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Correlation Between the Transdermal Permeation of Ketoprofen and its Solubility in Mixtures of a pH 6.5 Phosphate Buffer and Various Solvents

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The passage of a drug through the skin is directly proportional to the concentration of the drug in the donor phase and to the permeability coefficient constant Kp. Kp is determined essentially by two factors: the dissolution of the drug in the stratum corneum (measured by the partition coefficient P) and the diffusion in the same stratum (measured by the diffusion constant D). In our study, several saturated solutions of ketoprofen in mixtures of a pH 6.5 phosphate buffer and various co-solvents were studied to find correlations between the solubility of the ketoprofen in the mixtures and its permeation parameters in in vitro permeation studies with Franz cells. The results show that D does not change in the different mixtures; the diffusion of the drug into the stratum corneum is not influenced by the presence of the co-solvents, whereas the partition coefficient is strongly influenced. In particular, Kp and P were found to be inversely proportional to solubility, meaning that when the co-solvent increases the solubility, the partition of the drug and consequently Kp decrease. These findings were confirmed in some developed gels, and the developed gels were found to enhance the ketoprofen permeation with respect to the formulation in a commercial Fastum gel.

Keywords Diffusion Constant, Ketoprofen, Partition Coefficient, Permeability, Transdermal Permeation

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic actions. It is equally or more potent than other NSAIDs with respect to anti-inflammatory and analgesic activity. But it causes some gastrointestinal side affects such as nausea, dyspepsia, diarrhea, constipation, and some renal side effects, like other NSAIDs (Hersh et al. 2000; Saxena and Saxena 1978). Therefore, transdermal drug delivery would be an ideal route for the administration of this drug, to avoid the oral side effects and provide relatively constant drugs levels at the application site for prolonged periods. However, transdermal administration of many drugs is often precluded because of the stratum corneum barrier.

In the formulation of vehicles for topical administration, the efficacy of the dosage form often depends on the composition of the vehicle (Goto et al. 1983; Obata et al. 1993; Ostrenga, Steinmetz, and Poulsen 1971a, 1971b; Ross and Shah 2000). Percutaneous absorption is a passive diffusion process determined essentially by two factors: the dissolution and the diffusion of the drug into the stratum corneum. The contribution of each of these is expressed in Fick's equation in terms of the partition coefficient of the drug between the stratum corneum and the donor phase (P) and the diffusion constant (D cm^2/h) of the drug in the barrier (Dugard and Scott 1986).

P is an index of the affinity of the drug for the vehicle or the skin and can be optimized by decreasing its solubility in the vehicle whereas D is related to the characteristics of the drug (Cordero et al. 1997). It could change using enhancers that fluidize the lipids or induce structural changes in proteins of the stratum corneum (Kommuru, Khan, and Reddy 1998; Rhee et al. 1999; Walter, Olejinik, and Harris 1984; Williams and Barry 1991; Yamane, Williams, and Barry 1994) or using cosolvents that increase the partition tendencies of the permeant in the rate-limiting lipid phase (Kurihara-Bergstrom, Flynn, and Higuchi 1986; Okamoto, Hashida, and Sezaki 1988).

The aim of our study was to find any correlation between the permeability of ketoprofen through the skin and its solubility in mixtures of water and co-solvents and to choose the co-solvent that best enhances the permeability of ketoprofen in the development of hydrophilic topicals.

To do this, we performed in vitro infinite dose permeation studies on standard Franz diffusion cells using ketoprofen suspensions in mixtures of water and co-solvents. The effectiveness of the studies on the suspensions was also tested in developing hydrophilic gels using some of the co-solvents.

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MATERIALS AND METHODS

Chemicals

Ketoprofen was a gift from Aldrich (Milan, Italy), 1,2-Propylen glycol was obtained from the Fluka Chemical Company (Milan, Italy), ethoxyethylendiglycol Transcutol® from Gattefossé (Saint-Priest, France), ethyl alcohol absolute, isopropyl alcohol, glycerol 90%, and PEG 400 from Carlo Erba (Rodano, Italy). All the materials were used as received.

Analyses

Ketoprofen in samples was determined using a HPLC device (Model 305, Gilson,) equipped with a variable-wavelength ultraviolet detector (model Spectra 200, Spectra-Physics,). A Nova-Pak C18 (150 × 3.9 mm, 4 μm, Waters) column was used. Elution was carried out at room temperature with a mobile phase consisting of phosphate buffer 0.025 M adjusted to pH 3 with phosphoric acid and acetonitrile (5:5, v/v); the injecting volume was 20 μl. The flow rate was 1 ml/min, and the detection was at 276 nm. In this condition the retention time of ketoprofen was 7.50 min.

Solubility Studies

The solubilities of ketoprofen in the mixtures made up of a pH 6.5 phosphate buffer 0.5 M and various co-solvents at different concentrations were determined at 37°C. Excess drug was added to the systems at room temperature, heated to 50°C to dissolve the drug, and then equilibrated at 37°C ± 0.5°C for 24 h. Aliquots of the saturated systems were filtered through Millipore filters (W-13-2, Tosoh Company,) diluted with mobile phase, and analyzed by HPLC. Saturated solutions were used to ensure equal thermodynamic activity.

Tissue Preparation

Porcine skin is largely used for in vitro experiments because it is similar to the human epidermis as demonstrated by differential scanning calorimetric studies in which the porcine and the human stratum corneum showed a very similar thermogram (Potts et al. 1991) and by permeation studies that showed that porcine skin offers similar resistance to permeation as human skin (Walker et al. 1997; Wester et al. 1998). Full-thickness skin with a fair amount of underlying connective tissue was surgically removed from the ears of freshly killed male pigs (30–50 Kg) obtained, on each study day, from a local slaughter house (CLAI, Imola, Italy). The skin was placed in ice-cold phosphate buffered saline, pH 7.4. The connective tissue of the skin was carefully removed using fine-point forceps and surgical scissors. The cleaned membrane was then placed in ice-cold PBS until it was mounted in the diffusion cells.

In vitro Diffusion Study

The in vitro diffusion studies were carried out in standard Franz diffusion cells having 0.64 cm^2 diffusion area (Franz 1975; Friend 1992). The receptor compartment has a volume of 4.8 ml and was maintained at 37°C by a water bath, circulator, and a jacket surrounding the cells. The cells were filled with fresh PBS. The solution in the receptor compartments was continuously stirred at 600 rpm using a Tefloncoated magnetic stirrer. The porcine skin, 1 ± 0.1 mm thick, was clamped between the donor and receiving compartments. Then 1 ml of the saturated solutions was placed in the donor compartment. We also tested 1 ml of developed gels and Fastum® gel.

The amount of ketoprofen diffused through porcine skin was determined by removing aliquots of 2 ml from the receptor compartments using a syringe and immediately replacing with the same volume of PBS (kept at 37°C). The sampling schedule was 0.5, 1, 2, 4, 6, and 8 h. All experiments were carried out 6 times.

Data Analysis

The transport of drugs across the skin barrier may be considered a process of passive diffusion. The *in vitro* skin flow was determined from Fick's law of diffusion:

$$Js = (1/A)(dM/dt) = Kp\,\Delta C, \quad [1]$$

where Js is the skin flow ($\mu g\ cm^{-2}\ h^{-1}$), dM/dt is the amount of drug permeated per unit of time, A is the diffusion area (cm^2), Kp is the permeability coefficient ($cm\ h^{-1}$), and ΔC is the concentration gradient. In all the experiments, the concentrations in the donor cell remained constant, the receiver cell concentrations did not exceed 10% of the donor cell concentrations, and ΔC was assumed to be equal to the donor cell concentrations. The steady-state flux Js was determined from the slope of the linear portion of the cumulative amount permeated per unit area versus time plot. The lag time was determined by extrapolating the linear portion of the curve to the abscissa.

The Kp value is also:

$$Kp = (D * P)/h \quad [2]$$

where D is the diffusion coefficient of the drug into the stratum corneum, P is the partition coefficient of the drug between stratum corneum and vehicle of administration, and h is the stratum corneum thickness. D was approximated indirectly from the lag time:

$$\text{Lag time} = h^2/6D. \quad [3]$$

Knowing Kp and D, it was then possible to determine the value of P (Ostrenga, Steinmetz, and Poulsen 1971).

RESULTS AND DISCUSSION

In all experiments, the permeation profiles showed a curved portion, corresponding to a lag phase, followed by a linear

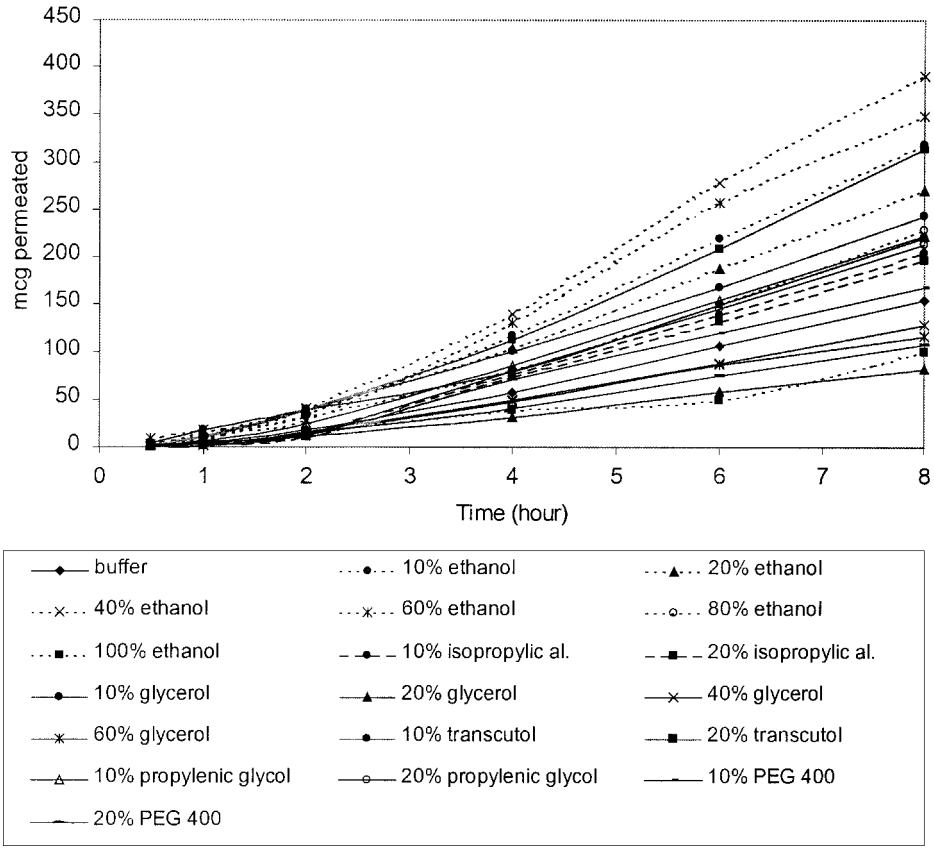

FIG. 1. Permeation profiles of ketoprofen from the saturated solutions.

portion, which means that an apparent steady state of ketoprofen penetration was attained (Figure 1). The solubilities of the ketoprofen in the different mixtures and the calculated permeation parameters are shown in Table 1. When statistical analysis was carried out for D values, statistical significance ($p < 0.05$) was not recognized. This means that the presence of the cosolvents does not change the diffusion rate of ketoprofen.

The graph of permeability constant Kp values versus ketoprofen solubilities in the saturated solutions is showed in Figure 2 and the partition P values versus ketoprofen solubilities is showed in Figure 3. The correlation between the variables was found to be high in the two graphs: $R^2 = 0.86$ for Kp and $R^2 = 0.77$ for P. Considering that D is constant in all the tested mixtures, the variation in permeability constant was due

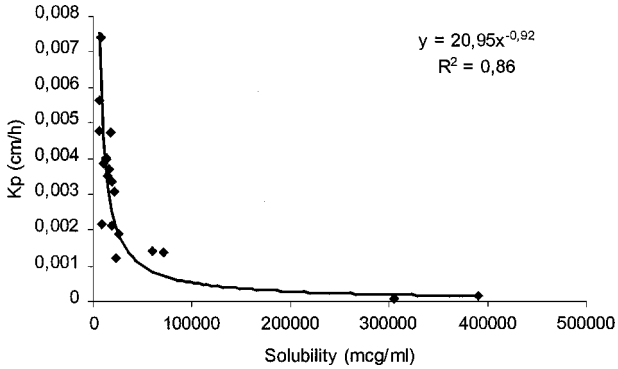

FIG. 2. Permeability constant Kp values versus ketoprofen solubilities in the saturated solutions.

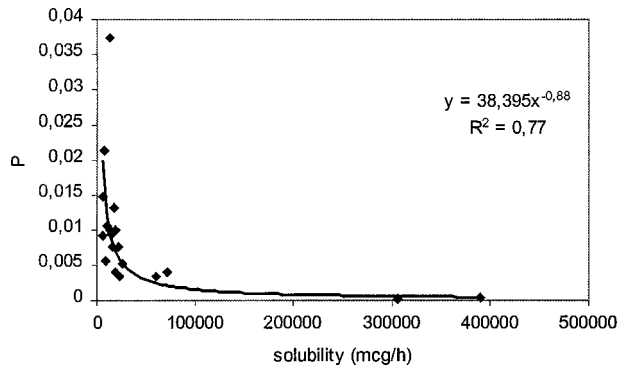

FIG. 3. Partition P values versus ketoprofen solubilities in the saturated solutions.

TABLE 1
Solubilities and permeation parameters of the ketoprofen in all the tested mixtures

(PB)	Solubility (μg/ml)	Kp * 10^{-3} (cm/h)	J (μg/ cm^2 h)	(D * 10^{-3} (cm^2/h)	P * 10^{-3}	Lag time (h)
Phosphate buffer pH 6.5	9900.56	3.848	38.102	36.332	10.592	1.65
	sd 20.23	sd 0.213	sd 2.11	sd 4.63	sd 0.587	sd 0.36
PB and ethanol 10% v/v	16647.58	4.737	78.859	36.062	13.136	1.66
	sd 100.23	sd 0.220	sd 3.66	sd 5.05	sd 0.610	sd 0.33
PB and ethanol 20% v/v	21193.47	3.078	65.223	40.028	7.688	1.50
	sd 56.33	sd 0.194	sd 4.12	sd 5.75	sd 0.486	sd 0.29
PB and ethanol 40% v/v	71151.15	1.386	98.630	34.801	3.983	1.72
	sd 78.98	sd 0.016	sd 1.11	sd 5.38	sd 0.045	sd 0.31
PB and ethanol 60% v/v	60306.15	1.406	84.766	40.928	3.434	1.47
	sd 89.22	sd 0.054	sd 3.23	sd 3.70	sd 0.131	sd 0.45
PB and ethanol 80% v/v	391001.7	0.147	57.500	32.75	0.449	1.83
	sd 102.52	sd 0.007	sd 2.55	sd 3.27	sd 0.020	sd 0.51
PB and ethanol 100% v/v	305985.1	0.079	24.172	27.868	0.283	2.15
	sd 125.63	sd 0.009	sd 2.62	sd 5.05	sd 0.031	sd 0.33
PB and isopropylic alcohol 10% v/v	12556.02	3.971	49.863	37.355	9.875	1.52
	sd 12.35	sd 0.157	sd 1.97	sd 0.02	sd 0.420	sd 0.23
PB and isopropylic alcohol 20% v/v	25797.26	1.875	48.380	36.072	5.199	1.66
	sd 35.26	sd 0.142	sd 3.66	sd 5.21	sd 0.393	sd 0.32
PB and glycerol 10% v/v	7433.975	7.404	55.044	34.656	21.365	1.73
	sd 32.32	sd 0.447	sd 3.32	sd 5.05	sd 1.289	sd 0.33
PB and glycerol 20% v/v	9209.467	2.187	20.145	39.388	5.554	1.52
	sd 26.21	sd 0.446	sd 4.11	sd 7.94	sd 1.133	sd 0.21
PB and glycerol 40% v/v	5570.873	5.652	31.489	37.998	14.876	1.58
	sd 98.23	sd 0.555	sd 3.09	sd 9.80	sd 1.460	sd 0.17
PB and glycerol 60% v/v	5697.315	4.766	27.156	51.344	9.283	1.17
	sd 53.21	sd 0.563	sd 3.21	sd 15.15	sd 1.097	sd 0.11
PB and Transcutol¨ 10% v/v	15101.35	3.707	55.988	49.121	7.548	1.22
	sd 56.22	sd 0.154	sd 2.33	sd 10.42	sd 0.314	sd 0.16
PB and Transcutol¨ 20% v/v	23402.25	3.356	78.531	33.625	9.98	1.78
	sd 59.06	sd 0.133	sd 3.11	sd 6.41	sd 0.395	sd 0.26
PB and propylenic glycol 10% v/v	13322.99	4.02	53.555	40.493	9.927	1.48
	sd 52.01	sd 0.161	sd 2.14	sd 7.58	sd 0.397	sd 0.22
PB and propylenic glycol 20% v/v	14907.53	3.507	52.286	37.256	9.414	1.61
	sd 32.02	sd 0.142	sd 2.11	sd 5.05	sd 0.380	sd 0.33
PB and PEG 400 10%	17967.18	2.14	38.453	54.167	3.951	1.11
	sd 33.01	sd 0.168	sd 3.01	sd 5.38	sd 0.309	sd 0.31
PB and PEG 400 20%	22286	1.202	26.786	36.258	3.315	1.65
	sd 21.22	sd 0.134	sd 2.98	sd 7.25	sd 0.369	sd 0.23

to a change in partition coefficient that is itself shown to be inversely proportional to the solubility. In fact, the exponent of the x variable was found to be −0.92 for Kp and −0.88 for P correlations meaning that an inverse proportionality was found.

The highest Kp was obtained using glycerol at 10% concentration, followed by glycerol at 40% and 60% concentration; in all these mixtures the solubility of ketoprofen was low, between 5570 and 7433 μg/ml.

The highest flux was obtained using ethanol at a concentration of 40% (98.63 $\mu g/cm^2 h$), followed by ethanol at 60% (84.76 $\mu g/cm^2 h$), and 10% concentration (78.85 $\mu g/cm^2 h$). In these mixtures, the solubility of ketoprofen was high (between 60306 and 71151 μg/ml) with the exception of ethanol at 10%

TABLE 2
Composition of developed gels

	PB gel	Isopropylic Alcohol 10% gel	Isopropylic Alcohol 20% gel	Ethanol 10% gel	Ethanol 40% gel	Transcutol 10% gel
Ketoprofen	1% w/v	1% w/v	1% w/v	1% w/v	1% w/v	1% w/v
Carbopol 940P	2% w/v	2% w/v	2% w/v	2% w/v	2% w/v	2% w/v
Solvent and its concentration	—	Isopropylic alcohol 10% v/v	Isopropylic alcohol 20% v/v	Ethanol 10% v/v	Ethanol 40%	Transcutol 10%
pH 6.5 phosphate buffer	To 100%	To 100%	To 100%	To 100%	To 100%	To 100%

concentration in which the solubility of ketoprofen is lower (16647 μg/ml).

These results suggest that to have a high flux it is necessary to use a solvent that can solubilize the ketoprofen. But if the ketoprofen concentration is to be low in the topical formulation, the flux from an ethanol mixture would be low because otherwise the flux in the experiments was found to be high, the Kp was low. The results show that the solvents can modulate the partition of the drug and thus the drug flux.

To test these findings, we developed gels using the same polymer (carbopol 940 P at 2% w/w concentration) and various solvents. The developed gel compositions are shown in Table 2. We developed formulations with the drug completely solubilized in the gel matrix at 1% w/v concentration because we wanted to test solvents with a large range of Kp values. We chose as co-solvent in the hydrophilic gels, isopropylic alcohol at 10% and 20% concentrations because they had very different Kp values, although they had almost the same composition. We used ethanol at 10% concentration because it showed the higher Kp than the one shown by the solvents that were able to solubilize ketoprofen at a concentration higher than 1%. We also used ethanol at 40% to simulate the commercial Fastum gel formulation whose composition in shown in Table 3. We used Transcutol at 10% of concentration because it was found to be a permeation enhancer (Harrison et al. 1996). We made a gel without co-solvent to establish the effect of the various solvents used. We also performed an in vitro permeation study on Fastum gel in which ketoprofen was at 2.5% of w/w concentration. The permeation profiles are shown in Figure 4 while the corresponding fluxes are presented in Table 4 where the enhancer effect (ER) of the polymer carbopol 940 P is also represented. ER was calculated from the following equation:

$$ER = Kp_{\text{of gel}}/Kp_{\text{of saturated solution}} \quad [4]$$

TABLE 3
Fastum gel composition

Components	Composition
Ketoprofen	2.5 w/w
Carbopol 940P	2 w/w
Ethanol	40 v/w
p-hydroxy benzoic esters	0.1 w/w
Neroli essence	0.05 v/w
Lavander essence	0.1 v/w
Diethanol amine	1.35 w/w
Distilled water	To 100%

The fluxes from the gels were different with respect to the saturated solution because the concentrations were different. The highest flux was obtained with the gel at 10% ethanol concentration, followed by the gel containing isopropyl alcohol at 10% concentration and the gel without co-solvents.

From the results of the permeability coefficients, all the developed gels showed an enhancer effect with respect to the saturated solution meaning that carbopol 940 P enhances drug permeation. The enhancer effect of the carbopol 940 P was essentially constant in all the different gels—between 1.286 and 1.604.

We found that the ratio between Kp values of the gel containing 10% isopropyl alcohol concentration and the gel containing 20% concentration of the same solvent was almost the same as the ratio between the Kp values of the corresponding saturated solutions (1.81 for the gels and 2.12 for the saturated solutions). The similarity of the ratios between the Kp of the gels and of the saturated solutions confirms that the differences in the fluxes of the saturated solutions are not due to an effect on the drug diffusion, but from the partition of the drug into the stratum corneum because the two mixtures of solvents act very differently on the drug solubility.

This result clearly demonstrates that the Kp and thus the flux can be easily modulated using a co-solvent that changes the

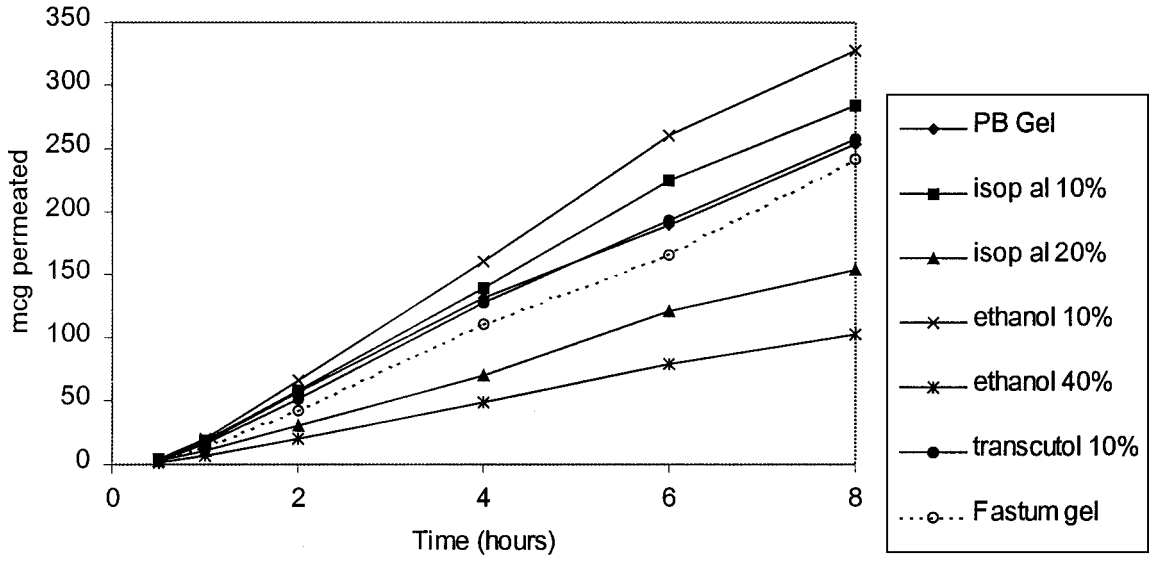

FIG. 4. Permeation profiles of ketoprofen from the developed gels and from Fastum gel.

partition of the drug into the stratum corneum. The flux and Kp of the gel with ethanol at 10% concentration, with Transcutol at 10%, with isopropyl alcohol at 10%, and of the gel without co-solvent are almost the same and, in parallel, also the ketoprofen solubility in these mixtures is the same. From these results we conclude that Transcutol does not have any enhancer effect on the ketoprofen permeation.

The ketoprofen flux from the gel containing ethanol at 40% concentration presents the lowest flux. Its Kp value is also the lowest, and the ratio between the Kp values of the gel with 40% ethanol concentration and the gel without co-solvent is not different from the ratio between the Kp of the corresponding saturated solutions (0.41 and 0.36).

The flux from the Fastum gel is not very high considering that it has a concentration of ketoprofen of 2.5% w/w. Otherwise, its Kp is the same as the developed gel containing 40% ethanol concentration. The interesting finding is that the flux from Fastum gel, which has the highest drug concentration, is not the highest and so it is possible to improve the ketoprofen flux by choosing solvents that enhance the drug partition into the stratum corneum.

CONCLUSION

From our results we found that the permeation of ketoprofen can be modulated using various co-solvents. Since D values of the in vitro permeation studies of the saturated solutions are not significantly altered in the tested mixtures, the variation in permeability coefficient of ketoprofen across skin is a result of a variation in partitioning of the drug from the vehicle into the stratum corneum.

These findings are confirmed in gels that were formulated using co-solvents that solubilize the drug with a large range of concentrations.

The present investigation demonstrates that the permeation ability of ketoprofen across skin can be successfully predicted from the knowledge of only the physiochemical parameter of solubility into an aqueous mixture of phosphate buffer and a

TABLE 4
Fluxes, permeability coefficients, and enhancer effects of the developed gel and of the Fastum gel

	PB gel	Isopropylic alcohol 10% gel	Isopropylic alcohol 20% gel	Ethanol 10% gel	Ethanol 40% gel	Transcutol 10% gel	Fastum gel
Flux (μg/cm^2 hr)	49.479	54.615	30.078	64.063	20.117	50.391	47.205
	sd 4.251	sd 4.561	sd 3.65	sd 5.23	sd 1.98	sd 4.568	sd 5.012
Kp * 10^{-3}	4.948	5.462	3.008	6.406	2.012	5.039	4.721
ER	1.286	1.375	1.604	1.352	1.451	1.359	—

co-solvent. This is possible because the permeability constant for ketoprofen is inversely proportional to the solubility in the vehicle. Moreover, in the developed gels, we obtained a flux through the skin higher than Fastum gel, which has a concentration 2.5 times more.

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