IPA and IPM fractions in water were increased. The lag times of ketorolac acid in the IPA/water/IPM ternary vehicle mixtures ranged from 0.8 to 2.6 h, which

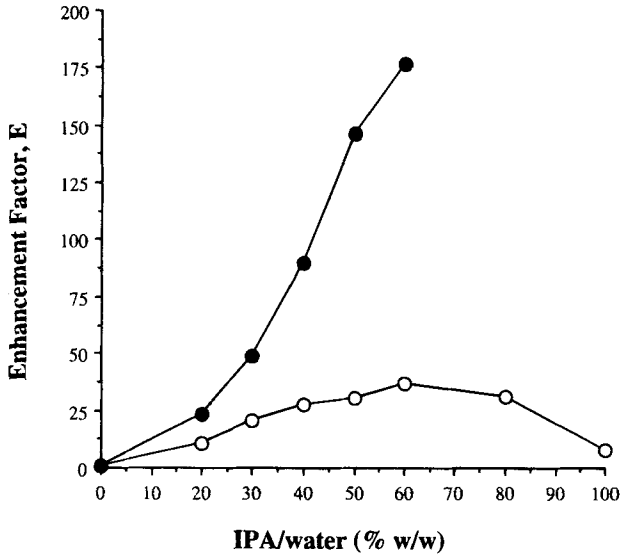

Figure 4—Relationship between the in vitro skin flux enhancement factor (E) and the percent weight fraction of IPA in water. Key: IPA/water (open circle), IPA/water/IPM (closed circle).

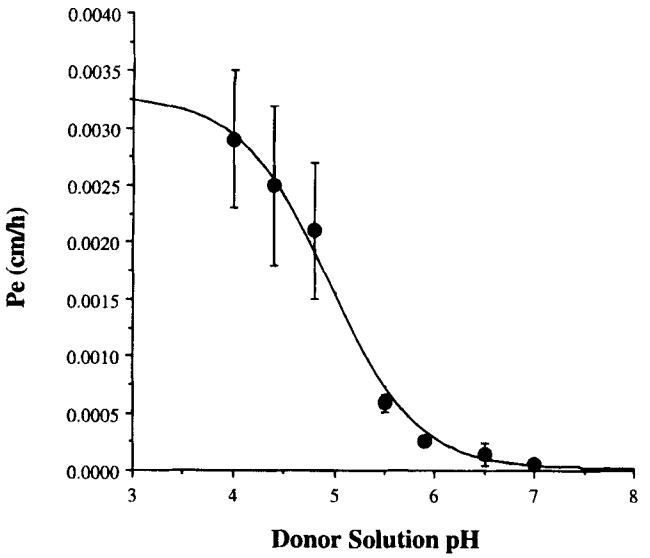

Figure 5—The effect of donor solution pH on the in vitro skin permeability (P_e) of ketorolac. The solid line is the theoretical curve predicted from eq 6. Each data point represents the mean ± SD of three or four skin diffusion experiments.

was slightly shorter than the lag times in the IPA/water binary vehicle mixtures.

The skin permeability enhancement factor (E) may be determined from the following equation as described by Kim *et al.*:[10]

$$E = (P_v/P_0)(S_v/S_0) = (K_v/K_0)(D_v/D_0) \quad (4)$$

where P_v and P_0 are the permeability coefficients in the vehicle mixture and in the purified water, respectively, S_v and S_0 are the solute solubilities in the vehicle mixture and in the purified water, respectively, K_v and K_0 are the partition coefficients when the solvent is vehicle mixture or purified water, respectively, and D_0 are diffusion coefficients of ketorolac in the stratum corneum when the solvent is the vehicle mixture or purified water, respectively. The right hand side of eq 4 [i.e., $(P_v/P_0)(S_v/S_0)$] can be readily determined experimentally (see Table 2).

Figure 4 shows a plot of E versus IPA/water and IPA/water/IPM vehicle compositions. An interesting trend in the IPA/water vehicle systems was observed. As the IPA fraction in water was increased from 20 to 60%, E increased linearly and then plateaued between 60% and 80% IPA. The skin flux, however, dropped severalfold in the neat IPA even though the drug solubility in the neat IPA decreased only by half that of the 80% IPA. Because the T_{lag} in the neat IPA was virtually the same as other binary vehicle compositions, a significant drop in the skin flux of ketorolac acid was most likely caused by a decrease in the stratum corneum/vehicles partition coefficient of in ketorolac neat IPA.

In contrast to the IPA/water binary vehicle mixtures, the skin flux of ketorolac acid from the IPA/water/IPM ternary vehicle systems increased exponentially as the weight fraction of IPA/IPM in water was increased (Figure 4). The magnitude of the flux enhancement factor in the presence of IPM was 2–5 times higher than that of the IPA/water binary vehicle mixtures. This implied that IPM had the ability to modify the lipid of the stratum corneum, which acts as the principal diffusion barrier for the transport of ketorolac acid across human skin. Because E is the product of K_v/K_0 (thermodynamic factors) and D_v/D_0 (kinetic factors), it is possible that high partitioning of ketorolac acid into the lipid of the stratum corneum as well as high diffusivity was responsible for the flux enhancement of ketorolac acid in the presence of small fraction of IPM. It is rather difficult to pinpoint with this limited data whether thermodynamic or kinetic factors played a predominant role in enhancing the flux of ketorolac acid through human skin.

The effect of donor solution pH on the in vitro skin flux of ketorolac acid was also studied. The ionization of ketorolac acid (HA) in water may be expressed as follows:

$$HA \leftrightarrow A^- + H^+ \quad (5)$$

The net permeability coefficient (P_T) may be written as follows:[11]

$$P_T = P_A^-(K_a/[H^+] + 1) + P_{HA}([H^+]/K_a + 1) \quad (6)$$

where P_{A^-} is the permeability coefficient of ionized species, and P_{HA} is the permeability coefficient of un-ionized species, K_a is the equalibrium constant, and $[H^+]$ is the hydronium ion concentration. The permeability coefficients of un-ionized (free acid) and ionized species can be readily estimated by curve fitting of the plot of P_T vs $[H^+]$.

Plotted in Figure 5 is the best fitted curve according to eq 6 with ketorolac's $pK_a = 4.95$ in 35% IPA,[12] assuming that a small fraction of IPM in the solution had no effect on the pK_a of ketorolac. The fit for ketorolac acid appeared to be excellent. The permeability coefficients for un-ionized (P_{HA}) and ionized (P_{A^-}) species were estimated to be 3.3×10^{-3} and 1.1×10^{-5} cm/h (95% confidence interval), respectively. These data clearly suggest that the free acid species was roughly 2 orders of magnitude more permeable than that of the ionized form of ketorolac primarily because of the high lipophilicity of the free acid, as reflected by its high $K_{o/w}$ of 630.[6] It should be emphasized that even though low donor solution pH provided high in vitro skin flux, an optimum pH (say, ranged from 5.0 to 5.5) should be preferred to circumvent formation of the isopropyl ester of ketorolac, which may lead to a diminished potency and stability of ketorolac acid on long-term storage. Indeed, about 2% of the isopropyl ester of ketorolac acid in 2 years was estimated for IPA/water/IPM formulation at pH 5.0 (data not shown). The chemical kinetics of formation of ketorolac isopropyl ester will be published elsewhere.

Table 3—Permeability of Ketorolac Free Acid and Tromethamine Salt from IPA/Water/IPM (50:50:1.4) Ternary Vehicle Mixtures through Human Cadaver Skin at 32 °C[a]

Chemical Form of Ketorolac	C_d (mg/mL)	J_s (μg/cm^2/h)	$P_e \times 10^3$ (cm/h)	T_{lag} (h)
Tromethamine	32.7	93 ± 14	3.0 ± 0.4	4.1 ± 0.6
Free acid	38.3	115 ± 14	2.8 ± 0.4	4.7 ± 0.2

[a] Each value is the mean ± SD of three or four diffusion experiments. $P_e = J_s/C_d$, where C_d is the drug concentration in vehicle mixtures.

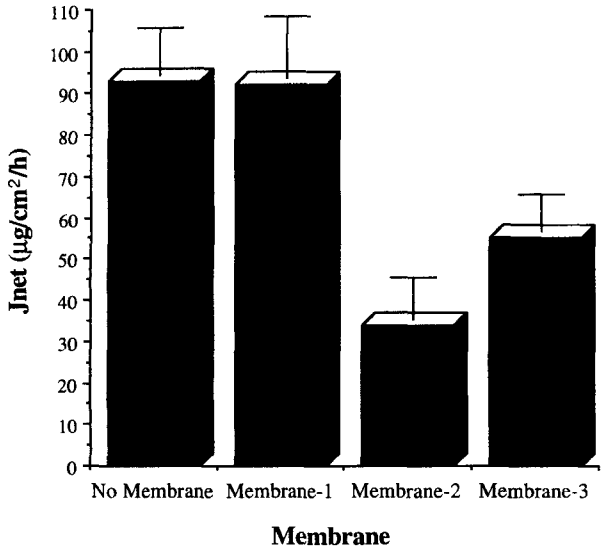

Figure 6—Comparison of the in vitro flux (J_{net}) of ketorolac through human cadaver skin from a gel with or without a membrane at 32 °C. Key: membrane 1 = microporous membrane, membrane 2 = microporous membrane/silicone adhesive, membrane 3 = microporous membrane/acrylate adhesive.

The skin permeation of ketorolac free acid and ketorolac tromethamine from IPA/water/IPM (50:50:1.4) at pH = 5.0 was compared. Table 3 summarizes the skin permeation parameter of free acid and tromethamine salt. The solubility of free acid in the IPA/water/IPM ternary vehicle mixture was slightly higher than that of ketorolac tromethamine. Such a suppression in solubility of ketorolac tromethamine salt may be partly be due to the common ion effect of tromethamine as a counterion. Regardless of chemical species, the permeability coefficient of ketorolac was virtually the same whether the donor compartment was charged with a saturated solution of ketorolac free acid or ketorolac tromethamine salt (Table 3). Moreover, no significant difference in the steady-state lag time was observed for these two species. Thus, ketorolac tromethamine salt was made as suitable as the free acid for transdermal formulation by merely adjusting the solution pH. Therefore, ketorolac tromethamine salt was selected for the transdermal gel formulation and patch fabrication.

Characterizations of Membrane and Transdermal Devices—In order to design a liquid-reservoir transdermal prototype device, the permeability of ketorolac through a microporous membrane and adhesive film was evaluated. The 6.5% ketorolac tromethamine gel formulation was used for membrane transport studies. Figure 6 shows the flux of ketorolac from the gel through a membrane and cadaver skin in series. The skin flux of ketorolac was virtually the same with and without a microporous membrane, suggesting that a microporous membrane offered practically no diffusional resistances for transport of the drug and vehicles. This was not surprising, because the pore size of the microporous membrane was large enough to allow both vehicles and drug molecules to percolate through the membrane without significant diffusion resistances across the membrane. On the other hand, the skin flux of ketorolac substantially decreased through a bilaminated microporous adhesive membrane. The skin fluxes were 34 and 55 μg/cm^2/h for silicone and acrylate adhesive, respectively, which were roughly half the skin flux value obtained from a gel directly in contact with cadaver skin. The diffusion resistance was calculated to be 7.4×10^{-2} and 1.8×10^{-2} (cm/h)$^{-1}$ for acrylate and silicone adhesives, respectively.[13] Thus, the diffusivity of ketorolac in the acrylate adhesive was substantially higher than that of the silicone adhesive.

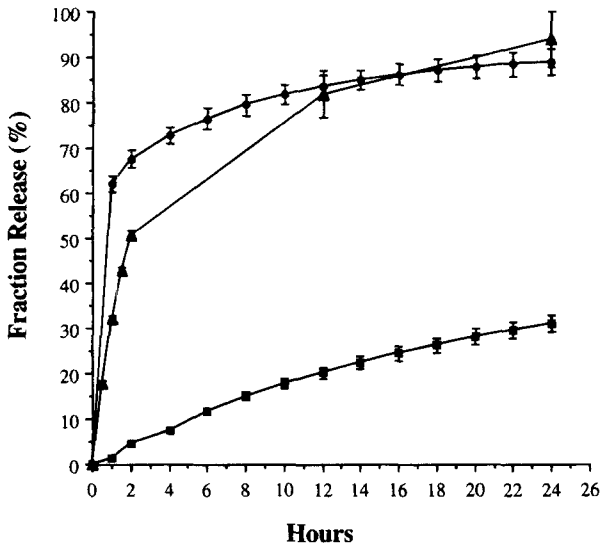

Figure 7—Release profile of ketorolac from transdermal devices into water at 32 °C. Key: TD-A (closed triangle), TD-B (closed square), TD-C (closed circle).

The liquid-reservoir transdermal device was fabricated using ketorolac tromethamine gel, a microporous membrane, a bilaminated microporous adhesive membrane, and a polyester backing film. The release kinetics of ketorolac tromethamine from transdermal devices into an aqueous media at room temperature is illustrated in Figure 7. A perfect sink condition was maintained throughout the release experiment to offset any aqueous boundary layer effect on the drug release profile. The drug release from TD-C was instantaneous because microporous membrane offered practically no diffusional barrier. A similar trend in the release pattern of ketorolac from TD-A was observed. At the end of 24 h, about 90% of the initial drug loading was recovered from TD-A and TD-C transdermal patches. In contrast, a shallower release profile of ketorolac from TD-B patch was observed and only 30% of the drug was release in 24 h from this patch. This trend in release pattern was consistent with in vitro skin flux data where the silicone adhesive offered relatively higher diffusional resistances than the acrylate adhesive.

The in vitro flux of ketorolac from the transdermal devices through human cadaver skin was also evaluated. Figure 8 shows the skin flux of ketorolac from gel without a membrane, from TD-B, and from TD-C, using a single skin donor sample. The skin flux of ketorolac from the transdermal devices decreased by a factor of 2–3-fold as compared to the gel (no membrane), which was consistent with membrane transport experiments (Figure 5). These results suggested that the adhesive membrane modulated the drug delivery rate through the cadaver skin. The skin flux of ketorolac from the TD-A patch was about 1.5 times higher than that of the TD-B patch. The diffusion lag time of the two transdermal devices was roughly 2 times longer than that of the ketorolac gel alone (data not shown).

Pharmacokinetics of Ketorolac Tromethamine in Humans—The absorption of transdermally administered

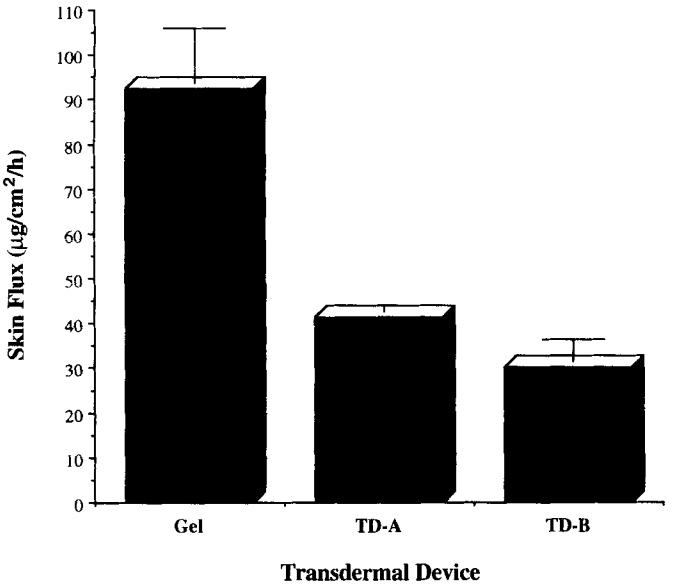

Figure 8—In vitro skin flux of ketorolac from three transdermal devices through cadaver skin at 32 °C (see the text for gel formulation and patch description).

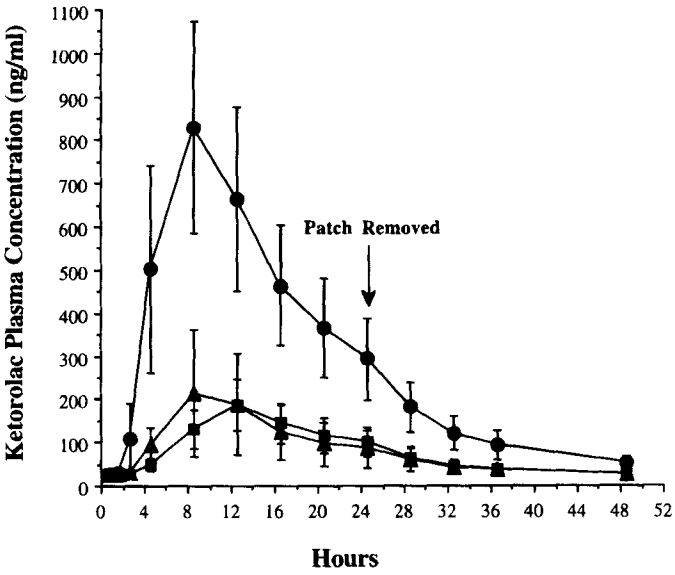

Figure 9—Ketorolac plasma concentration following application of transdermal devices for 24 h in 10 healthy subjects. The devices were removed after 24 h of application. Key: TD-A (closed triangle), TD-B (closed square), TD-C (closed circle).

ketorolac tromethamine was evaluated in 10 healthy subjects. The plasma drug concentration–time profiles are illustrated in Figure 9. Each plasma data point is the mean (±standard deviation) of 10 subjects receiving a transdermal patch. The plasma drug concentration following application of the TD-C device rose faster than those of the TD-A and TD-B devices. The TD-C device provided relatively higher drug plasma levels at every measured time point. The time to reach maximum concentration (T_{max}) ranged from 8 to 12 h. In all cases, the drug concentration declined exponentially on removal of the transdermal devices at 24 h.

The mean pharmacokinetic parameters of ketorolac following application of the transdermal devices for 24 h in 10 volunteers are summarized in Table 4. The maximum plasma concentrations (C_{max}) were 0.20, 0.18, and 0.82 μg/mL for TD-A, TD-B, and TD-C, respectively. The TD-C device provided the highest plasma levels among the three transdermal devices. This was not surprising, because the microporous

Table 4—Mean Pharmacokinetic Parameters of Ketorolac following Application of Transdermal Device for 24 h in 10 Healthy Subjects in a Three-Way Randomized Fashion[a]

Pharmacokinetic Parameters	Transdermal Device			p value
	TD-A	TD-B	TD-C	
C_{max} (μg/mL)	0.20 ± 0.15	0.18 ± 0.06	0.82 ± 0.24	<0.001
T_{max} (h)	8.4 ± 1.3	12.4 ± 1.3	8.8 ± 1.7	
AUC_{0-24} (μg h/mL)	2.66 ± 1.68	2.37 ± 0.74	11.22 ± 3.50	<0.001
$AUC_{0-\infty}$ (μg h/mL)	3.48 ± 2.02	3.19 ± 0.98	14.25 ± 4.35	<0.001
Half-life, $T_{1/2}$ (h)	7.4 ± 2.7	6.6 ± 1.7	9.7 ± 2.3	0.015

[a] Each value is the mean ± SD of 10 healthy subjects.

membrane of the TD-C device offered very little or no resistance for the transport of ketorolac and vehicles, which was consistent with in vitro findings (Figure 6). In the case of the TD-C, after attaining C_{max} at 8.4 h, a steep decline in the drug plasma concentration was observed. On the other hand, a shallow decline in drug levels was observed for the TD-A and TD-B. This may be partly caused by a relatively fast depletion of isopropyl alcohol from the TD-C device, as there was no diffusional barrier for its permeation through the microporous membrane.[7] In contrast, the TD-A and TD-B devices maintained relatively flat plasma profiles even though the drug plasma levels were significantly lower than that of the TD-C device.

The area under the plasma concentration–time curve (AUC) decreased in the following order: TD-C > TD-A > TD-B. Although the AUCs for TD-A and TD-B were virtually the same, a statistically significant difference between the TD-C and the two adhesive membrane devices was observed ($p < 0.001$). The AUC_{0-24} rank order for the three transdermal devices was consistent with in vitro skin flux data where TD-A and TD-B devices provided lower flux than ketorolac gel directly in contact with skin (similar to the TD-C device). These results were consistent with a previously reported human study from our laboratories where we demonstrated an excellent correlation of transdermal ketorolac in vitro and in vivo.[7]

The terminal half-lives ($T_{1/2}$) ranged from 6.6 to 9.7 h, and no statistically significant differences among the three formulations were observed ($p = 0.0153$). The mean terminal half-life of transdermally administered ketorolac ($T_{1/2} = 7.9$) was slightly higher than that of an intramuscular injection ($T_{1/2} = 5.5$) of ketorolac.[3,5] It is possible that the stratum corneum of the skin might have retained a small fraction of ketorolac and continued to deliver residual drug from the skin after removal of the transdermal device. The peak plasma level of ketorolac following application of the TD-C device was comparable to that of a 10 mg oral dose administered every six hours, while the desired therapeutic plasma level of 500 ng/mL was maintained for about 16 h following a single patch application. Obviously, transdermal delivery of ketorolac appears to be more desirable than existing oral or intramuscular administration for alleviating pain in postoperative patients, ultimately leading to better patient compliances.

References and Notes

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