

RESEARCH PAPER

Transdermal Delivery of Ketorolac Tromethamine: Effects of Vehicles and Penetration Enhancers

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ABSTRACT

The effects of vehicles and penetration enhancers on the in vitro permeation of ketorolac tromethamine (KT) across excised hairless mouse skins were investigated. Among pure vehicles examined, propylene glycol monolaurate (PGML) showed the highest permeation flux, which was $94.3 \pm 17.3 \mu\text{g}/\text{cm}^2/\text{h}$. Even though propylene glycol monocaprylate (PGMC) alone did not show high permeation rate, the skin permeability of KT was markedly increased by the addition of diethylene glycol monoethyl ether (DGME); the enhancement factors were 19.0 and 17.1 at 20% and 40% of DGME, respectively. When DGME was added to PGML, the permeation fluxes were almost two times at 20–60% of DGME compared to PGML alone. In the cosolvent system consisting of propylene glycol (PG)-oleyl alcohol, the permeation rate increased as the ratio of PG increased. In the study to investigate the effect of drug concentration on the permeation rate of KT, the permeation rates increased as the drug concentration increased in all vehicles used, and the dramatic increase in permeation rate was obtained when the drug concentration was higher than its solubility. For the effects of fatty acids on the permeation of KT, five fatty acids were added to PG at concentrations of 1%-, 3%-, 5%- and 10%- caprylic acid, capric acid, lauric acid, oleic acid, and linoleic acid. The enhancing effects of fatty acids were different, depending on the concentration as well as the sort of fatty acids. The highest enhancing effect was attained with 10% caprylic acid in PG; the permeation flux was $113.6 \pm 17.5 \mu\text{g}/\text{cm}^2/\text{h}$. The lag time of KT was reduced as the concentration of fatty acids increased except for caprylic acid.

Key Words: Transdermal delivery; Ketorolac tromethamine; Vehicles; Penetration enhancers.

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INTRODUCTION

Ketorolac is a nonsteroidal anti-inflammatory drug with potent analgesic and moderate anti-inflammatory activities by inhibiting prostaglandin synthesis.^[1,2] Unlike narcotic analgesics, ketorolac does not alter gastric motility or hemodynamic variables or adversely affect respiration, nor it is associated with adverse central nervous system effects, abuse, or addiction potential; therefore, ketorolac is a relatively more favorable therapeutic agent for the management of moderate to severe pain.^[3] Ketorolac (as the tromethamine salt) is currently administered intramuscularly, intravenously, or orally. Although oral bioavailability of ketorolac was reported to be 90% with a very low first-pass metabolism, its short biological half-life (4–6 h) and many adverse effects, such as upper abdominal pain and gastrointestinal ulceration, restrict its oral use.^[1,4]

To avoid invasive drug therapy such as injections and to eliminate frequent dosing regimen with oral administration, a transdermal drug delivery system has been studied as an alternative dosage form. In addition to the noninvasive therapy and maintaining the drug blood levels for an extended period of time, the transdermal delivery system has several advantages: it avoids first-pass metabolism, it is easy to discontinue the administration, and it reduces side effects. Despite these advantages, only a limited number of drugs can be administered percutaneously, due to low skin permeability of most drugs through the skin. The stratum corneum was recognized as an excellent barrier against skin penetration. To overcome this problem, vehicles, penetration enhancers, and electrotransport-facilitated transdermal systems have been attempted in the development of a transdermal delivery system of ketorolac.^[3,5,6] However, the numbers or kinds of enhancers or vehicles used were very limited.

In the present study, we investigated the effects of various pure solvents, cosolvents, and penetration enhancers on the *in vitro* permeation of ketorolac from solution formulation across hairless mouse skin to examine the feasibility of developing a ketorolac transdermal system.

EXPERIMENTAL

Materials

Ketorolac tromethamine (KT), oleyl alcohol (OAl), caprylic acid, capric acid, lauric acid, oleic acid, and linoleic acid were purchased from Sigma Chemical Co. (St. Louis, MO). Propylene glycol laurate (PGL,

Lauroglycol[®] FCC), propylene glycol monocaprylate (PGMC, Capryol[®] 90), propylene glycol monolaurate (PGML, Lauroglycol[®] 90), caprylocaproyl macrogol-6 glycerides (LBS, Labrasol[®]), oleyl macrogol-6 glycerides (1944, Labrafil[®] (LBF) M 1944 CS), linoleoyl macrogol-6 glycerides (2125, LBF M 2125 CS), polyethylene glycol-8 glyceryl linoleate (2609, LBF WL 2609 BS), and diethylene glycol monoethyl ether (DGME, Transcutol[®] P) (Gattefossé, Gennevilliers Cedex, France) were used. Propylene glycol (PG), isopropyl myristate (IPM), and ethanol were of analytical grade. Acetonitrile and methanol used were of HPLC grade. Other reagents were of analytical grade.

Analysis

Samples from solubility and permeation studies were analyzed by a high-performance liquid chromatography (HPLC) system (Shimadzu Scientific Instruments, Tokyo, Japan), consisting of a pump (LC-10AD), an automatic injector (SIL-10A), and an ultraviolet detector (SPD-10A) set at 300 nm. An ODS column (μ Bondapak C18, 3.9×300 mm, $10 \mu\text{m}$, Waters, Milford, MA) was used. The mobile phase was composed of acetonitrile, methanol, water, and triethylamine (45:10:45:0.1, v/v), whose pH was adjusted to 3.2 by phosphoric acid, and delivered at a flow rate of 1.0 mL/min. The injection volume was 50 μL . A calibration curve was constructed based on peak area measurements.

Methods

Solubility Determination

An excess amount of KT was added to the various pure solvents or cosolvents, and shaken at 37°C for more than 48 h. The solutions were then centrifuged at 7500 rpm for 5 min, and the supernatant was assayed by HPLC after appropriate dilution.

Preparation of Donor Solutions

To determine the effects of various vehicles and enhancers on the permeation of KT, appropriate amounts of KT were dissolved in pure solvent or cosolvents. For the preparation of saturated solutions, KT suspension was shaken at 37°C for 24 h before permeation experiments.

Procedure for Skin Permeation *In Vitro*

Male hairless mice aged 6–8 weeks were used. After sacrificing with ether, the skin of each hairless



mouse was excised and then was mounted on a flow-through diffusion cell system consisting of a multi-channel peristaltic pump (205S, Watson Marlow, North Wilmington, MA), a fraction collector (Retriever IV, ISCO, Lincoln, NE), and a circulating water bath (RB-10, Jeo Tech, Kimpo, Korea). The surface area of the receiver cell opening was 2 cm², and the cell volume was 5.5 mL. The receiver cells were filled with pH 7.4 isotonic phosphate buffer solution, and the media were stirred by a Teflon-coated magnetic bar to keep them well mixed. Donor compartment was filled with 300 µL of KT solution or suspension in various pure solvents or cosolvents. The skin permeation studies were performed at 37°C.

Data Analysis

The permeation data were analyzed by the method developed for the flow-through diffusion cell system.^[7] 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).^[8]

$$J_s = (dQ/dt)_{ss} \cdot 1/A = DKC/h \quad (1)$$

$$D = h^2/6T_L \quad (2)$$

$$P_{app} = dQ/dt \cdot 1/A \cdot 1/C \quad (3)$$

where

A = the effective diffusion area,

h = the thickness of skin,

C = the constant concentration of the donor solution, and

$(dQ/dt)_{ss}$ = the steady-state slope.

RESULTS AND DISCUSSION

Effect of Vehicles

The permeation parameters of KT from different vehicles across the excised hairless mouse skin are listed in Table 1. The steady-state flux of KT from water was found to be 3.25 ± 1.14 µg/cm²/h. Among various types of vehicles, ester-type vehicles showed relatively high enhancing effects. Especially, PGML resulted in the highest enhancing effect when a fixed drug concentration of 5 mg/mL was used; its enhancement factors were 29 and 3.79 compared to water and PGL, respectively. From Eq. (1), the permeation flux is determined by diffusivity, partitioning, and solubility. The high permeation rate of PGML was attributed to the relatively high values of the three determinants. Compared to PGML, PGMC showed lower diffusivity and partitioning. The IPM was not

Table 1. Permeation parameters of KT through excised hairless mouse skin from 5 mg/mL solution or suspension in various pure vehicles.

Solvent	J_s (µg/cm ² /h)	T_L (h)	P_{app} (cm/h, × 1000)	D (cm ² /h, × 10 ⁵)	K	Solubility (mg/mL)
Water	3.25±1.14	8.29±1.10	0.65±0.23	1.83±0.23	1.11±0.53	
DGME	0.69±0.29	3.79±2.79	0.14±0.06	13.4±5.29	0.09±0.05	211±11.0
IPM	13.2±3.35	9.51±1.30	143±36.2	1.60±0.21	278±49.5	0.09±0.01
LBS	0.55±0.22	0.63±0.02	0.11±0.05	23.8±1.92	0.01±0.004	6.1±1.13
2609	1.38±0.43	6.25±1.17	0.64±0.38	2.62±0.94	0.91±0.69	2.16±0.54
1944	34.9±8.59	6.72±0.32	39.7±9.76	2.24±0.11	53.5±14.1	0.88±0.10
2125	30.6±2.56	9.71±2.34	71.9±6.02	1.61±0.41	139±29.7	0.43±0.08
PGL	24.9±16.6	5.27±2.11	4.98±3.32	3.18±1.30	6.11±3.16	10.16±0.91
PGMC	6.08±2.29	9.52±2.47	1.22±0.46	1.63±0.42	2.43±1.47	51.3±5.68
PGML	94.3±17.3	2.36±0.41	18.9±3.46	6.49±1.10	8.53±0.17	15.2±1.87
Alcohol	17.9±12.5	2.64±2.63	6.51±4.54	12.65±10.58	5.04±4.90	2.75±0.57
IPA	12.7±11.8	6.70±3.53	2.54±1.36	2.95±2.07	2.61±2.18	36.7±4.72
OAI	43.2±4.53	4.54±0.17	8.63±0.90	3.31±0.13	7.83±0.83	25.2±1.67
PG	0.78±0.34	NA	0.16±0.06	NA	NA	64.8±4.90
PEG400	0.28±0.15	NA	0.06±0.03	NA	NA	32.0±0.56

Data were expressed as the mean±S.D. (n=3). NA: not available.

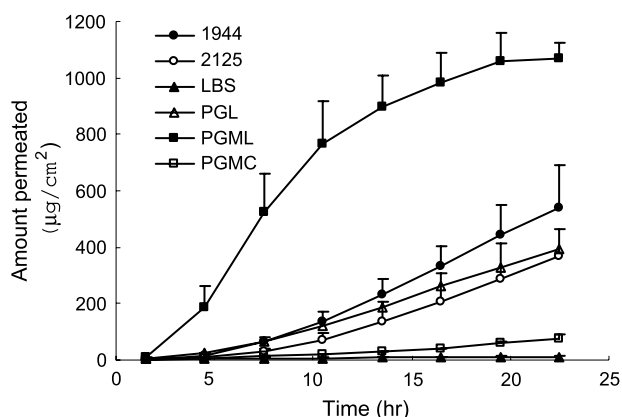


Figure 1. Cumulative amount of KT permeated across hairless mouse skin from 5 mg/mL solution in ester-type vehicles as a function of time ($n=3$).

able to exert a very high enhancing effect, due to the extremely low solubility in spite of very high partitioning. As depicted in Fig. 1, PGML showed a different permeation profile compared to other ester-type vehicles. It initially provided a very high permeation rate followed by a gradual decrease. A relatively short lag time was obtained with PGML by the high diffusivity. The later decrease in the permeation rate was thought to be due to the rapid drop in drug concentration in the donor compartment.

Among alcohol-type vehicles, OAl showed a high permeation rate, possibly due to the high partitioning. Even though the IPA permeation flux slightly increased as the drug concentration increased from 5 to 30 $\mu\text{g/mL}$, it increased dramatically as the drug concentration increased from 30 to 50 $\mu\text{g/mL}$ as described in Table 2. This was attributed to the maximized thermodynamic activity at the concentration of which the drug was above its solubility. This trend was observed in most vehicles. Four pure vehicles, DGME, PGMC, PGML, and IPA and two cosolvents, DGME-PGMC (4:6) and DGME-PGML (4:6) were employed to investigate the effect of drug concentration on the permeation of KT. As shown in Table 2, permeation flux increased as the drug concentration increased; the marked increase of permeation flux was observed when the drug concentration increased above the drug solubility. However, permeability coefficient decreased as the drug concentration increased with exception of PGMC and PGML.

It has been suggested that vehicles may act as permeation enhancers by increasing the thermodynamic activity of the drug, and the thermodynamic activity and drug solubility in the vehicle have an inverse relationship in the absence of solvent-induced skin damage.^[9] As depicted in Fig. 2, the relationship was not found in this study, indicating that permeation profiles are caused by the change in the skin barrier property with time as well as the change in driving force. Thus, to achieve high penetration rate, vehicles

Table 2. Effect of the drug concentration on the permeation parameters of KT from various pure vehicles and cosolvents.

Solvent (solubility, mg/mL)	Dose (mg/mL)	J_s ($\mu\text{g}/\text{cm}^2/\text{h}$)	T_L (h)	P_{app} (cm/h, $\times 1000$)
DGME (211)	5	0.69 ± 0.29	3.79 ± 2.79	0.14 ± 0.06
	30	3.43 ± 0.02	6.56 ± 2.18	0.11 ± 0.001
	200	14.8 ± 1.22	10.1 ± 1.98	0.07 ± 0.01
PGMC (51.3)	5	6.08 ± 2.29	9.52 ± 2.47	1.22 ± 0.46
	30	70.4 ± 9.78	3.99 ± 1.78	2.35 ± 0.33
	200	1362 ± 31.6	5.54 ± 1.43	26.6 ± 0.61
PGML (15.2)	5	94.3 ± 17.3	2.36 ± 0.41	18.9 ± 3.46
	30	415 ± 19.5	4.70 ± 0.73	27.4 ± 1.29
	50	629 ± 67.1	1.99 ± 0.74	41.5 ± 4.43
IPA (36.7)	5	12.7 ± 11.8	6.70 ± 3.53	2.54 ± 1.36
	30	14.7 ± 4.60	0.73 ± 0.44	0.29 ± 0.09
	50	43.9 ± 5.73	1.98 ± 1.01	1.20 ± 0.15
DGME/PGMC 4/6 (69.4)	5	104 ± 13.1	6.79 ± 0.27	20.8 ± 2.62
	30	405 ± 23.9	11.3 ± 0.76	13.5 ± 0.80
	50	526 ± 34.1	11.0 ± 1.09	10.5 ± 0.68
DGME/PGML 4/6 (85.6)	5	183 ± 13.3	12.6 ± 0.10	36.5 ± 2.66
	30	435 ± 35.5	5.75 ± 0.44	14.5 ± 1.18
	50	534 ± 24.2	4.77 ± 0.26	10.7 ± 0.48

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

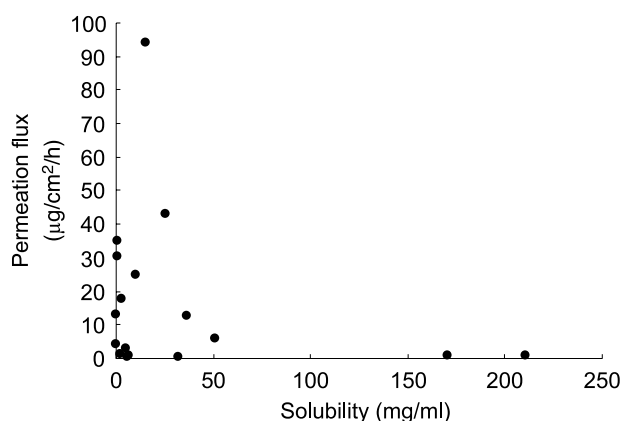


Figure 2. Relationship between KT solubility in various vehicles and the permeation flux from the vehicle.

that can greatly change skin barrier property and have appropriate solubility to solubilize the desired amount of drug while minimizing the decrease of thermodynamic activity, should be employed. To change skin barrier property, several mechanisms have been suggested: the reduction of skin resistance as a permeability barrier by disruption of tightly packed lipid regions of stratum corneum;^[10] increased skin/vehicle partitioning of the drug;^[11] and increased solvent transport into or across the skin.^[12]

As DGME has been reported to have an effect on drug penetration by easing the partition by increasing the solubility of the compound in the skin,^[13] we added it to PGMC or PGML at the concentrations of 20%, 40%, 60% and 80%. Figure 3 reveals the relationship between DGME concentration and permeation flux. The skin permeability of KT from PGMC was markedly increased by the addition of DGME; the enhancement factors were 19.0 and 17.1 at 20% and 40% of DGME, respectively. When DGME was added to PGML, the permeation fluxes were almost two times at 20–60% of DGME compared to PGML alone. The solubility of KT in the binary cosolvent system of DGME-PGMC and DGME-PGML increased as the concentration of DGME increased as follows: 0% DGME (41.0±3.37 and 15.2±1.61 mg/mL), 20% DGME (51.3±5.24 and 50.4±4.43 mg/mL), 40% DGME (69.4±2.10 and 85.6±3.20 mg/mL), 60% DGME (77.3±11.9 and 181.5±19.3 mg/mL), 80% DGME (170.6±17.7 and 209.1±7.07 mg/mL), and 100% DGME (211.0±11.0 mg/mL).

In the cosolvent system consisting of PG-OAl, the permeation rate markedly increased compared to PG alone, while the cosolvent system rarely affected the permeation flux compared to OAl alone. The per-

meation flux (µg/cm²/h) and solubility (mg/mL) of KT in PG-OAl cosolvent at the ratios of 0:100, 20:80, 40:60, 60:40, 80:20 and 100:0 were 43.2±4.53 and 25.2±2.67, 36.3±3.85 and 32.4±4.02, 49.9±7.76 and 80.6±7.97, 56.2±3.52 and 94.8±10.7, 44.4±10.5 and 102.9±8.36, and 0.78±0.34 and 170.3±9.90.

Effect of Enhancers

Fatty acids are 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.^[11,14–16] The binary system was considered to disorganize the multilaminate hydrophilic-lipophilic layers located intercellularly in the stratum corneum, consequently promoting percutaneous absorption of drugs.^[17] Five sorts of fatty acids—C8 (caprylic acid), C10 (capric acid), C12 (lauric acid), C18 with one double bond (oleic acid), and C18 with two double bonds (linoleic acid)—at concentrations of 1%, 3%, 5% and 10% were employed for examining their enhancing effects of KT when they are added to PG.

Compared to PG alone, the addition of fatty acids increased permeation flux regardless of the kind or concentration of fatty acid; the enhancement factor ranged from 1.72 to 146. As shown in Fig. 4, the permeation flux of KT from C8 and C10 increased as the fatty acid concentration increased. The other saturated fatty acid, C12, showed high permeation rate at the concentration of 3–5%. Both unsaturated fatty acids resulted in a relatively high permeation rate in all concentrations tested, and the highest flux was observed at 5% concentration; the flux of KT from

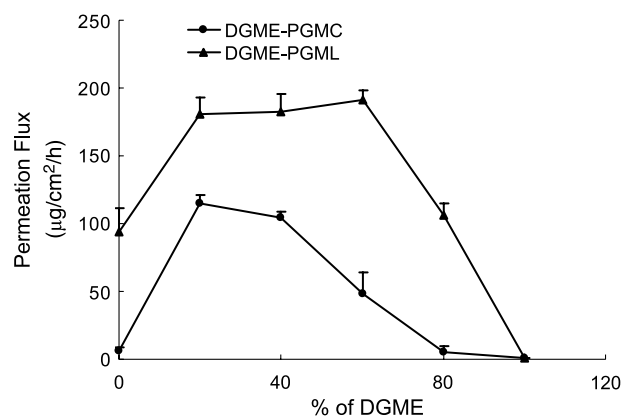


Figure 3. Effect of PGMC-DGME and PGML-DGME cosolvents on the permeation of KT across hairless mouse skin from 5 mg/mL solution as a function of time (n=3).

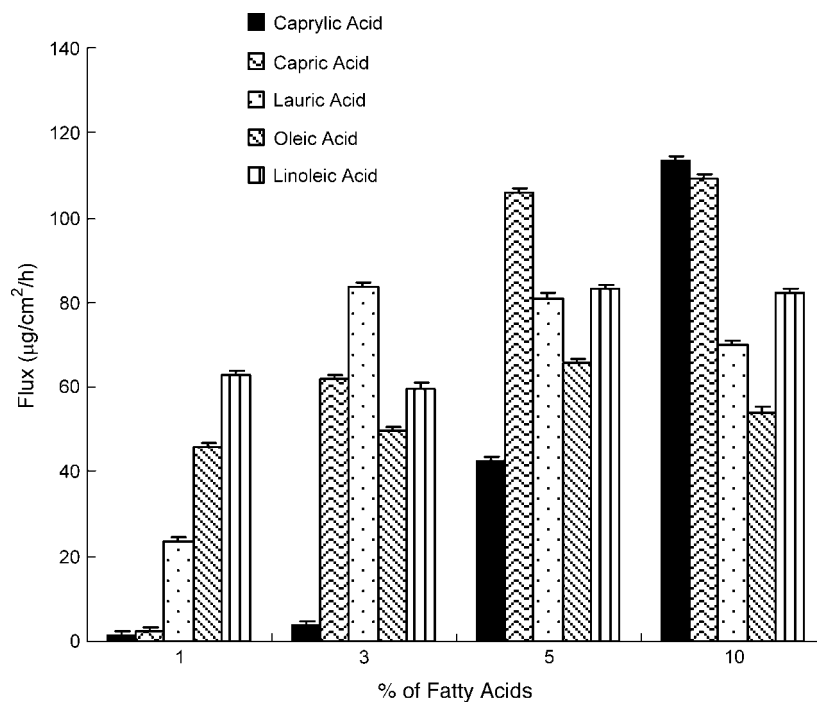


Figure 4. The permeation flux of KT from various concentrations of fatty acids in PG (n=3).

oleic acid and linoleic acid at 5% was 65.8 ± 1.39 and 83.2 ± 3.58 $\mu\text{g}/\text{cm}^2/\text{h}$, respectively. The highest enhancing effect was attained with 10% caprylic acid in PG; the permeation flux was 113.6 ± 17.5 $\mu\text{g}/\text{cm}^2/\text{h}$. It was

reported that the most effective saturated fatty acids were C10~C12 chain lengths for naloxone permeation enhancement.^[16] Also, in our earlier studies of tenoxicam and ondansetron hydrochloride, it was

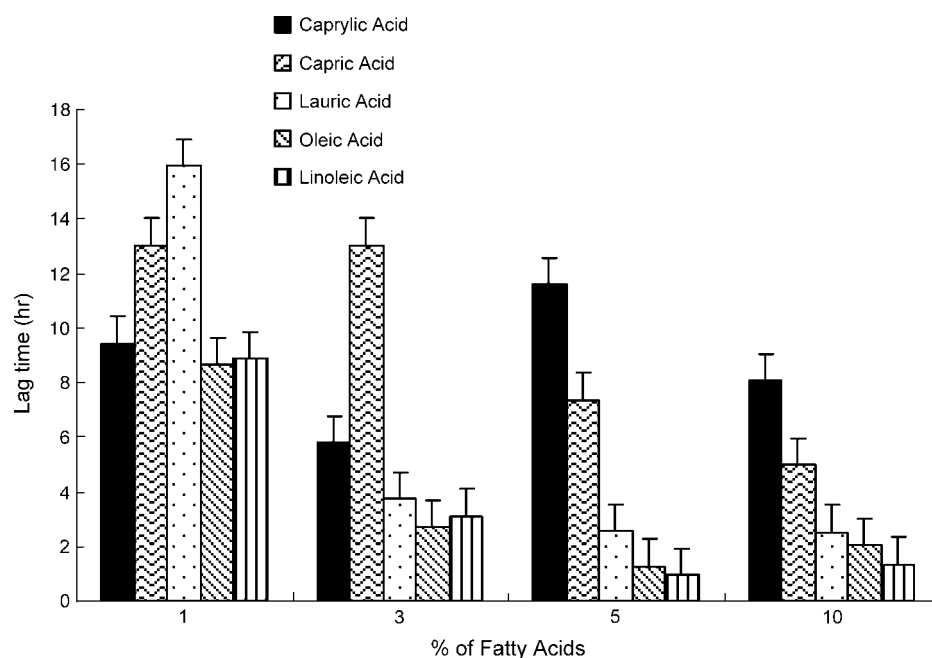


Figure 5. The lag time of KT from various concentrations of fatty acids in PG (n=3).



demonstrated that unsaturated fatty acids such as oleic acid or linoleic acid had the most significant enhancing effects when used with PG.^[18,19] In those studies, the concentrations of fatty acids in PG were 10% in naloxone and 3% in tenoxicam and ondansetron hydrochloride. When fatty acids were used at 3%, the highest enhancing effect for KT permeation was achieved with C12, while it was obtained with C8 at the 10%. From these results, it was suggested that the enhancing effects of fatty acids were different, depending on the concentration as well as the sort of fatty acids.

As plotted in Fig. 5, the lag time of KT was reduced as the concentration of fatty acids increased except for C8, indicating increased diffusivity by the increased concentrations of fatty acids. On the contrary, it was speculated that the enhanced permeation of KT by C8 was mainly due to the increased partitioning of the drug into skin as the concentration of C8 increased, considering that the permeation flux was enhanced without shortening the lag time.

From the results, it was concluded that for effective solution formulations, DGME-PGMC or DGME-PGML cosolvents at the concentrations of 20–60% of DGME, or the addition of fatty acids at the concentrations of 5–10% to PG could be used to enhance the skin permeation of KT. Considering that hairless mouse skin is very sensitive to the effect of enhancers due to its large amount of lipid, however, further investigation using human skin should be explored.^[20]

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