ELSEVIER

International Journal of Pharmaceutics 169 (1998) 95–104

international journal of pharmaceutics

Enhancement of percutaneous absorption of ketoprofen: effect of vehicles and adhesive matrix

Y.-J. Cho, H.-K. Choi *

College of Pharmacy, Chosun University, 375 Seoseok-dong, Kwangju 501-759, South Korea

Received 21 November 1997; received in revised form 10 February 1998; accepted 6 March 1998

Abstract

The effects of various vehicles on percutaneous absorption of ketoprofen in a solution formulation and in a pressure-sensitive adhesive (PSA) matrix were evaluated. The permeation rate of ketoprofen across hairless mouse skin was evaluated using a flow-through diffusion cell system at 37°C. The solubility of ketoprofen was determined using the equilibrium solubility method. Among tested vehicles, octanol, ethanol, and propylene glycol (PG)/oleyl alcohol (OA) mixture showed the highest flux of 30 $\mu g/cm^2$ per h from 5 mg/ml solution. However, it was not possible to demonstrate any correlation between the solubility of ketoprofen and its permeation rate, indicating change in the barrier property of the skin and/or carrier mechanism by vehicles used. When the effects of various vehicles on the percutaneous absorption of ketoprofen from acrylic PSA matrix were evaluated, oleic acid showed a slightly higher flux of 2 $\mu g/cm^2$ per h than all other solvents tested. As the concentration of ketoprofen in acrylic PSA matrix increased from 6.3 to 16.7%, the permeation rate also increased almost linearly. The permeation rate of ketoprofen from polyisobutylene (PIB)-type PSA matrix was more than three times higher than that from acrylic PSA matrix.

Keywords: Pressure-sensitive adhesive; Transdermal; Ketoprofen; Vehicle effect; Matrix

1. Introduction

Ketoprofen, a non-steroidal anti-inflammatory drug, has been administered per oral, 150–300 mg divided into three or four doses per day, for the acute and long-term management of rheumatoid arthritis and osteoarthritis, as well as mild to moderate pain and dysmenorrhea (Gennaro, 1995). However, its short elimination half-life and many adverse effects, such as upper abdominal pain and ulceration of the gastro-intestinal mucosa restrict the oral use of the drug. To overcome those disadvantages, ketoprofen can be administered using a transdermal drug delivery system. The transdermal drug delivery system has the

* Corresponding author. Tel.: + 82 62 2203742; fax: + 82 62 2225414; e-mail: hgchoi@chosun.ac.kr

0378-5173/98/$19.00
PII S0378-5173(98)00115-X

following advantages: (1) it avoids first-pass metabolism; (2) it reduces side effects due to reduction of the peaks in plasma levels; (3) it improves therapy due to maintenance of plasma levels; (4) it is easy to discontinue the administration; (5) it can be used for drugs with a short half-life; (6) it avoids side effects in the GI tract, etc.

In spite of many advantages of transdermal delivery system over oral delivery, only a limited number of drugs have been used to develop the system due to the excellent barrier function of the skin. Transdermal drug delivery systems consist of several components, including active ingredient, backing membrane, pressure-sensitive adhesive, permeation enhancer, etc. Among these it is particularly important to choose an appropriate enhancer and a pressure-sensitive adhesive compatible with the other components. The former is used to overcome the intrinsic resistance of the stratum corneum to the permeation of a drug and may also act as a solubilizer, a fluidizer, or a plasticizer (Irion et al., 1995). The latter not only maintains intimate contact between the system and the skin surface (Kokubo et al., 1994), but controls the release rate of a drug from the matrix. Extensive studies have been conducted regarding the effect of various vehicles on the percutaneous absorption of a compound; however, most of the studies were conducted using solution formulations. The enhancers selected, based on the results of those studies, may be incorporated into the transdermal matrix formulation to optimize the rate of percutaneous absorption required for effective therapeutic response. However, the remarkable effect of enhancers obtained from solution formulations may or may not be achievable when they are incorporated within a pressure-sensitive adhesive matrix.

In the present study, we investigated the effect of various vehicles on the percutaneous absorption of ketoprofen from solution formulations and from a pressure-sensitive adhesive matrix, through the hairless mouse skin, and the results were compared to investigate their relationship. In addition, the influence of the functional groups in acrylic adhesives and the nature of pressure-sensitive adhesive on the permeability of ketoprofen were evaluated.

2. Materials and methods

2.1. Materials

Ketoprofen was a gift from Jeil Pharm. Co. (Seoul, South Korea). Diethylene glycol monoethyl ether (Transcutol®), PEG-8 glyceryl caprylate/caprate (Labrasol®), PEG-6 glyceryl monooleate (Labrafil® 1944), and PEG-8 glyceryl linoleate (Labrafil® 2609) were obtained from Gattefosse Korea (Seoul, South Korea). Fractionated coconut oil (Miglyol® 812) and propylene glycol dicaprylate/dicaprate (Miglyol® 840) were obtained from Hüls America (Somerset, NJ). Mineral oil was purchased from Sigma (St. Louis, MO). Peanut oil was obtained from Croda (Parsippany, NJ). Acrylic pressure-sensitive adhesive solutions in organic solvents were obtained from National Starch and Chemical Company (Bridgewater, NJ). Polyisobutylene (Vistanex LM-MH, Vistanex MML-100) were purchased from Exxon (Houston, TX). All other chemicals were reagent grade or above and were used without further purification.

2.2. Solubility test

Excess amount of ketoprofen was added to the various solvents in screw-capped vials. The contents were stirred by an externally driven teflon-coated magnetic bar at room temperature until equilibrated. The saturated solution was then filtered through 0.45-μm Millipore filters (Millipore, Bedford, MA). The concentration of ketoprofen was measured by HPLC after appropriate dilution.

2.3. Preparation of test solution

To determine the effects of various vehicles on the permeation of ketoprofen, appropriate amounts of ketoprofen were dissolved in each test vehicle. The saturated solutions were prepared by adding excess amount of ketoprofen to each test vehicle, and mixing the solution in a shaker bath at room temperature for 24 h.

2.4. Preparation of adhesive matrices

The acrylic adhesive solution with ketoprofen was prepared by mixing ketoprofen solution in toluene with acrylic adhesive solution in mixed solvents. Polyisobutylene (PIB) solution with ketoprofen was prepared by dissolving ketoprofen, PIB cut into small pieces, and other necessary components in a chloroform/toluene mixture. Pressure-sensitive adhesive matrix was prepared by casting the above solutions on a polyester release liner coated with silicone using a casting knife. They were set at room temperature for 10 min and were subsequently oven-dried at 90°C for about 15–30 min to remove the residual organic solvents. The dried film was transferred onto a backing film.

2.5. Diffusion cell system

A flow-through diffusion cell system consisting of a multichannel peristaltic pump (205S, Watson Marlow), a fraction collector (Retriever IV, ISCO), a circulating water bath (RB-10, JeioTech, Korea), and flow-through diffusion cells was used. The flow-through cell consists of two side arms, which enabled conduction of receiver cell media from a peristaltic pump to a fraction collector. The temperature was maintained at 37°C by circulating constant temperature water through the outer jacket of the receiver cell. The surface area of the receiver cell opening was 2 cm^2, and the cell volume was 5.5 ml.

2.6. Procedure

Full-thickness hairless mouse skin was excised from the fresh carcasses of animals that were humanely sacrificed with diethyl ether. Subcutaneous fat was removed carefully with scissors and scalpel. Each of the flow-through diffusion cell components was connected via silicone rubber tubing with an internal diameter of 0.015 in. The receiver cell was filled with a pH 7.4 isotonic phosphate buffer solution, and the media were stirred by an externally driven, teflon-coated magnetic bar to keep them well mixed. The hairless mouse skin was mounted onto each receiver cell, and an O-ring and cell top were placed on each skin. These components were then clamped securely in place. The system was first equilibrated for 30 min, then any air bubbles remaining in the receiver cells were removed. When solution formulations were tested, 300 μl of ketoprofen solution or suspension in various vehicles were placed in the donor compartment. When matrix formulations were tested, a disc with a surface area of 2 cm^2 was cut by a punch. The discs were applied to the epidermal side of the skin with slight pressure before mounting on the receiver cell. The samples were collected every 3 h for 21 h or longer.

2.7. Data reduction

The following equation was used to calculate the amount of the compound permeated (Choi and Angello, 1994). It should be noted that the calculated amounts in the figures are plotted at the midpoint between sampling times, since they are average values between sampling points.

$$M_n = C \times V + \frac{S_n}{2} + \sum_{i=1}^{n} S_i \text{ (when } n \geq 2)$$

$$M_n = C \times V + \frac{S_1}{2} \text{ (when } n = 1)$$

where M_n is cumulative amount permeated; C is concentration in the receiver cell; V is volume of the receiver cell; S_n is total amount in the nth sample.

2.8. Assay

Ketoprofen was analyzed by an HPLC system (Shimadzu Scientific Instruments, MD), consisting of a UV detector (SPD-10A), a pump (LC-10AD), and an automatic injector (SIL-10A). The wavelength of the UV detector was 250 nm and the retention time of ketoprofen was 2.8 min. A reversed-phase column (Alltima, Alltech Associates, IL) was used. The column temperature was maintained at 30°C by a thin foil temperature controller (CH 1445, SYSTEC, MN). The flow rate was 1 ml/min. The mobile phase used consisted of methanol/water/phosphoric acid (80/20/0.1).

3. Results and discussion

3.1. Effect of vehicles in solution formulation

One of the approaches to improve the topical bioavailability of a drug is to incorporate vehicles, which may have two modes of action (Møllgaard and Hoelgaard, 1983a). One is to favor a high drug concentration in the stratum corneum by selecting vehicles leading to an increase in the thermodynamic activity of the drug, thereby promoting the interfacial drug transfer into the stratum corneum. The other is to include a vehicle which affects the barrier function by its own transport through the stratum corneum or indirectly by changing the state of hydration of the skin. In order to achieve high drug concentration in the stratum corneum, the thermodynamic activity in the vehicle needs to be maximized.

If the solubility of a drug in the vehicle is too high, the thermodynamic activity of the drug in the vehicle will be low, leading to low percutaneous absorption rate unless the vehicle alters the barrier property of the skin. Since thermodynamic activity is approximately proportional to the ratio of concentration to the solubility of the drug in the vehicle, two different methods can be used to compare the effect of vehicles on percutaneous absorption of a drug. One approach is to select a fixed concentration of a drug in all vehicles. This method will be useful to select an appropriate vehicle when the concentration of a drug is already determined at a fixed level. In this case, the activity of the drug will vary depending on the vehicles used. The other approach is to use a saturated solution, where the solute activity is constant as unity, to compare the rate of percutaneous absorption. In this case, the flux from all of the vehicles should be equal in the absence of solvent-induced skin damage (Twist and Zatz, 1989). Therefore, it is necessary to investigate the enhancing effect of various vehicles both at fixed concentration and at saturated concentration to fully understand their effects, and to utilize the results in the development of transdermal drug delivery systems. Based on the above arguments, we measured the effect of various vehicles on the percutaneous absorption of ketoprofen across the hairless mouse skin using 5- and 30-mg/ml solutions and a saturated solution. Table 1 shows the maximal permeability coefficients of ketoprofen across the hairless mouse skin obtained from the 5- and 30-mg/ml and saturated solutions in various vehicles for 21 h, and the solubility in those vehicles. Maximal permeability coefficient was compared since permeation profiles of ketoprofen were quite different from each other depending on the vehicles used. The change in driving force and/or the change in the barrier property of the skin with time may have resulted in various permeation profiles. In the following discussions the ratio of the concentration of a drug in the vehicle to its solubility is defined as degree of saturation. Fig. 1 shows the permeation of ketoprofen from a 5-mg/ml solution in propylene glycol (PG), oleyl alcohol (OA), and PG/OA mixtures across hairless mouse skin. Among those, PG/OA mixtures with various volume fractions showed a remarkable enhancing effect, regardless of the volume fraction of each solvent. The amount of ketoprofen permeated from those mixtures for 21 h was 2.3 and 9.8 times higher than that from PG and OA only, respectively.

The solubility of ketoprofen in PG/OA mixtures increased as the volume fraction of PG increased when compared to that in OA. The rank order of degree of saturation was OA > PG/OA (2:8) > PG/OA (5:5) ~ PG/OA (8:2) > PG. However, the permeability of ketoprofen was highest in PG/OA (8:2) followed by PG/OA (5:5), PG/OA (2:8), OA, and PG. OA showed the highest degree of saturation, however, the extent of permeation was less than half of PG/OA mixtures. PG is a nonvolatile, hydrophilic solvent and is a good solvent for both hydrophilic and lipophilic drugs. It has been used quite frequently to enhance the permeability of many drugs in topical formulations. The mechanism of the enhancing effect of PG is reported to be solvation of the stratum corneum by unfolding the keratinized protein matrix, and it is also known that this vehicle penetrates the skin (Niazy et al., 1990). Addition of 1–10% OA in PG enhanced the transport rate of metronidazole across human skin significantly (Hoelgaard et al., 1988). Addition of 20% OA in PG vehicle provided a rather large increase in the

Table 1
Permeability coefficient (mean ± S.D.) of ketoprofen from 5- and 30-mg/ml and saturated solutions in various vehicles across hairless mouse skin

Vehicle	Permeability coefficient ($\times 10^3$ cm/h)			Solubility (mg/ml)
	5 mg/ml	30 mg/ml	Saturated	
Oleyl alcohol	3.07 ± 0.694			48 ± 6
PG:OA (2:8)	9.46 ± 1.51			92 ± 14
PG:OA (5:5)	13.74 ± 4.08	8.781 ± 0.46	2.64 ± 0.58	186 ± 38
PG:OA (8:2)	17.6 ± 1.84			187 ± 9
PG	1.75 ± 0.21	2.21 ± 0.53	0.64 ± 0.11	199 ± 23
PG:EtOH (5:5)	15.78 ± 1.61	9.27 ± 0.36		
Phosphate buffer	0.89 ± 0.18			
Water	0.60 ± 0072			
Ethanol	19.41 ± 0.97	8.03 ± 2.53	0.63 ± 0.16	459 ± 28
Octanol	18.0 ± 0.30	13.4 ± 1.1	4.94 ± 1.11	139 ± 7
Transcutol®	0.52 ± 0.31			412 ± 64
Oleic acid	3.92 ± 0.45	2.37 ± 0.39	5.33 ± 1.3	24 ± 4
Lauroglycol	10.7 ± 11.4	2.65 ± 0.17	3.47 ± 0.32	85 ± 21
Miglyol® 812	1.42 ± 0.21			22 ± 2
Miglyol® 840	0.74 ± 0.3			29 ± 2
IPM	3.89 ± 0.53	2.20 ± 0.19	4.79 ± 0.35	15 ± 4
Mineral oil	63.3 ± 40.1			0.19 ± 0.1
Peanut oil	1.18 ± 0.54			7.8 ± 2
Labrasol®	0.07 ± 0.03			248 ± 57
Labrafil® 1944	6.50 ± 0.29			53 ± 7
Labrafil® 2609	2.98 ± 1.8	0.65 ± 0.10	0.51 ± 0.08	91 ± 10
Tween 20	0.07 ± 0.01			275 ± 12
Tween 80	0.28 ± 011			280 ± 56

ketoprofen transport similar to the case of metronidazole. Because of the mechanism of PG/OA mixtures in enhancing percutaneous absorption, it has been suggested that these binary systems are capable of disorganizing the multilaminate hydrophilic–lipophilic layers located intercellularly in the stratum corneum (Hoelgaard et al., 1988), resulting in a decrease in the resistance of the skin.

The cumulative amount of ketoprofen permeated across hairless mouse skin from the 5-mg/ml solution in various well-known enhancers, ethanol, octanol, and Transcutol®, is shown in Fig. 2. Among the three vehicles tested, ethanol and octanol showed much higher permeability. However, these two vehicles showed quite different permeation profiles. Octanol initially provided very high permeation rate followed by a gradual decrease until 21 h of diffusion. The decrease in permeation rate with time may result from the rapid reduction in driving force owing to initial high permeation rate, i.e. rapid drop in ketoprofen concentration in the donor compartment. It may also result from the loss of octanol during the permeation study. Ethanol showed a low permeation rate for the initial 9 h, followed by remarkable enhancement from 9 to 15 h. When degrees of saturation of both vehicles were compared, octanol was 3 times higher than ethanol. The total amount of ketoprofen permeated for 21 h was similar between octanol and ethanol; however, their permeation profiles were quite different. It was suggested that these vehicles have different mechanisms of permeation enhancement. The large permeability of ketoprofen with ethanol has been explained by its solvent drag mechanism and fluidization of lipid structure of stratum corneum (Goto et al., 1993). These authors attributed the long lag time of ethanol to its stabilization of the gel structure of the lipid bilayer.

The rise in permeation rate of ketoprofen in the later phase can also be explained by the increase of driving force in the donor compartment and slower rate of diffusion of ethanol into the skin.

When the water back diffuses into the donor compartment, it mixes with ethanol leading to decrease in the solubility of ketoprofen, i.e. increase in the thermodynamic activity. It was reported that octanol, having a relatively low molecular weight, may migrate rapidly and have a great capacity to liquefy the lipid layer (Loth, 1991). Transcutol® showed no significant influence on the percutaneous absorption rate of ketoprofen. Transcutol® and ethanol have almost identical degrees of saturation; however, only ethanol had a marked influence on the permeation rate of ketoprofen. These results obtained with Transcutol® are different from the results obtained by other researchers. Most studies showing an enhancing effect of Transcutol® used other components that may have provided the enhancing effect. It is, therefore, probable that Transcutol® may not have a profound effect on the structural integrity of the skin, and it just eases

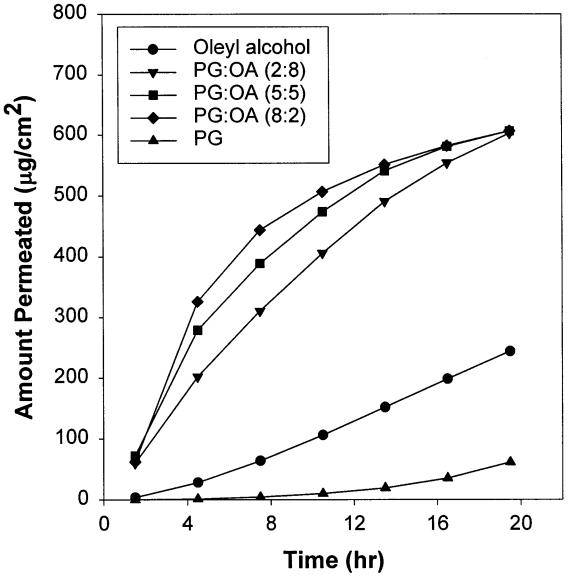

Fig. 1. Cumulative amount of ketoprofen permeated across hairless mouse skin from 5 mg/ml solution in propylene glycol (PG), oleyl alcohol (OA), or their mixtures as a function of time. Each point represents average of four measurements.

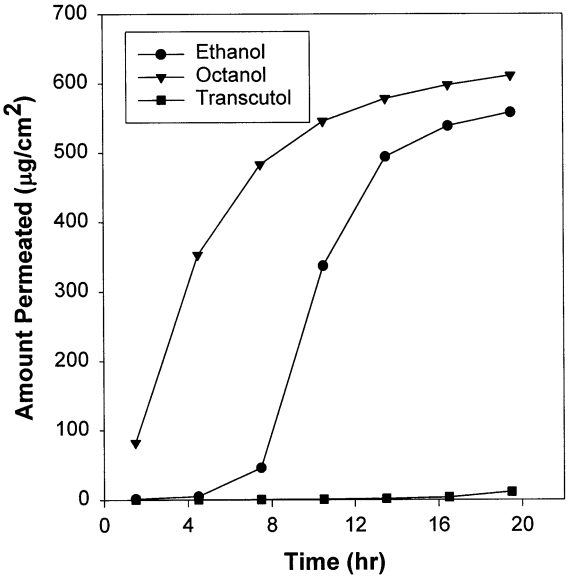

Fig. 2. Cumulative amount of ketoprofen permeated across hairless mouse skin from 5 mg/ml solution in ethanol, octanol, or Transcutol® as a function of time. Each point represents average of four measurements.

the partition of a compound by increasing the solubility of the compound in the skin. The action of Transcutol® as a penetration enhancer has been attributed to its effect on the partition behavior of a drug and to its ability to absorb water (change of vehicle composition), maximizing thermodynamic activity due to change of drug solubility (Ganem-Quintanar et al., 1997). In the present study, the solubility of ketoprofen in Transcutol® may be too high for the thermodynamic activity of ketoprofen to be affected by the ability of Transcutol® to absorb water from the skin.

The effect of lipophilic vehicles, oleic acid, lauroglycol, isopropyl myristate (IPM), Miglyol® 812, Miglyol® 840, mineral oil, and peanut oil, on the permeation of ketoprofen across hairless mouse skin is shown in Fig. 3. These vehicles showed relatively lower enhancement effect. Among these, IPM and oleic acid showed the highest enhancing effect, followed by lauroglycol and mineral oil. Oleic acid acts as a penetration enhancer by disruption of the ordered, lamellar structure of the bilayer in the stratum corneum, leading to an increased fluidization of the intercel-

lular medium (Walters and Hadgraft, 1993). IPM is known to act as a fluidizer of intercellular lipids. Fig. 4 shows the data from studies with liquid compounds commonly included in pharmaceutical formulations as a surfactant. Labrafil® 1944, 2609 and Labrasol® are non-ionic emulsifiers made by esterification of PEG with fatty acids. In more lipophilic surfactants, Labrafil® 1944 and 2609, the permeation rate of ketoprofen was increased moderately. In more hydrophilic surfactants, Tween 20, Tween 80 and Labrasol®, the permeation rate of ketoprofen seemed to be retarded. The low permeability of estradiol in Tween 80 has also been demonstrated, and was attributed to its emulsifying properties by favoring drug affinity to the vehicle (Møllgaard and Hoelgaard, 1983b). The permeability data obtained with vehicles mentioned above can also be correlated with the degree of saturation to some extent. Labrafil® 1944, with the highest degree of saturation, also showed the highest permeability followed by Labrafil® 2609, Tween 20, Tween 80, and Labrasol®.

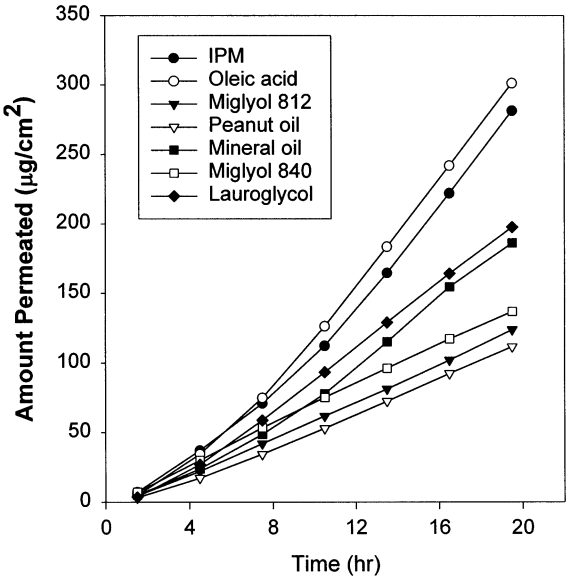

Fig. 3. Cumulative amount of ketoprofen permeated across hairless mouse skin from 5 mg/ml solution in various lipophilic vehicles as a function of time. Each point represents average of four measurements.

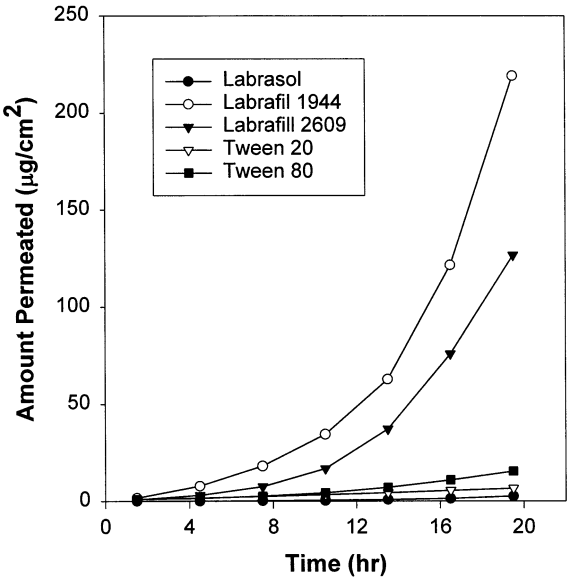

Fig. 4. Cumulative amount of ketoprofen permeated across hairless mouse skin from 5 mg/ml solution in various surfactants as a function of time. Each point represents average of four measurements.

3.2. Effect of concentration

To investigate the effect of drug concentration on the permeation rate of ketoprofen, eight vehicles which showed good enhancing effect in 5-mg/ml solutions were selected and tested using 30-mg/ml and saturated solutions of ketoprofen. Table 1 shows the permeability coefficient at three different concentrations. In all cases tested, the flux of ketoprofen increased significantly. However, permeability coefficients tend to become lower as the concentration increases in the case of PG/OA (5:5), ethanol, octanol, and Labrafil® 2609. The results indicate that diffusion coefficient is a function of concentration, assuming partition coefficient is independent of concentration. In the case of isopropyl myristate and oleic acid, the permeability coefficient was higher in saturated solution than in the 30-mg/ml solution, even though the solutions are already saturated at 30 mg/ml. More solids are added in the case of the saturated solution, and faster dissolution rate can be expected from the saturated solution. Overall, the shape of the permeation profile was similar

within the same vehicle regardless of concentration used. In saturated solutions, octanol showed the best enhancing effect in terms of flux, followed by propylene glycol/oleyl alcohol (PG/OA) mixture (5/5) and ethanol, while ethanol showed the best enhancing effect in the 5-mg/ml solution. The rank order of enhancement effect obtained with the 5-mg/ml solution was somewhat different from that obtained with the 30-mg/ml or saturated solution, indicating that the concentration to be used for the delivery system must be used for the screening of an appropriate vehicle. Theoretically, the effect of vehicles on the absorption process could in part be predicted from knowledge of solute solubility (thermodynamic activity) in the vehicle (Hilton et al., 1994).

When the permeation rates of ketoprofen in saturated solutions were compared, theoretically, the flux of ketoprofen should be same in all cases, unless the vehicles affect the barrier properties of the skin. The results from our study showed a wide range of permeation rates, indicating vehicle effects on the barrier property of the skin and/or carrier mechanism by vehicles used.

3.3. Effect of adhesive matrix

To develop a matrix-type transdermal delivery system for a drug, an appropriate vehicle is required to enhance the permeation rate and/or to solubilize the drug. The effect of some vehicles on the permeation of ketoprofen from acrylic adhesive matrix was investigated to identify the optimum permeation enhancer and to compare their effects with the results obtained using solution formulation. The amount of ketoprofen permeated across hairless mouse skin from an acrylic adhesive matrix is shown in Fig. 5. Each vehicle was added to acrylic adhesive at the 10% level. Some of the vehicles caused significant loss of adhesive force at higher level. The remarkable enhancement effects obtained from the solution formulations were not observed from the acrylic adhesive matrix, indicating that the effect of vehicles in the solution formulation may not be extrapolated to predict their effects in acrylic adhesive matrix. In addition, the fluxes were significantly lower when compared to those obtained from solution formulations. It was speculated that the low flux of ketoprofen might be due in part to its high solubility in the acrylic adhesive matrix, i.e. low thermodynamic activity. Thus, we examined the effect of drug loading in the acrylic adhesive matrix on the flux of ketoprofen (Fig. 6). As the drug loading in acrylic adhesive matrix increased, the flux of ketoprofen also increased, indicating that high drug loading is required to achieve appropriate permeation rate.

The effect of the chemical nature of the adhesive matrix on the permeation of ketoprofen was evaluated. Fig. 7 shows the effect of functional groups, –OH and –COOH, of acrylic adhesive matrix, on the permeation of ketoprofen across hairless mouse skin. One group of samples contained PG/OA (5:5) and the other group contained oleic acid as an enhancer. The acrylic adhesive with a hydroxyl functional group tends to provide a higher permeation rate, followed by one without a functional group. The acrylic adhesive with a carboxyl functional group provided the lowest permeation rate, which may be due to

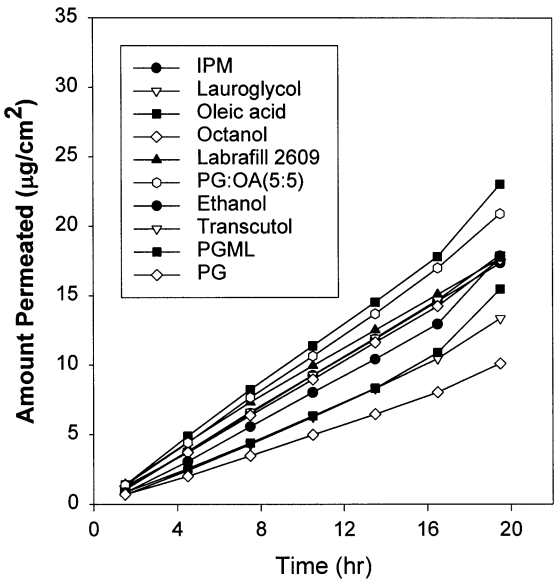

Fig. 5. Effect of various vehicles on the permeation of ketoprofen across hairless mouse skin from acrylic adhesive. The amount of each vehicle used was 10% of the weight of acrylic adhesive polymer. Each point represents average of four measurements.

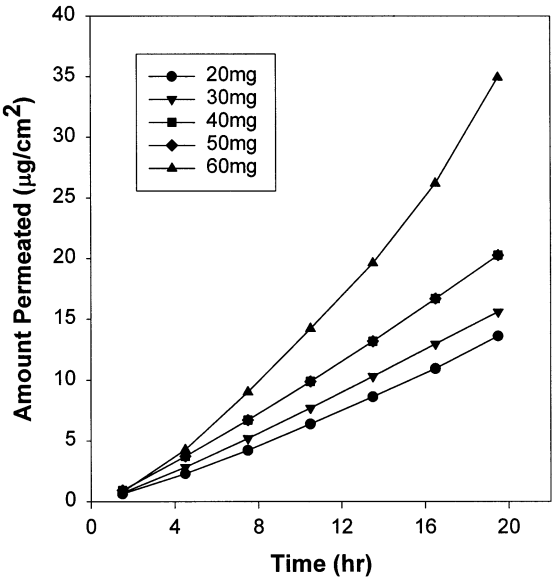

Fig. 6. Effect of drug loading on the permeation of ketoprofen across hairless mouse skin from acrylic adhesive matrix. The amounts of drug in the legend represent amount of ketoprofen loaded in 300 mg of acrylic adhesive polymer. Each point represents average of four measurements.

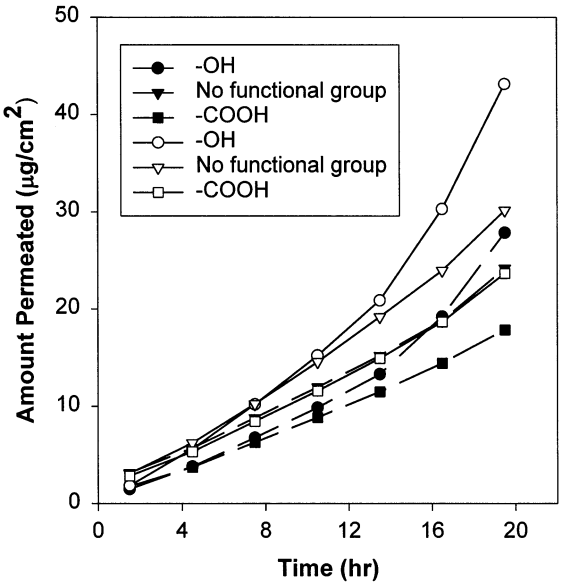

Fig. 7. Effect of functional group of acrylic adhesive on the permeation of ketoprofen across hairless mouse skin from acrylic adhesive matrix. Each point represents average of four measurements. Closed symbols: the matrix contains propylene glycol/oleyl alcohol (5:5). Open symbols: the matrix contains oleic acid.

the better compatibility of the polymer with ketoprofen. When the effect of the two enhancers was compared, the group with oleic acid showed slightly better enhancing effect. The results suggest that the chemical nature of the adhesive must be considered before the selection of an adhesive matrix. When the permeability of ketoprofen in two different kinds of adhesive matrix was compared, a marked difference was observed, as shown in Fig. 8. The permeability of ketoprofen was lower in acrylic adhesive than in polyisobutylene adhesive, which may be due to the higher solubility in acrylic adhesive as discussed before. While the drug was completely dissolved in the acrylic adhesive matrix, it existed as solid particles in the polyisobutylene adhesive matrix, indicating that the thermodynamic activity reached unity in the polyisobutylene adhesive. When a plasticizer, mineral oil, was incorporated in polyisobutylene adhesive, the permeability of ketoprofen was further increased due to increased fluidity within the adhesive matrix. Mineral oil as a plasticizer plays an important role not only in

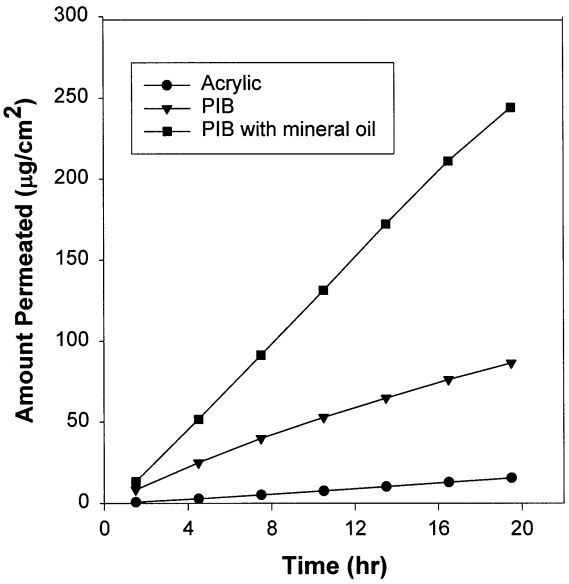

Fig. 8. Effects of the type of pressure-sensitive adhesive and the addition of plasticizer on the permeation of ketoprofen across hairless mouse skin. Each point represents average of four measurements.

increasing the mobility of the drug in the matrix, but also in improving the tacky property of the matrix.

Acknowledgements

This paper was supported by Non-Directed Research Fund, Korea Research Foundation, 1996.

References

Choi, H.-K., Angello, J.T., 1994. Mathematical analysis and optimization of flow-through diffusion cell system. Pharm. Res. 11, 595–599.

Ganem-Quintanar, A., Lafforgue, C., Falson-Rieg, F., Buri, P., 1997. Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss. Int. J. Pharm. 147, 165–172.

Gennaro, A. R., 1995. Remington: The Science and Practice of Pharmacy, 19th Ed. Mack Publishing Company, Easton, PA, pp. 1207–1218.

Goto, S., Uchida, T., Lee, C.K., Yasutake, T., Zhang, J.-B., 1993. Effect of various vehicles on ketoprofen permeation across excised hairless mouse skin. J. Pharm. Sci. 82, 959–963.

Hilton, J.B., Woollen, H., Scott, R.C., Auton, T.R., Trebilcock, K.L., Wilks, M.F., 1994. Vehicle effects on in vitro percutaneous absorption through rat and human skin. Pharm. Res. 11, 1396–1399.

Hoelgaard, A., Møllgaard, B., Baker, E., 1988. Vehicle effect on topical drug delivery. IV. effect of *N*-methylpyrrolidone and polar lipids on percutaneous drug transport. Int. J. Pharm. 43, 233–240.

Irion, G.D., Garrison, M.D., Abraham, W., 1995. Effect of PGML excipient mixture in a transdermal system on the in vitro transport of estradiol across skin. Pharm. Res. 12, 1618–1622.

Kokubo, T., Sugibayashi, K., Morimoto, Y., 1994. Interaction between drugs and pressure-sensitive adhesives in transdermal therapeutic systems. Pharm. Res. 11, 104–107.

Loth, H., 1991. Vehicular influence on transdermal drug penetration. Int. J. Pharm. 68, 1–10.

Møllgaard, B., Hoelgaard, A., 1983a. Vehicle effect in topical drug delivery I. influence of glycols and drug concentration on skin transport. Acta. Pharm. Suec. 20, 433–442.

Møllgaard, B., Hoelgaard, A., 1983b. Permeation of estradiol through the skin-effect of vehicles. Int. J. Pharm. 15, 185–197.

Niazy, E.M., Molokhia, A.M., El-Gorashi, A.S., 1990. Effect of vehicle and drug concentration on transdermal delivery of dehydroergotamine using excised animal skin. Drug Dev. Ind. Pharm. 16, 1697–1715.

Twist, J.N., Zatz, J.L., 1989. The effect of solvents on solute penetration through fuzzy rat skin in vitro. J. Soc. Cosmet. Chem. 40, 231–242.

Walters, K.A., Hadgraft, J., 1993. Pharmaceutical Skin Penetration Enhancement. Marcel Dekker, New York.