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Effect of vehicles and penetration enhancers on the in vitro percutaneous absorption of tenoxicam through hairless mouse skin

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Abstract

The effects of vehicles and penetration enhancers on the in vitro permeation of tenoxicam from saturated solutions through dorsal hairless mouse skin were investigated. Various types of vehicles, including ester-, alcohol-, and ether-types and their mixtures, were used as vehicles, and then a series of fatty acids and amines were employed as enhancers, respectively. Even though the fluxes of tenoxicam from saturated pure vehicles were generally low (0.1–1.1 $\mu g/cm^2$ per h), the skin permeability of tenoxicam was significantly increased by the combination of diethylene glycol monoethyl ether (DGME) and propylene glycol monolaurate (PGML) or propylene glycol monocaprylate (PGMC); the highest fluxes were achieved at 40% of DGME in both of the two cosolvents. The marked synergistic enhancement was also obtained by using propylene glycol (PG)–oleyl alcohol (OAl) cosolvent. The greatest flux was attained by the addition of unsaturated fatty acids at 3% concentration to PG. But saturated fatty acids failed to show a significant enhancing effect. The enhancement factors with the addition of oleic acid (OA) or linoleic acid (LOA) to PG were 348 and 238, respectively. Tromethamine (TM) showed an enhancing effect by the increased solubility; however, triethanolamine (TEA) did not show a significant enhancing effect. Rather, it decreased the fluxes of tenoxicam when added to PG with fatty acids. The above results indicate that the combinations of lipophilic vehicles like OA, LOA or OAl and hydrophilic vehicles like PG can be used for enhancing the skin permeation of tenoxicam.

Keywords: Percutaneous absorption; Tenoxicam; Penetration enhancers; Fatty acids; Amines

1. Introduction

Tenoxicam is a nonsteroidal anti-inflammtory drug (NSAID) of the oxicam group with potent anti-inflammatory and analgesic actions by inhibiting prostaglandin synthesis (Morof et al., 1988). Like other oxicam derivatives, tenoxicam has been found to be about 99% protein bound with a mean elimination half-life of 67 h, which allows the administration of a daily single oral dose of 20 mg (Nilson, 1994). Tenoxicam is completely absorbed by oral administration (Heintz et

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al., 1984); however, its oral route has been associated with many gastrointestinal side effects (Caughey and Waterworth, 1989).

Since the transdermal delivery reduces the gastrointestinal problem, it has been recognized as an alternative route to oral delivery (Ansel et al., 1995). In addition, the transdermal delivery has the following general advantages: avoidance of first-pass metabolism by oral administration, and constant maintenance of plasma drug concentration. Some studies have been carried out in order to predict percutaneous absorption of NSAIDs, including tenoxicam (Cordero et al., 1997). It was found that the percutaneous activity of tenoxicam was about two to five times higher than that of indomethacin and acemetacin in a study, which assessed the efficacy of cutaneously applied NSAIDs; this suggested that tenoxicam can be recommended for lipophilic skin preparations (Bernhard and Bernhard, 2000).

The stratum corneum is known to have an excellent barrier property against skin penetration. Four mechanisms have been suggested to overcome this problem. One possible mechanism is the reduction of skin resistance as a permeability barrier by disruption of tightly packed lipid regions of stratum corneum, which consequently increases penetration through the intercellular lipid matrix (Barry, 1987). Another mechanism is increased skin/vehicle partitioning of the drug. Green et al. (1988) reported that the permeation enhancement of naphazoline by fatty acids could be caused by ion pair formation between drug and fatty acids, resulting in the increase of partitioning into the stratum corneum. A third likely mechanism of skin permeation enhancement is increased solvent transport into or across the skin. The results of increased solvent penetration may include increased drug solubility in the skin and increased skin penetration of the drug if the drug has a high affinity for the solvent (Yamada et al., 1987). The remaining proposed mechanism is increased drug solubility in the vehicle. Generally, acidic enhancers have been used to increase the solubility of basic drugs, and vice versa (Aungst et al., 1990).

The objective of this paper was to examine the effect of pure solvents, cosolvents and penetration enhancers on the in vitro permeation of tenoxicam from saturated solution through dorsal hairless mouse skin.

2. Materials and methods

2.1. Materials

Tenoxicam and piroxicam were kindly provided by Dong-A Pharm. Co., Ltd. (Seoul, Korea). Propylene glycol monolaurate (PGML, Lauroglycol® 90), propylene glycol laurate (PGL, Lauroglycol® FCC), propylene glycol monocaprylate (PGMC, Capryol® 90), diethylene glycol monoethyl ether (DGME, Transcutol® P), caprylocaproyl macrogol-6 glycerides (LBS, Labrasol®), oleoyl macrogol-6 glycerides [LBF 1944, Labrafil® (LBF) M 1944 CS], linoleoyl macrogol-6 glycerides (LBF 2125, LBF M 2125 CS), polyethylene glycol-8 glyceryl linoleate (LBF 2609, LBF WL 2609 BS) (Gattefossé, Gennevilliers Cedex, France), and propylene glycol dicaprylate/caprate (CT 200, Captex® 200) was obtained from Abitec Corp. (Columbus, OH, USA). Oleyl alcohol (OAl), triethanolamine (TEA), polyethylene glycol 400 (PEG 400), propylene glycol (PG), ethanol, *n*-octanol, and chloroform were of analytical grade. Acetonitrile and methanol used were of high-performance liquid chromatography (HPLC) grade. Isopropyl myristate (IPM), lauric acid, oleic acid (OA), linoleic acid (LOA), capric acid, caprylic acid, tromethamine (TM) and prazosin hydrochloride were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Other reagents were of analytical grade.

2.2. Analysis

Samples from solubility and permeation studies were analyzed by HPLC. The HPLC system consisted of a pump (Model SCL-100, Samsung, Korea) with a detector (Model LC 90, Perkin–Elmer, USA) set at 355 nm and an integrator (Model 4290, Varian, USA). An ODS column (Bondapak C_{18}, Waters, USA) equipped with a C_{18} Radial Pak insert was used. The mobile phase was composed of pH 2.8 phosphate buffer

and acetonitrile (65:35), and delivered at a flow rate of 1.0 ml/min. The injection volume was 20 μl. The internal standard used was prazosin hydrochloride. A calibration curve was constructed based on peak area measurements.

2.3. Solubility determination

An excess amount of tenoxicam was added to the various pure solvents, cosolvents or aqueous buffered solutions (pH 0.92–9.95), and shaken at 32 °C for more than 48 h. The buffers used were KCl–HCl buffer for pH 0.92, phosphate buffers for pH 2.12–7.94, and boric acid buffers for pH 8.95–9.95. The solutions were then centrifuged at 10 000 rpm for 5 min, and the supernatant was assayed by HPLC after appropriate dilution.

2.4. Determination of n-octanol/water partition coefficient (P_c)

n-Octanol and water were saturated with each other for 24 h before the experiment. Tenoxicam solution (100 μg/ml) was prepared with water saturated with *n*-octanol. One milliliter of this solution was then transferred to 10 ml centrifuge tube containing 1 ml of *n*-octanol saturated with water. The tube was vortexed for 3 min and centrifuged at $3000 \times g$ for 5 min. After centrifugation, 100 μl was withdrawn from water phase and *n*-octanol phase, respectively, and the intrinsic P_c was determined by HPLC.

2.5. Preparation of saturated solutions

To determine the effects of various vehicles and enhancers on the permeation of tenoxicam, an excess amount of tenoxicam was added to the pure solvents or cosolvents with/without enhancers, and shaken at 32 °C for 24 h.

2.6. Procedure for skin permeation in vitro

Male hairless mice aged 6–8 weeks were used. After sacrificing with ether, the dorsal skin of each hairless mouse was excised, and the full skin thickness was measured using dial thickness gauge (Mitutoyo, Japan, 0.01–10 mm). And then it was mounted on a side-by-side permeation system; the dermal side was in contact with the receptor compartment. Receptor compartment cells were filled with 3 ml of 40% PEG 400 in saline and the media were stirred by a Teflon-coated magnetic bar to keep them well mixed. Donor compartment was filled with 3 ml of saturated tenoxicam solutions in various pure solvents or cosolvents. At predetermined time intervals, 100 μl of receptor solutions were withdrawn, and the permeated amount of tenoxicam was determined by HPLC. The skin permeation studies were performed at 32 °C.

2.7. Data analysis

As described by Barry (1983), the steady-state flux (J_s), lag time (T_L), diffusion coefficient (D), skin/vehicle partition coefficient (K), and apparent permeation coefficient (P_{app}) are defined by Eqs. (1)–(3).

$$J_s = \left(\frac{dQ}{dt}\right)_{ss}\frac{1}{A} = \frac{DKC}{h} \quad (1)$$

$$D = \frac{h^2}{6T_L} \quad (2)$$

$$P_{app} = \frac{dQ}{dt}\frac{1}{A}\frac{1}{C_s} \quad (3)$$

where, A is the effective diffusion area; h, the thickness of skin; C, the constant concentration of the donor solution; C_s, the drug concentration in the saturated solution and $(dQ/dt)_{ss}$ is the steady-state slope.

3. Results and discussion

3.1. Effect of pure solvents

It was suggested that the flux of a drug molecule could be enhanced by chemicals possessing the ability to alter the structure of lipophilic and/or keratinized domains in stratum corneum (Walters, 1989). Table 1 shows the effects of various pure vehicles in saturated solution formulations on the percutaneous penetration profile of tenoxicam. This result indicates that the perme-

Table 1
Permeation parameters of tenoxicam through excised hairless mouse skin from saturated solutions in various pure vehicles

Vehicle	J_s (μg/cm^2 per h)	T_L (h)	P_{app} ($\times 10^7$, cm/s)	Solubility (mg/ml)
Water	0.15 ± 0.04	3.47 ± 1.05	3.13 ± 0.76	10 ± 0.006
Ethanol	0.47 ± 0.30	4.22 ± 1.22	1.90 ± 1.21	0.69 ± 0.20
PEG 400	0.11 ± 0.01	NA	0.03 ± 0.004	11.0 ± 0.17
PG	0.12 ± 0.06	2.26 ± 2.12	0.34 ± 0.18	0.95 ± 0.19
PGL	1.06 ± 0.39	5.60 ± 0.69	5.90 ± 2.17	0.50 ± 0.03
LBS	0.15 ± 0.14	NA	0.10 ± 0.09	4.34 ± 0.09
DGME	1.13 ± 0.42	5.16 ± 1.66	0.66 ± 0.24	4.74 ± 0.03
PGMC	1.02 ± 0.35	3.52 ± 1.84	2.24 ± 0.78	1.27 ± 0.04
PGML	0.93 ± 0.14	5.10 ± 0.58	4.42 ± 0.68	0.59 ± 0.008
IPM	0.45 ± 0.05	NA	7.65 ± 0.93	0.16 ± 0.03
OAl	0.31 ± 0.08	NA	38.1 ± 10.7	0.02 ± 0.0002
CT 200	1.06 ± 0.57	2.82 ± 1.82	7.10 ± 3.79	0.42 ± 0.02
LBF 1944	0.28 ± 0.04	4.59 ± 0.59	1.13 ± 0.17	0.69 ± 0.21
LBF 2125	0.83 ± 0.95	3.39 ± 1.42	4.27 ± 4.87	0.54 ± 0.05
LBF 2609	0.48 ± 0.36	5.93 ± 1.92	1.06 ± 0.81	1.25 ± 0.03

Data were expressed as the mean $\pm$ S.D. ($n = 3$). NA, not available.

ation fluxes of tenoxicam from saturated solutions in various vehicles were generally low (0.1–1.1 μg/cm^2 per h), and no individual vehicle possessed the necessary intrinsic activity to dramatically promote the permeation. The solubility of tenoxicam at 32 °C in various vehicles decreased in the rank order of PEG 400 $\gg$ DGME > LBS > PGMC > LBF - 2609 > PG > EtOH $\approx$ LBF - 1944 > PGML > LBF - 2125 > PGL = CT 200 > IPM > water > OAl; and solubility in water was very low, around 0.10 mg/ml.

Roy and Flynn (1988) suggested that the transdermal transport of a drug is related to its physicochemical characteristics. Tenoxicam has a relatively large molecular weight (337.4), high melting point (209–213 °C), low intrinsic solubility in water, and low intrinsic P_c (0.42 ± 0.05) compared with ketoprofen, which is known to have high permeability; the molecular weight, melting point, intrinsic solubility in water, and intrinsic P_c of ketoprofen are reported to be 254.3, 94 °C, 0.29 ± 0.008 mg/ml, and 5.2 ± 0.01, respectively (Cordero et al., 1997). Therefore, it was thought that the low permeation fluxes of tenoxicam in various pure vehicles are possibly due to its physicochemical properties as mentioned above. Thermodynamic activity was considered to be constant, because saturated tenoxicam solutions were used in this study.

3.2. Effect of cosolvents

The effects of cosolvents containing DGME–PGML, DGME–PGMC and PG–OAl on the tenoxicam permeation were investigated. Fig. 1 shows the fluxes of tenoxicam permeated across hairless mouse skin from saturated solutions with various ratios of DGME–PGMC and DGME–PGML cosolvents. Both of the two cosolvents showed the highest fluxes at 40% of DGME,

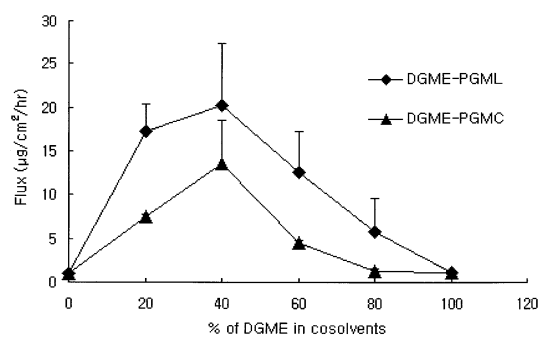

Fig. 1. Effect of DGME concentration (%) in PGML–DGME and PGMC–DGME cosolvents on the steady-state flux of tenoxicam through excised hairless mouse skin ($n = 3$). Donor dose was a saturated solution in each vehicle.

Table 2
Solubility of tenoxicam in various ratio of DGME–PGMC and DGME–PGML cosolvents at 32 °C

DGME–PGMC		DGME–PGML	
Ratio (v/v)	Solubility (mg/ml)	Ratio (v/v)	Solubility (mg/ml)
0:100	1.27 ± 0.04	0:100	0.59 ± 0.01
20:80	1.33 ± 0.05	20:80	0.82 ± 0.11
40:60	1.85 ± 0.04	40:60	1.52 ± 0.12
60:40	2.69 ± 0.74	60:40	2.23 ± 0.36
80:20	3.60 ± 0.13	80:20	3.23 ± 0.40
100:0	4.74 ± 0.03	100:0	4.74 ± 0.03

Data were expressed as the mean ± S.D. ($n = 3$).

which were 13.6 ± 7.9 and 20.3 ± 7.0 μg/cm^2 per h, respectively. Although, the solubility of tenoxicam in the two cosolvents increased as the concentration of DGME increased as shown in Table 2, these fluxes were 13–20 times greater than that of PGMC, PGML or DGME alone.

The marked synergistic enhancement was also achieved by using PG–OAl cosolvent. As Fig. 2 illustrates, the binary cosolvents showed very high fluxes of 29.0 ± 11.2 μg/cm^2 per h at the 80:20 ratio and 22.8 ± 8.79 μg/cm^2 per h at the 50:50 ratio; using PG and OAl alone, fluxes were 0.12 ± 0.06 and 0.31 ± 0.09 μg/cm^2 per h, respectively. Expectedly, the solubility of tenoxicam in the cosolvents decreased as the concentration of OAl increased, which were 0.95 ± 0.18, 0.85 ± 0.06, 0.44 ± 0.01, and 0.02 ± 0.0002 mg/ml at the 0, 20, 50 and 100% OAl in PG, respectively.

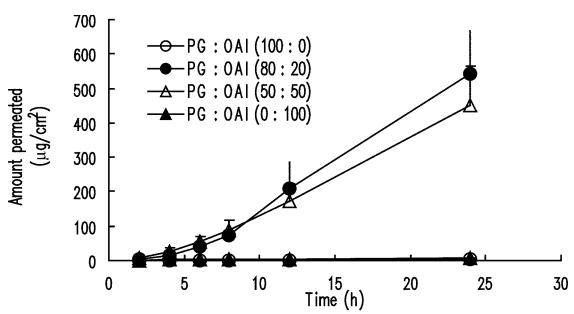

Fig. 2. Effect of PG–OAl cosolvents on the permeation of tenoxicam through excised hairless mouse skin as a function of time. Donor dose was a saturated solution in each vehicle. Data were expressed as the mean ± S.D. ($n = 3$).

It has been suggested that penetrants with both hydrophilic and lipophilic properties probably penetrate the stratum corneum most readily, because there is a physical-chemical evidence of separate hydrophilic and lipophilic domains in the barrier area, as shown in morphological and biochemical studies (Elias, 1983). Other studies demonstrated that the use of fatty alcohols in conjunction with a polar solvent like PG significantly enhanced skin permeation of acyclovir and salicylic acid (Cooper, 1984; Cooper et al., 1985).

The mechanism of fatty alcohols has been explored in many studies. Kitagawa et al. (1985) suggested that fatty alcohols increase lipid fluidization in the stratum corneum by interacting with phospholipids at the boundary lipid layer, but less than their acid analogues. It has been also reported that skin permeability increases with increasing chain length due to the increased distribution of fatty alcohols from aqueous vehicles to the skin (Scheuplein and Blank, 1971).

3.3. Effect of enhancers

Fatty acids are also known to be enhancers with lipophilic properties, and many studies have shown that the skin permeability enhancing effects of fatty acids are greatest with PG vehicles (Cooper, 1984; Cooper et al., 1985; Aungst et al., 1986; Yamada et al., 1987). The binary system was considered to disorganize the multilaminate hydrophilic–lipophilic layers located intercellularly in the stratum corneum, consequently promoting percutaneous absorption of drugs (Nomura et al., 1990).

We investigated the effect of various fatty acids on the tenoxcam permeation. Five fatty acids were compared: three were saturated fatty acids—C_8 (caprylic acid), C_{10} (capric acid) and C_{12} (lauric acid); and two were unsaturated fatty acids—C_{18} with one double bond (OA), and C_{18} with two double bonds (LOA). Aungst et al. (1986) reported that the most effective saturated fatty acids were C_{10}–C_{12} chain lengths for naloxone permeation enhancement. As shown in Table 3, the increase in the chain length of saturated

Table 3
Permeation parameters of tenoxicam through excised hairless mouse skin from PG containing enhancers

Fatty acids	Permeation parameters				
	J_s (μg/cm^2 per h)	T_L (h)	D ($\times 10^5$, cm^2/h)	K	P_{app} ($\times 10^7$, cm/s)
No enhancer	0.12 ± 0.06	2.26 ± 2.12	17.7 ± 16.2	0.07 ± 0.09	0.34 ± 0.17
Caprylic acid (3%)	0.53 ± 0.31	2.71 ± 1.38	4.79 ± 2.44	0.30 ± 0.02	1.56 ± 0.90
Capric acid (3%)	0.72 ± 0.52	3.30 ± 0.96	6.85 ± 4.00	0.38 ± 0.13	2.11 ± 1.53
Lauric acid (3%)	1.18 ± 0.96	4.34 ± 1.09	4.39 ± 3.33	0.87 ± 0.32	3.43 ± 2.80
OA (3%)	41.8 ± 6.84	2.89 ± 0.39	3.82 ± 3.22	35.4 ± 15.5	122 ± 20.0
OA (5%)	8.74 ± 1.20	3.52 ± 0.73	5.02 ± 0.74	5.92 ± 0.57	25.5 ± 3.52
LOA (3%)	28.5 ± 8.55	5.90 ± 0.84	1.52 ± 0.71	52.0 ± 31.9	83.3 ± 25.0

Data were expressed as the mean $\pm$ S.D. ($n = 3$).

fatty acids resulted in the increase in the enhancement of tenoxicam permeation. However, their enhancing effects were very low compared with those of unsaturated fatty acids. OA and LOA at 3% concentration in PG showed very high enhancing effects; their enhancement factors were 348 and 238, respectively. When the concentration of OA increased to 5%, the enhancing effect on tenoxicam permeation decreased. The results of enhancing effects by unsaturated fatty acids are consistent with the study of Santoyo et al. (1995). The authors reported that OA was the most potent penetration enhancer for piroxicam penetration through excised abdominal rat skin from carbopol gels containing 40% PG. They also suggested that LOA had a significant enhancing effect.

The mechanism of OA as a penetration enhancer in this study was attributed to the partitioning rate and its skin disturbance. As shown in Table 3, the parameter K increased markedly with the addition of 3% OA. As Barry (1983) suggested, under many conditions, the surface layers of membrane rapidly equilibrate with the adjacent phases; these equilibria can be expressed in terms of K. Although, the addition of LOA showed higher K, the J_s was lower than that of OA, due to the decreased D.

Barry (1987) explored the mechanism of OA as a penetration enhancer using differential scanning calorimetry (DSC) of human stratum corneum. He demonstrated that OA melts the lipid chain portion buried within the bilayer structure, together with some non-polar material. It also breaks associations between lipid polar groups together with disruption of cholesterol-stiffened regions. It was proposed that the *cis* double bond at C_9 on OA causes a kink in the alkyl chain, which is likely to disrupt the ordered array of the predominantly saturated straight chain skin lipids and increase the fluidity of the lipid regions (Barry, 1987; Golden et al., 1987).

Barry (1987) further explored the mechanism of PG using DSC, and reported that it appears to solvate alpha-keratin and occupy hydrogen-bonding sites, thus reduces drug–tissue binding.

The pK_a of tenoxicam is known to be about 5.5 (Albengres et al., 1993). Consequently, as Fig. 3 depicts, the solubility of tenoxicam was very low at pHs below the pK_a, and it increased exponentially from pH 6 to 9, which are above the pK_a. Increasing the drug solubility can be one of the

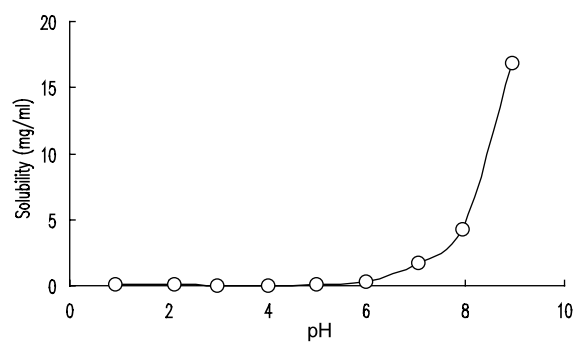

Fig. 3.

Fig. 3. Effect of pH on the solubility of tenoxicam at 32 °C.

Table 4
Permeation parameters of tenoxicam through excised hairless mouse skin from PG containing fatty acids and/or amines

Enhancers	Permeation parameters		
	J_s (μg/cm^2 per h)	T_L (h)	P_{app} ($\times 10^7$, cm/s)
None	0.12 ± 0.06	2.26 ± 2.12	0.34 ± 0.17
TEA (1%)	0.44 ± 0.26	3.25 ± 0.38	0.05 ± 0.03
TM (1%)	2.39 ± 3.09	NA	0.41 ± 0.54
TEA (1%) + OA (3%)	27.0 ± 14.0	7.41 ± 3.29	5.26 ± 2.68
TEA (1%)+ LOA (3%)	3.69 ± 2.13	10.8 ± 0.41	0.70 ± 0.41
TM (1%)+ OA (3%)	19.3 ± 10.5	9.96 ± 0.65	3.69 ± 2.00
OA (3%)	41.8 ± 6.84	2.89 ± 0.39	122 ± 20.0
LOA (3%)	28.5 ± 8.55	5.90 ± 0.84	83.3 ± 25.0

Data were expressed as the mean $\pm$ S.D. ($n = 3$). NA,: not available.

mechanisms for increasing the flux, using the equation of $J = DKC/h$. Some studies showed that the increase in the solubility of indomethacin by the addition of dodecylamine could completely account for the increased flux, because, P_{app} was unchanged (Aungst et al., 1990). In this study, TEA and TM were used to examine the penetration enhancing effect of tenoxicam by increasing the solubility.

As shown in Table 4, TM increased the permeation flux 20-fold; however, TEA did not show a significant enhancing effect on the tenoxicam permeation when added to PG. The permeation enhancing effect by the addition of TM could be attributed to the increased solubility of tenoxicam, because of the unchanged P_{app}. The addition of TEA to PG with either OA or LOA decreased the permeation fluxes even though solubility markedly increased, which resulted in a considerable decrease in P_{app}. It was thought that the flux was reduced by the decreased enhancing effect by fatty acids, probably due to the interaction between fatty acids and amines. T_L was significantly prolonged with the addition of amines to PG with fatty acids, which was possibly caused by the decrease in the diffusion of tenoxicam. The permeation rate of tenoxicam with the addition of amines to PG with fatty acids decreased; however, the permeation fluxes of tenoxicam were still greater than those with the addition of amines to PG without fatty acids, especially when using OA as a fatty acid.

In conclusion, for effective solution formulations, combinations of lipophilic vehicles like OA, or OAl and hydrophilic vehicles like PG could be used to enhance the skin permeation of tenoxicam.

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