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Formulation and Evaluation of Ketorolac Transdermal Systems

조선대학교 대학원

약학과

조 영 아

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케토로락 경피흡수제제의 설계 및 평가

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이 논문을 약학박사학위신청 논문으로 제출함.

2006 년 4 월 일

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조 영 아

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Abstract

Formulation and Evaluation of Ketorolac Transdermal Systems

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The effects of vehicles and penetration enhancers on the in vitro permeation of ketorolac tromethamine (KT) across excised hairless mouse skins were investigated. By this results, effects of pressure-sensitive adhesives and vehicles on the *in vitro* permeation of ketorolac and *in vivo* pharmacokinetics were studied.

Among pure vehicles examined, propylene glycol monolaurate (PGML) showed the highest permeation flux, which was 94.3 ± 17.3 μg/cm^2/hr. 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 co-solvent 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 the 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 ± 17.5 $\mu g/cm^2/hr$. The lag time of KT was reduced as the concentration of fatty acids increased except for caprylic acid.

Duro-Tak 87-2196® showed the highest *in vitro* permeation profiles, and propylene glycol monolaurate-diethylene glycol monoethyl ether (DGME) (60 : 40, v/v) and propylene glycol monocaprylate-DGME (60 : 40, v/v) revealed the most favorable *in vitro* and *in vivo* results. The decreased C_{max} and prolonged T_{max} and half-life were obtained with the ketorolac transdermal systems compared to oral administration, indicating that the ketorolac transdermal systems may have prolonged effect with reduced toxic event. There was an excellent relationship between *in vitro* permeation flux and *in vivo* $AUC_{0-\infty}$ found.

Key Words: Transdermal delivery, Ketorolac tromethamine, Vehicles, Penetration enhancers, Ketorolac Transdermal Systems, Pharmacokinetics, Pressure-sensitive Adhesives.

국 문 초 록

케토로락 경피흡수제제의 설계 및 평가

조 영 아

지 도 교 수: 최 준 식

조선대학교 대학원 약 학 과

Hairless mouse 피부를 이용하여 여러 용제와 투과촉진제의 ketorolac tromethamine(KT) 투과도 효과를 실험하고 이 결과를 토대로 Pressure-sensitive Adhesives 와 용제의 *in vitro* 상의 투과도와 *in vivo* 의 약물동태학을 연구하였다. 실험한 용제 중에서 propylene glycol monolaurate (PGML) 가 94.3 ± 17.3 μg/cm^2/hr 로 가장 높은 투과 flux 를 나타내었다. propylene glycol monocaprylate (PGMC) 단독으로는 높은 투과력을 보이지 않았지만 diethylene glycol monoethyl ether (DGME)의 첨가에 의해 투과 factor 는 20,40 % 에서 각각 19.0 과 17.1 로 두드러지게 증가하였다. PGML 과 DGME 의 배합시 PGML 단독 투과력 보다 DGME 20-60%에서 거의 두배 가까운 투과력을 나타냈다. propylene glycol (PG)-oleyl alcohol 계 공용제 배합 비율 실험에서 투과율은 PG 증가비 만큼 증가되었고, 모든 용제에서 약물농도가 증가될수록 투과력은 높아졌다. 또한 약물농도가 용해도보다 높은 경우 투과력은 괄목할만하게 증가되는 결과가 나타났다. 5 가지 지방산- caprylic acid, capric acid, lauric acid, oleic acid, linoleic acid 을 1,3,5,10 %의 농도로 PG 에

첨가하였다. 지방산류의 투과 촉진효과는 종류와 농도에 따라서 다르게 나타났다. PG - 10% caprylic acid 배합이 permeation flux 113.6 ± 17.5 μg/cm^2/hr 로 가장 높은 투과 촉진 결과를 보였고 ketorolac tromethamine 의 lag time 은 caprylic acid 를 제외하고 지방산 농도의 증가에 따라 감소되었다.

In vitro 상태에서 감압접착제와 용제의 ketorolac tromethamine 투과력과 *in vivo* 의 약물동태학 실험에서는 Duro-Tak 87-2196® 가 *in vitro* 에서 가장 높은 투과력을 나타냈고 propylene glycol monolaurate-diethylene glycol monoethyl ether (DGME) (60 : 40, v/v) 와 propylene glycol monocaprylate-DGME (60 : 40, v/v)가 in vitro 와 in vivo 에서 가장 좋은 결과를 보였다. Ketorolac 경피 흡수제제는 경구투여제와 비교시 C_{max} 는 감소하고 T_{max}, half-life 는 연장되어지는 결과를 얻었다. 이는 Ketorolac 경피 흡수시스템이 부작용은 감소하면서 효과는 더욱 연장되는 결과를 가질 수 있음을 보여주는 것이다. *In vitro 상태의 투과* flux 와 *in vivo 의* $AUC_{0-\infty}$ 사이엔 뛰어난 상관 관계가 있는 것으로 나타난다.

1. Introduction

Ketorolac tromethamine[(+/-)-5(benzoyl)-2,3-dihydro-1N-pyrrolizine-1-arboxylic acid tris hydroxymethylaminomethane is a nonsteroidal anti-inflammatory drug (NSAID) with potent analgesic and moderate anti-inflammatory activities by inhibiting prostaglandin synthesis (Buckley and Brogden,1990;Rooks et al.,1985). It is administered as the tromethamine salt orally, intramuscularly, intravenously, and as a topical ophthalmic solution.

ketorolac has been reported to have a similar efficacy to narcotic analgesics. Unlike narcotic analgesics, ketorolac does not alter gastric motility or hemodynamic variables or adversely affect respiration, nor it is associated with adverse CNS effects abuse or addiction potential problems. ; therefore ketorolac is a relatively more favorable therapeutic agents for the management of moderate to severe pain (Tiwari,2003).

Clinical studies indicate single-dose efficacy greater than that of morphine, pethidine (meperidine) and pentazocine in moderate to severe postoperative pain, with some evidence of a more favourable adverse effect profile than morphine or pethidine.

In single-dose studies ketorolac has also compared favourably with aspirin, paracetamol (acetaminophen) and a few other non-steroidal anti-inflammatory drugs. Additional multiple-dose studies are required to evaluate fully the potential of ketorolac in the management of chronic pain states where it has shown superior efficacy to aspirin (Buckley and Brogden,1990).

ketorolac will be a useful alternative to opioid agents in postsurgical pain. It may well also find use in acute musculoskeletal pain, where it appears at least as effective as other agents with which it has been compared. From the limited clinical data available, ketorolac also seems promising in the treatment of ocular inflammatory conditions.

A single 10 mg tablet given orally to human volunteers following surgery provided pain relief equivalent to that provided by 10 mg of morphine given intramuscularly (Rooks et al., 1985).

Ketorolac is widely used for various pain reliefs. The efficacy of local anaesthetic infiltration and/or non-steroidal anti-inflammatory drugs for post-operative analgesia following laparoscopic-assisted vaginal hysterectomy (LAVH) was investigated in 83 patients, Pre-incisional treatment with ketorolac IM and local infiltration with bupivacaine reduced post-operative pain after LAVH (Kim et al., 2005).

Ketorolac tromethamine is a well-tolerated, effective medication in the treatment of acute biliary colic. It showed similar efficacy to meperidine with a decreased number of adverse effects (Henderson et al., 2002).

Addition of morphine and ketolorac to ropivacaine intra-articularly enhances analgesic efficacy of local anesthesia, reduces postdischarge analgesic consumption, and improves activities of daily living. Activities of daily living without increasing side effects after ambulatory arthroscopic knee surgery.Ketorolac can be used to treat pain after congenital heart surgery without an increased risk of bleeding complications in infants and children (Gupta et al.,2004).

Transrectal ultrasound with prostate biopsies is a painful procedure. Intravenous Ketorolac significantly reduces the pain involved in the procedure and allows patients to tolerate it better for a more complete procedure (Mireku, 2004).

Also ketorolac can substantially reduce pain during chest tube removal without causing adverse sedative effects (Puntillo and Ley, 2004).

Ketorolac 0.4% ophthalmic solution is safe and effective in reducing ocular pain when used 4 times daily for up to 4 days post-operative photorefractive keratectomy patients (Solomon et al., 2004), and pain or discomfort associated with cataract surgery reduced in pain associated with cataract surgery (Price,

2004). Study to evaluate the analgesic efficacy of ketorolac tromethamine ophthalmic solution 0.5% after laser in situ keratomileusis (LASIK) supports the use of topical ketorolac for control of early postoperative pain following LASIK, significantly increasing patient comfort and reducing usage of other pain medications (Price and Jr, 2002).

Pain relief with ketorolac versus morphine after surgery and to determine whether the opioid-sparing effect of an NSAID reduces the magnitude of opioid side effects. When five hundred patients received morphine and 503 received ketorolac. Fifty percent of patients in the morphine group achieved pain relief, compared with 31% in the ketorolac group. The ketorolac-morphine group required less morphine and had a lower incidence of side effects. Adding NSAIDs such ketolorac to the opioid treatment reduces morphine requirements and opioid-related side effects in the early postoperative period (Cepeda et.,2005). Ketorolac 30 mg intravenously provides similar analgesic effects as Pethidine with much less incidence of nausea and drowsiness (Abbas et al.,2004).

The postoperative analgesic effect of intra-articular ketorolac, morphine, and bupivacaine during arthroscopic outpatient partial meniscectomy. Study conclude that 60 mg intra-articular ketorolac provides better analgesic effect than 10 cc intra-articular bupivacaine 0.25% or 1 mg intra-articular morphine.(Papacci et al.,2004). Ketorolac tromethamine is efficacious in reducing postoperative pain and narcotics usage after cesarean section (Lowder et al.,2003). IV ketorolac, as an adjunct to PCEA (patient-controlled epidural analgesia) after cesarean delivery, produced a meperidine dose-sparing effect of approximately 30%(Pavy et al.,2001).

There was a trend that the ketorolac and bupivacaine patients spent less time in the recovery room and used fewer analgesics postoperatively than the other patients. There were no hematomas requiring reoperation and no complications. Locally administered intraoperative ketorolac and bupivacaine with epinephrine significantly reduced pain in the postoperative period.(Mahabir et al.,2004)

Colorectal surgery patients in the intravenous PCA morphine plus ketorolac group received 29% less morphine than patients in the intravenous PCA morphine group with comparable pain scores. The first bowel movement (1.5 [0.7-1.9] vs. 1.7 [1.0-2.8] days, $P < 0.05$) and the first ambulation (2.2 +/- 1.0 vs. 2.8 +/- 1.2 days, $P < 0.05$) were significantly earlier in the morphin pius ketorolac group than in the morphine group.

Study was to compare the analgesic efficacy of a single-dose of preoperative intravenous tramadol versus ketorolac in preventing pain after third molar surgery. Sixty-four patients.Preoperative intravenous ketorolac 30 mg is more effective than tramadol 50 mg in the prevention of postoperative dental pain (Ong and Tan,2004).

The combination of ketorolac plus tramadol in the same patient-controlled analgesia (PCA) device was an effective and safe treatment for postoperative analgesia in abdominal surgery (Lepri et al.,2006). Diclofenac and ketorolac after refractive surgery were no statistical difference in the effectiveness of the medications on pain relief (Narvaez et al.,2004)

A study to compare the efficacy in migraine headache of nasal sumatriptan and intravenous ketorolac showed that both sumatriptan and ketorolac effectively reduced the pain associated with acute migraine headache, but that intravenous ketorolac produced a greater reduction in pain than did nasal sumatriptan (Meredith et al,.2003).

The efficacy of rofecoxib and ketorolac in controlling postoperative pain after outpatient surgery did not differ. Rofecoxib and ketorolac are equally effective in controlling postoperative outpatient orthopedic surgical pain(Kaeding et al.,2004).

As a results,ketorolac is widely used various pain analgesics in effects and safety.Aslo oral bioavailability of ketorolac was reported to be 90% with a very low first pass metabolism. But its short biological half-life (4-6 h) and many adverse effects, such as upper abdominal pain and gastro-intestinal ulceration restrict its oral use (Buckley and Brogden, 1990; Reinhart, 2000).

To avoid invasive drug therapy such as injections and to eliminate frequent dosing regimen with oral administration, a transdermal drug delivery system has been paid attention as an alternative dosage form. In addition to the non-invasive 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; 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 system have been attempted to develop a transdermal delivery system of ketorolac (Tiwari and Udupa,2003;Roy and Manoukian,1995;Roy et al.,1995). However, the numbers or kinds of enhancers or vehicles used were very limited.

We investigated the effects of various pure solvents, co-solvents and penetration enhancers on the in vitro permeation of ketorolac from solution formulation across hairless mouse skin to examine the feasibility of developing ketorolac transdermal system.

We performed a study using solution formulations to examine the feasibility of ketorolac transdermal system. The binary co-solvent system composed of propylene glycol monolaurate (PGML)-diethylene glycol monoethyl ether (DGME) or propylene glycol monocaprylate (PGMC)-DGME at the ratio of 60 : 40 showed high permeation rate. Also, saturated fatty acids such as caprylic acid, capric acid or lauric acid resulted in high permeation flux when they were added to propylene glycol (PG).

Several vehicles were selected based on the results from the study using solution formulations, and then pressure-sensitive adhesive (PSA) ketorolac transdermal systems were formulated. We investigated the effects of PSAs and vehicles on the permeation of ketorolac from formulated ketorolac transdermal

systems using a flow-through diffusion cell system. Also, the in vivo pharmacokinetic study was carried out using rats based on the in vitro permeation results.

2. Experimental

2.1. Materials

Ketorolac tromethamine (KT), , ketoprofen (internal standard, IS), oleyl alcohol (OAl), caprylic acid, capric acid, lauric acid, oleic acid, and linoleic acid were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Propylene glycol laurate (PGL, Lauroglycol® FCC), propylene glycol monocaprylate (PGMC, Capryol® 90), propylene glycol monolaurate (PGML, Lauroglycol® 90), caprylocaproyl macrogol-6 glycerides (LBS, Labrasol®), oleoyl 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. Acrylic PSA solutions in organic solvents were obtained from National Starch and Chemical Company (Bridgewater, NJ, USA). Other reagents were of analytical grade.

2.2. Analysis

Samples from solubility and permeation studies were analyzed by high-performance liquid chromatography (HPLC) system (Shimadzu Scientific Instruments, Tokyo, Japan), consisting of a pump (LC-10AD), an automatic injector (SIL-10A) and a UV detector (SPD-10A) set at 300 nm. An ODS column (μBondapak C18, 3.9 × 300 mm, 10 μm, Waters, Milford, MA, USA) 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.

2.3. Solubility determination

An excess amount of KT was added to the various pure solvents or co-solvents, and shaken at 37 ºC for more than 48 h. The solutions were then centrifuged at 7,500 rpm for 5 min, and the supernatant was assayed by HPLC after appropriate dilution.

2.4. 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 co-solvents. For the preparation of saturated solutions, KT suspension was shaken at 37 ºC for 24 h before permeation experiments.

2.5. Procedure for skin permeation i*n vitro*

Male hairless mice aged 6-8 weeks were used. After sacrificing with ether, the skin of each hairless mouse was excised, and then it was mounted on a flow-through diffusion cell system consisting of a multi-channel peristaltic pump (205S, Watson Marlow, North Wilminton, MA, USA), a fraction collector (Retriever IV, ISCO, Lincoln, NE, USA), a circulating water bath (RB-10, Jeo Tech, Kimpo, Korea), and a flow-through diffusion cells were used. The surface area of the receiver cell opening was 2 cm^2, 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 co-solvents.The skin permeation studies were performed at 37ºC.

2.6. Data Analysis

The permeation data were analyzed by the method developed for 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 equations 1-3 (8).

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

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

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

A: the effective diffusion area

h: the thickness of skin

C: the constant concentration of the donor solution

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

2.7. Preparation of Pressure-sensitive Transdermal Systems

Acrylic adhesive solutions were prepared by mixing 1 mL of ketorolac solutions in various vehicles with 3 g of acrylic solution in mixed solvents (Table 3). PSA transdermal systems were prepared by casting the above solutions on polyester release liner coated with silicone using a casting knife; the thickness spread was 300 μm. They were set at room temperature for 10 min to evaporate the solvents, and then were oven-dried at 90 ºC for about 20 min to remove the residual organic solvents. The dried film was transferred onto a backing film.

2.8. Stability of Pressure-sensitive Adhesive Transdermal Systems

The prepared PSA transdermal systems were stored at room temperature. Formulated ketorolac transdermal systems were cut by the size of 2 cm × 2.5 cm, and dissolved in 50 mL of 50% methanol immediately after preparation and at 15 and 30 days by sonicating for 2 h. The solutions were assayed by HPLC.

2.9. Procedure for I*n Vitro* Skin Permeation

Male hairless mice aged 6-8 weeks were used. After sacrificing with ether, the

skin of each hairless mouse was excised, and then it was mounted on a flow-through diffusion cell system consisting of a multi-channel peristaltic pump (205S, Watson Marlow, North Wilminton, MA, USA), a fraction collector (Retriever IV, ISCO, Lincoln, NE, USA), a circulating water bath (RB-10, Jeo Tech, Kimpo, Korea), and a flow-through diffusion cells. The surface area of the receiver cell opening was 2 cm^2, 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. The skin permeation studies were performed at 37 ºC.

2.10. Pharmacokinetic Studies of Ketorolac Transdermal Systems

Male Sprague-Dawley rats weighing 280-320 g were obtained from Samtako Bio Co., Ltd (Osan, Korea). The rats were anesthetized with 1 mL/kg of ketamine hydrochloride (50 mg/mL, Yuhan Corp., Seoul, Korea) and the right femoral artery was cannulated using a polyethylene tubes (0.58 mm i.d. × 0.96 mm o.d.; Naume Corp., Tokyo, Japan). After surgery, each animal was housed individually in cage. The animals fasted overnight until the end of the experiment but were allowed water ad libitum. Rats were then divided into five groups, comprising 6 rats each. Group 1-5 were administered by oral, transdermal delivery system (TDS) 1, 2, 3 and 4, respectively. The oral dose was 2487 μg/kg, and the compositions of TDS 1, 2, 3 and 4 were FN 8, FN 10, FN 16 and 24 in Table 1, respectively. For the administration of TDS, the hair of left side between back and abdomen was shaved carefully so that the stratum corneum remained intact. The size of TDS applied to the shaved site of rat was 2 cm × 2.5 cm. Serum samples (0.1 mL) were collected before and 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 h after drug administration and analyzed by HPLC. The pharmacokinetic studies of ketorolac transdermal delivery systems were carried out according to the Principles for Biomedical Research Involving Animals developed by the Council for International Organizations of Medical Sciences and had been approved by

the Ethical Review Committee at the Ewha Womans University.

2.11. Procedure for Serum Sample Preparation

Serum sample (0.1 mL) was mixed with 50 μL of the working IS solution (30 μg/mL) and acidified with 30 μL of 1N hydrochloric acid. The mixture was added with 6 mL of *n*-hexane : ether (70 : 30, v/v), vortex-mixed for 10 min, and centrifuged for 5 min. Five milliliter of organic phase was evaporated and the residue was reconstituted with 120 μL of mobile phase. And then 40 μL was injected directly into the HPLC system.

2.12. Statistical Analysis

The pharmacokinetic variables from the five groups were compared with a one-way ANOVA, which followed by a posterior testing with an unpaired *t*-test using the Bonferroni correction. A *P*-value of less than 0.05 was considered significant.

3. Results and discussion

3.1. 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/cm^2/h. Among various types of vehicles, ester-type vehicles showed relatively high enhancing effects. Especially, PGML resulted in the highest enhancing effect when fixed drug concentration of 5 mg/ml was used; its enhancement factors were 29 and 3.79 compared to water and PGL, respectively. From equation 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. IPM was not able to exert very high enhancing effect due to the extremely low solubility in spite of very high partitioning. As depicted in Fig 1, PGML showed different permeation profile compared to other ester-type vehicles. It initially provided 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 high permeation rate possibly due to the high partitioning. Even though IPA permeation flux slightly increased as the drug concentration increased from 5 to 30 μg/ml, it increased dramatically as the drug concentration increased from 30 to 50 μg/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 co-solvents, 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 has an inverse relationship in the absence of solvent-induced skin damage (Twist and Zata,1990). 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 which can greatly change skin barrier property and have appropriate solubility to solubilze the desired amount of drug with 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 (Barry,1987); increased skin/vehicle partitioning of the drug (Green et al.,1988); increased solvent transport into or across the skin (Yamada et al.,1987).

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 (Cho and Choi,1998), we added it to PGMC or PGML at the concentrations of 20, 40, 60 and 80%. Fig 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 co-solvent 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 co-solvent system consisting of PG-OAl, the permeation rate markedly increased compared to PG alone, while the co-solvent system rarely affected the permeation flux compared to OAl alone. The permeation flux (μg/cm^2/h) and solubility (mg/ml) of KT in PG-OAl co-solvent 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.

3.2. 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 (Green et al.,1988; Cooper,1984; Cooper,1985; Aungst and Rgers,1986). The binary system was considered to disorganize the multilaminate hydrophilic-lipophilic layers located intercellularly in the stratum corneum, consequently promoting percutaneous absorption of drugs (Hoelgaard et al.,1988). 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 the 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 of unsaturated fatty acids resulted in relatively high permeation rate in all concentrations tested, and the highest flux was observed at 5% concentration; the

flux of KT from oleic acid and linoleic acid at 5% was 65.8 ± 1.39 and 83.2 ± 3.58 μg/cm^2/hr, respectively. The highest enhancing effect was attained with 10% caprylic acid in PG; the permeation flux was 113.6 ± 17.5 μg/cm^2/hr. It was reported that the most effective saturated fatty acids were C10~C12 chain lengths for naloxone permeation enhancement (Aungst et al.,1986). Also, in studies of tenoxicam and ondansetron hydrochloride, it was demonstrated that unsaturated fatty acids such as oleic acid or linoleic acid had the most significant enhancing effects when used with PG (Gwak and Chun, 2002; Gwak et al.,2004). In those studies, the concentrations of fatty acids in PG were 10% in naloxone study 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 aci ds increased except for C8, indicating the 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 co-solvents 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 (Sato et al.,1991).

3.3. Effect of Pressure-sensitive Adhesives

To evaluate the effects of PSAs, four kinds of acrylic adhesives were employed; Duro-Tak® 87-2196 (FN 4), 87-2100 (FN 1), 87-2510 (FN 3) and 87-2097 (FN 2) (Table 3). One hundred milligram of ketorolac tromethamine was dissolved in 1 mL of methanol, and mixed with 3 g of PSA. As depicted in Fig. 6, the highest penetration rate was obtained with Duro-Tak® 87-2196; the permeation rate of Duro-Tak® 87-2196, 87-2100, 87-2097 and 87-2510 was 3.25 ± 1.69, 1.17 ± 0.07, 0.47 ± 0.15 and 0.32 ± 0.05 μg/cm^2/h, respectively. The lag time was not quite different from each other, which was around 8 h. The steady-state flux (J_s) and lag time (T_L) are expressed as follows (Barry, 1983): J_s = DKC/h and $T_L = h^2/6D$ (J_s: the steady-state flux, D: diffusion coefficient, C: the solubility of drug in PSA, K: partition coefficient between skin and the PSA, h: the thickness of skin). Based on the results that the lag time was almost the same, the diffusion coefficient was estimated to be constant among PSAs used. Therefore, the difference of permeation flux was thought to be due to the KC, which is the solubility of ketorolac in the skin. Although the underlying mechanism was not directly investigated in this study, the difference of functional group in PSAs may be involved in the solubility difference. The PSAs with carboxyl functional group (Duro-Tak® 87-2196, Duro-Tak® 87-2100) showed higher permeation rate, followed by one without a functional group (Duro-Tak® 87-2097). The acrylic adhesive with a hydroxyl functional group (Duro-Tak® 87-2510) provided the lowest permeation rate. The copolymer type also affected the permeation flux, which acrylate-vinylacetate (Duro-Tak® 87-2196) produced better permeability rather than acrylate (Duro-Tak® 87-2100). Thus, it was speculated that the permeation rate of a drug compound can be varied by the chemical nature and copolymer of PSAs. In the case of ketorolac, the highest permeation rate was achieved when PSA with carboxylic functional group and acrylate-vinylacetate copolymer was used.

The effects of drug loading doses were examined using methanol and Duro-Tak® 87-2196 as a vehicle and PSA, respectively. The drug concentrations

employed were 2 (FN 7), 5 (FN 6), 7 (FN 5) and 10% (FN 4) in methanol as described in Table 3. The permeation flux and lag time at 2, 5, 7 and 10% were 0.34 ± 0.14 μg/cm^2/h and 9.2 ± 2.8 h, 0.55 ±0.19 μg/cm^2/h and 8.8 ± 1.4 h, 0.98 ± 0.21 μg/cm^2/h and 12.7 ± 0.8 h and 3.25 ± 1.69 μg/cm^2/h and 8.7 ± 1.0 h, respectively. From the results, which the drug loading in PSA transdermal system increased, the permeation flux also increased, indicating that the high drug loading is required to achieve appropriate permeation rate.

3.4. Effect of Vehicles on the Permeation of Ketorolac from a Ketorolac Transdermal System

In designing a PSA transdermal drug delivery system, it is essential to find an appropriate vehicle which solubilizes a drug, mixes well with PSA, and/or enhances the permeation rate. From our previous study using solution formulations of ketorolac (Cho and Gwak, 2004), PGML showed very high permeation rate and the permeation rate was increased by the addition of DGME. Also, DGME-PGMC and PG-fatty acids co-solvents showed high permeation fluxes. These vehicles were used for the fabrication of ketorolac PSA transdermal systems to identify the optimum penetration enhancers, and they were satisfactory in meeting the conditions for PSA trasndermal system. To examine the effects of vehicles, 50 mg of ketorolac tromethamine was dissolved in 1 mL of various solvents, and mixed with 3 g of Duro-Tak® 87-2196 (FN 8 ～38).

The effects of co-solvents containing DGME-PGML (FN 8～13) and DGME-PGMC (FN 13～18) on the ketorolac permeation from PSA transdermal system were investigated. Fig. 7 shows the fluxes of ketorolac at the various ratios of DGME-PGML and DGME-PGMC co-solvents. Both of the two co-solvents showed the highest fluxes at 40% of DGME, which were 8.2 ± 2.7 and 6.3 ± 1.0 μg/cm^2/h, respectively. This is consistent with the result from the study using solution formulations (Cho and Gwak, 2004) even though the enhancement factors by the addition of DGME to PGMC or PGML in the PSA transdermal

systems was much lower than those in solution formulations. The mechanism of enhancing effect by the addition of DGME was suggested that DGME itself may not have a profound effect on the structural integrity of the skin, and it just eases the partition of a compound by increasing the solubility of the compound in the skin. The DGME alone revealed low permeation rate (2.8 ± 0.8 μg/cm^2/h).

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). In this study, various concentrations of fatty acids were used with PG as vehicles shown in Table 3 (FN 19 ~ 38).

In our earlier study using solution formulations (Cho and Gwak, 2004), the highest permeation flux was attained with 10% caprylic acid in PG. As depicted in Fig. 8, the permeation flux from PSA transdermal system containing caprylic acid in PG, however, was low compared to systems containing other fatty acids. This result indicated that the effects of vehicles in the solution formulations may not be extrapolated to predict their effects in PSA transdermal systems. The overall permeation fluxes from ketorolac PSA transdermal systems containing fatty acids in PG ranged from 1.0 to 4.5 μg/cm^2/h, which was considerably low compared to solution formulations (1.3 – 113.6 μg/cm^2/h) from our study .

The overall low permeation rate was attributable to the lower loading dose (264-298 μg) applied to the 2 cm^2 receiver cells (Table 4), compared to that of solution formulations (1500 μg). In addition, the low permeation flux of ketorolac from PSA ketorolac transdermal systems was partly attributed to the low thermodynamic activity due to its high solubility in the acrylic adhesive matrix. The overall lag times of PSA transdermal delivery systems containing fatty acids in PG ranged between 5-11 h. Among them, the lag time of PSA transdermal

system containing linoleic acid in PG was relatively short at all concentrations used (Fig. 8). The longest lag time (11.0 h) was observed at the formulation of 3% capric acid in PG.

3.5. The Physicochemical Stability of Ketorolac Transdermal Systems

The stability of formulated ketorolac transdermal systems was evaluated. As shown in Table 4, the initial concentration remaining after 30 day storage was 90-100 %, which was not degraded significantly, regardless of the formulations. The appearance or adhesive property after 30-day storage at room temperature did not change.

3.6. Pharmacokinetics of Ketorolac Transdermal Systems in Rats

Based on the *in vitro* results from permeation of ketorolac from PSA transdermal systems, PGML, PGML-DGME (60 : 40, v/v), PGMC-DGME (60 : 40, v/v) and 3% capric acid in PG were employed as vehicles for the *in vivo* pharmacokinetic study of ketorolac transderrmal systems. The initial drug doses from transdermal delivery systems after drying were 661-746 μg (Table 4) while the oral dose was 746 μg for the mean rat weight of 300g used in this study.

It was found that there were statistically significant differences in the C_{max} ($P < 0.01$) and T_{max} ($P < 0.05$) between groups as shown in Table 5 and Fig. 9. The statistically significantly lower C_{max} were obtained from TDS 1, 3 and 4 compared to oral delivery ($P < 0.05$). Also, TDS 3 revealed more than 10 times increased T_{max} ($P < 0.05$) and TDS 4 showed more than two times $t_{1/2}$ ($P < 0.05$), compared to oral administration. The overall decreased C_{max}, and increased T_{max} and $t_{1/2}$ were observed in transdermal systems compared to oral administration even though all are not statistically significant. The T_{max} and half-life of ketorolac by oral administration were 0.3 ± 0.05 and 3.6 ± 0.5, respectively, which were similar to those investigated in other studies (Grandos-Soto et al., 1995; Pasloske et al., 1999). The high $AUC_{0-\infty}$ and AUC_{0-24} values were attained with TDS 2 and

TDS 3, which used PGML-DGME (60 : 40) and PGMC-DGME (60 : 40) as a vehicle, respectively, and the values were similar to those of oral administration.

The relationship between *in vitro* permeation flux through excised hairless mouse skin and *in vivo* $AUC_{0-\infty}$ in rats is depicted in Fig. 10.

A good relationship ($r = 0.9576$) between J_s and $AUC_{0-\infty}$ was obtained. It was thought that the *in vivo* plasma level of ketorolac can be predicted from the *in vitro* permeation profiles.

4. Conclusion

Ketorolac transdermal systems containing PGMC or PGML in combination with DGME at the ratio of 60 : 40 resulted in relatively high permeation rate from the in vitro study. When the ketorolac transdermal systems containing PGML-DGME (60 : 40) or PGMC-DGME (60 : 40) were applied to rat skins, high values of $AUC_{0-\infty}$ was attained, which was similar to that of oral administration. There was an excellent relationship between in vitro J_s and in vivo $AUC_{0-\infty}$ found. From the results of the reduced C_{max} and prolonged T_{max} and half-life in PSA transdermal systems, it was speculated that the ketorolac transdermal systems may have prolonged effect with reduced toxic event, compared to oral delivery.

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

Solvent	Js ($\mu g/cm^2/h$)	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
OAl	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.

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

Solvent (Solubillity, mg/ml)	Dose (mg/ml)	J_s ($\mu g/cm^2/h$)	T_L (h)	P_{app} (cm/h, ×1000)
DGME	5	0.69 ± 0.29	3.79 ± 2.79	0.14 ± 0.06
(211)	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	5	6.08 ± 2.29	9.52 ± 2.47	1.22 ± 0.46
(51.3)	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	5	94.3 ± 17.3	2.36 ± 0.41	18.9 ± 3.46
(15.2)	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	5	12.7 ± 11.8	6.70 ± 3.53	2.54 ± 1.36
(36.7)	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	5	104 ± 13.1	6.79 ± 0.27	20.8 ± 2.62
4/6	30	405 ± 23.9	11.3 ± 0.76	13.5 ± 0.80
(69.4)	50	526 ± 34.1	11.0 ± 1.09	10.5 ± 0.68
DGME/PGML	5	183 ± 13.3	12.6 ± 0.10	36.5 ± 2.66
4/6	30	435 ± 35.5	5.75 ± 0.44	14.5 ± 1.18
(85.6)	50	534 ± 24.2	4.77 ± 0.26	10.7 ± 0.48

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

Table 3. Formulation compositions for the preparation of ketorolac transdermal systems

FN	ount loaded (mg)	Vehicles	FN	Amount loaded (mg)	Vehicles
1[a)]	100	Methanol	20	50	PG containing 3% C_8
2[b)]	100	Methanol	21	50	PG containing 5% C_8
3[c)]	100	Methanol	22	50	PG containing 10% C_8
4	100	Methanol	23	50	PG containing 1% C_{10}
5	70	Methanol	24	50	PG containing 3% C_{10}
6	50	Methanol	25	50	PG containing 5% C_{10}
7	20	Methanol	26	50	PG containing 10% C_{10}
8	50	PGML	27	50	PG containing 1% C_{12}
9	50	DGME: PGML(20:80)	28	50	PG containing 3% C_{12}
10	50	DGME : PGML(40:60)	29	50	PG containing 5% C_{12}
11	50	DGME : PGML(60:40)	30	50	PG containing 10% C_{12}
12	50	DGME : PGML(80:20)	31	50	PG containing 1% C_{18}(1)
13	50	DGME	32	50	PG containing 3% C_{18}(1)
14	50	PGMC	33	50	PG containing 5% C_{18}(1)
15	50	DGME : PGMC(20:80)	34	50	PG containing 10% C_{18}(1)
16	50	DGME : PGMC(40:60)	35	50	PG containing 1% C_{18}(2)
17	50	DGME : PGMC(60:40)	36	50	PG containing 3% C_{18}(2)
18	50	DGME : PGMC(80:20)	37	50	PG containing 5% C_{18}(2)
19	50	PG containing 1% C_8	38	50	PG containing 10% C_{18}(2)

For all preparations, 1mL of ketorolac solutions in various vehicles was mixed with 3g of acrylic solutions. Acrylic solution employed in this study was Duro-Tak® 2196 except for [a)]2100, [b)]2097 and [c)]2510. The thickness of drug loaded layer was 300 μm. FN: formulation number. C_8: caprylic acid, C_{10}: capric acid, C_{12}: lauric acid, C_{18}(1): oleic acid, C_{18}(2): linoleic acid.

Table 4. Stability of ketorolac transdermal delivery systems containing various permeation enhancers

	TDS 1	TDS 2	TDS 3	TDS 4
Initial Dose (μg)	661.8	746.0	717.6	681.9
% remaining (Mean ± S.D., n = 3)				
15 day	92.5 ± 4.8	96.4 ± 2.7	97.4 ± 2.0	97.5 ± 1.2
30 day	91.2 ± 1.2	92.9 ± 2.2	91.7 ± 2.3	101.4 ± 0.8

The initial dose was obtained from the TDS size of 2 cm × 2.5 cm. TDS: transdermal delivery system. The enhancers used for TDS 1, 2, 3 and 4 were PGML, PGML-DGME (60 : 40), PGMC-DGME (60 : 40) and 3% capric acid in PG, respectively.

Table 5. Pharmacokinetic parameters of kerorolac from oral and transdermal administration

	Oral	TDS 1	TDS 2	TDS 3	TDS 4
C_{max} (μg/mL)	4.2 ± 0.6	1.3 ± 0.3*	2.5 ± 0.9	1.7 ± 0.6*	0.8 ± 0.3*
T_{max} (h)	0.3 ± 0.05	1.4 ± 0.4	2.0 ± 0.8	3.3 ± 0.6*	2.2 ± 0.3
$t_{1/2}$ (h)	3.6 ± 0.5	8.1 ± 5.3	5.0 ± 2.0	6.7 ± 1.7	8.4 ± 1.4*
AUC_{0-24} (μg · h/mL)	14.7 ± 4.8	9.2 ± 1.7	14.1 ± 6.0	12.5 ± 3.7	6.6 ± 2.3
$AUC_{0-\infty}$ (μg · h/mL)	15.7 ± 4.6	12.6 ± 3.5	14.7 ± 5.5	14.8 ± 4.6	8.4 ± 2.4

Data are expressed as the mean ± S.E. (n = 3). TDS: transdermal delivery system. The vehicles used for TDS 1, 2, 3 and 4 were PGML, PGML-DGME (60 : 40), PGMC-DGME (60 : 40) and 3% capric acid in PG, respectively. $^{*}P < 0.05$ vs. oral.

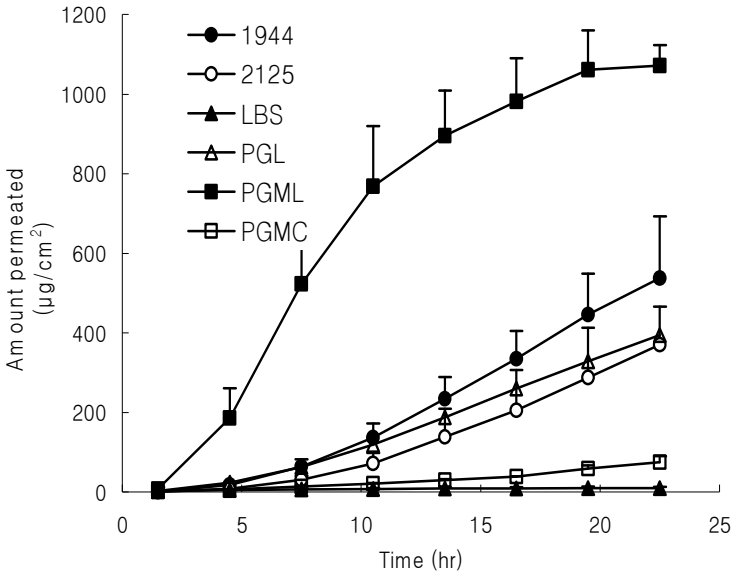

Figure 1. Cumulative amount of KT permeated across hairless mouse skin from 5 mg/ml solution in ester-type vehicles as a function of time (n = 3).

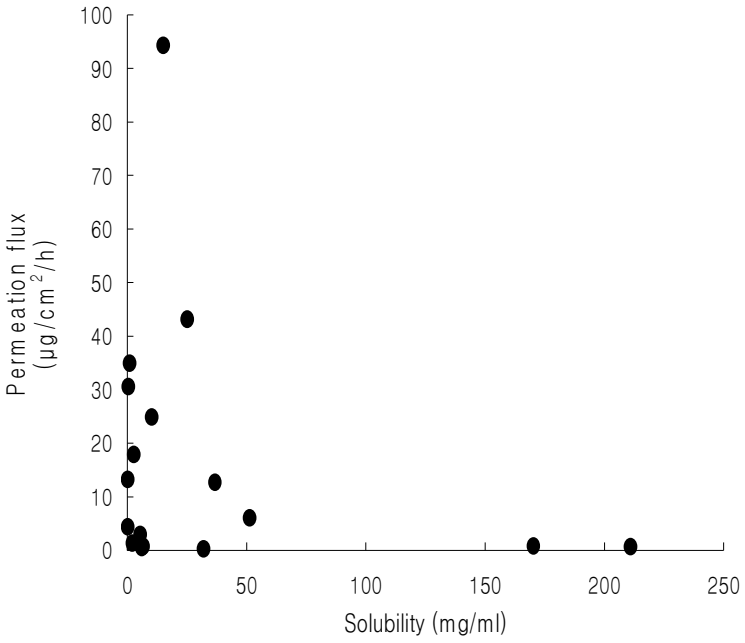

Figure 2. Relationship between KT solubility in various vehicles and the permeation flux from the vehicle

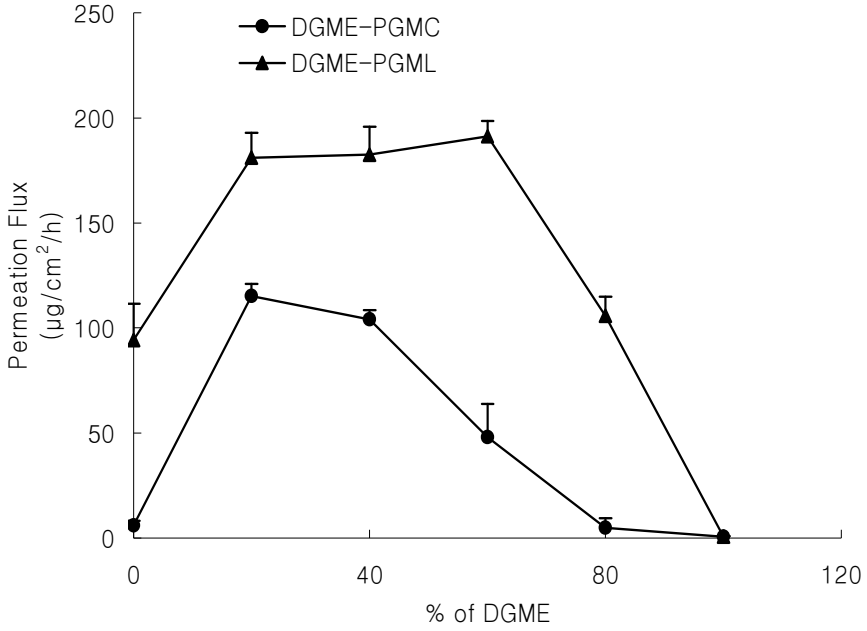

Figure 3. Effect of PGMC-DGME and PGML-DGME co-solvents on the permeation of KT across hairless mouse skin from 5 mg/ml solution as a function of time (n = 3).

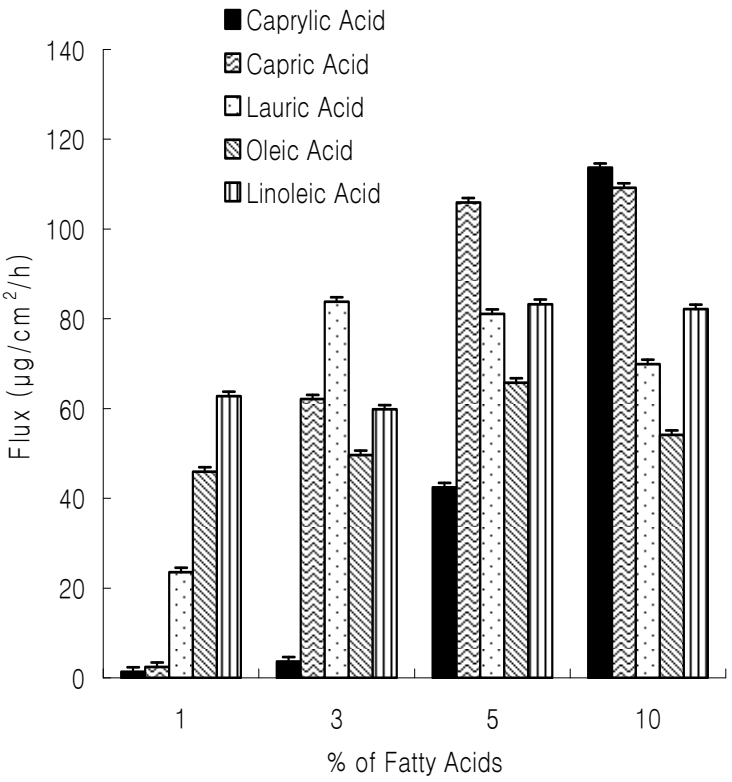

Figure 4. The permeation flux of KT from various concentrations of fatty acids in PG (n = 3).

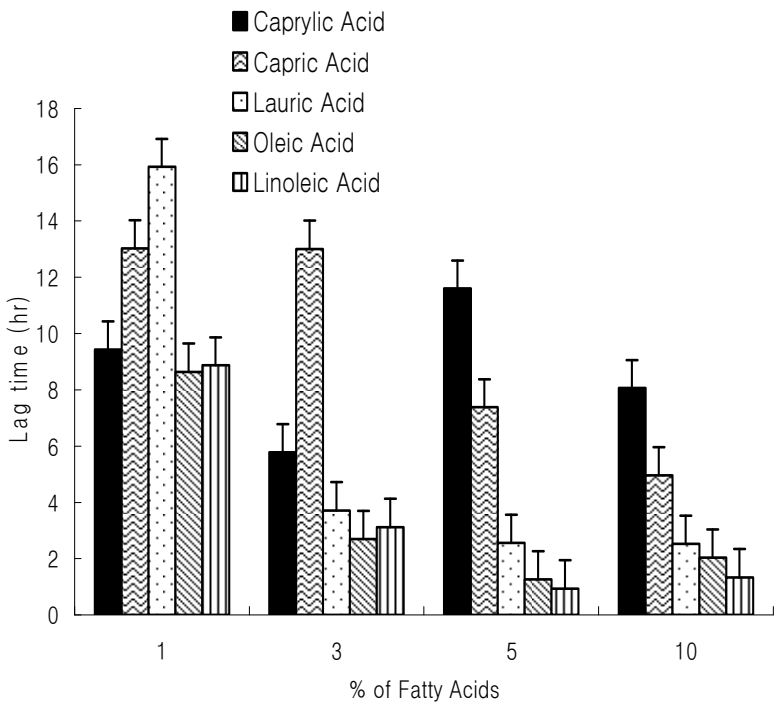

Figure 5. The lag time of KT from various concentrations of fatty acids in PG (*n* = 3).

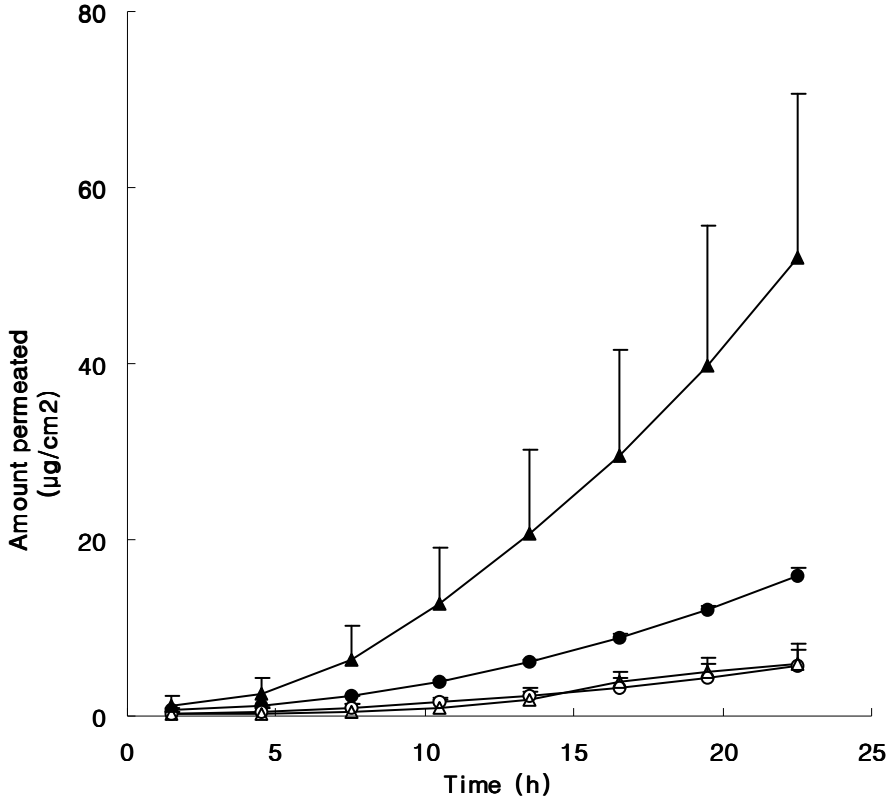

Fig. 6. Effect of PSA on the permeation of ketorolac through excised hairless mouse skin. Data were expressed as the mean ± S.D. (n = 3). ●: 87-2100; ○: 87-2510; ▲: 87-2196; △: 87-2097.

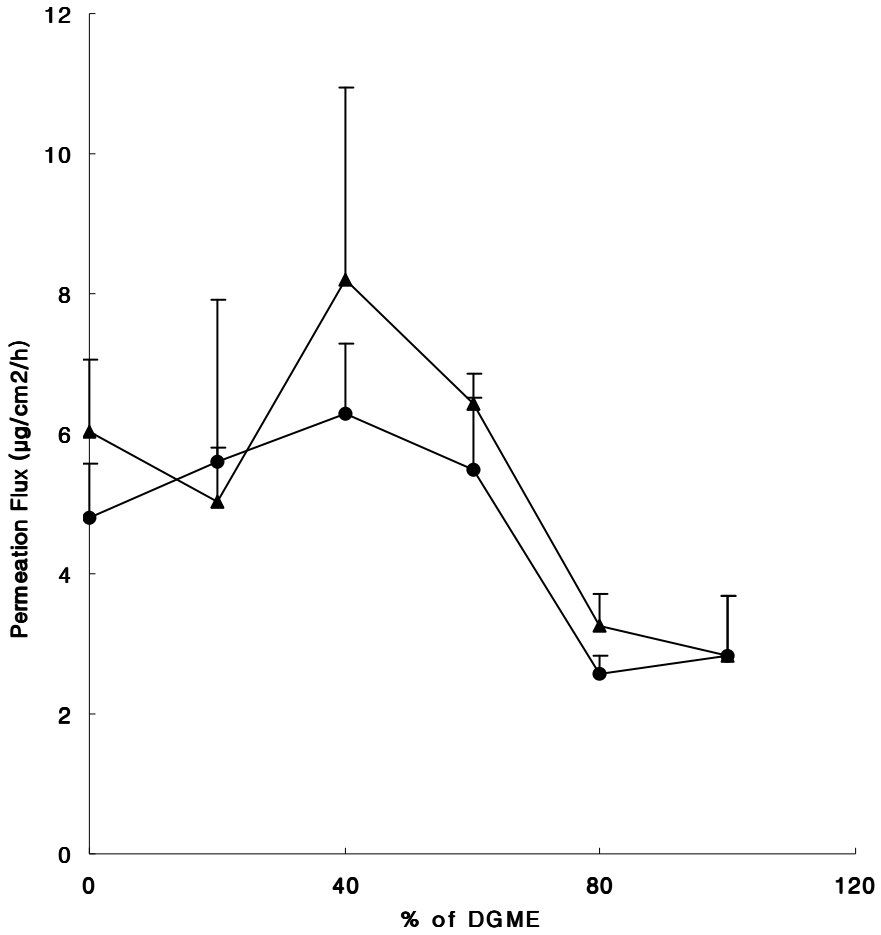

Fig. 7. Effect of PGML-DGME and PGMC-DGME co-solvents on the steady-state flux of ketorolac through excised hairless mouse skin. Data were expressed as the mean ± S.D. (n = 3). ●: DGME-PGMC; ▲: DGME-PGML.

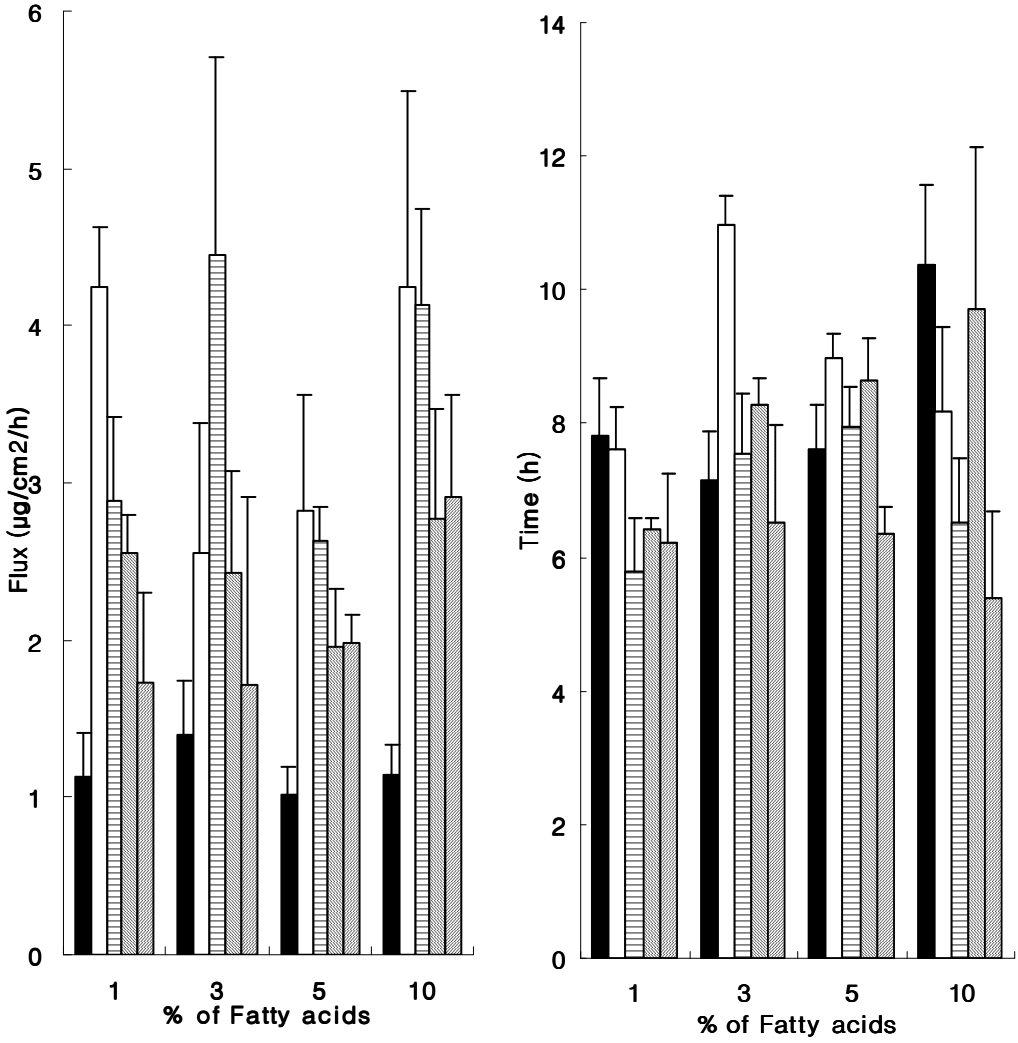

Fig. 8. The effects of fatty acids in PG on the permeation flux (A) and lag time (B) of ketorolac from ketorolac PSA transdermal systems. Data were expressed as the mean ± S.D. (n = 3). ■: caprylic acid; □: capric acid; ▤: lauric acid; ▧: oleic acid; ▨: linoleic acid.

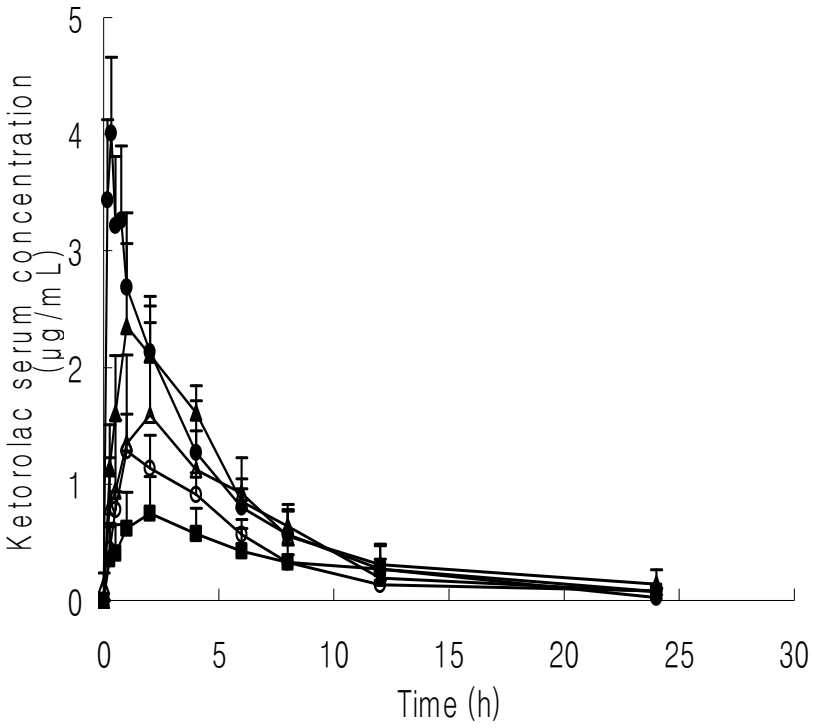

Fig. 9. Ketorolac serum concentrations after administration by oral and transdermal delivery systems containing various permeation enhancers. Data were expressed as the mean ± S.E. (n = 3). ●: oral; ○: PGML; ▲: PGML-DGME (60 : 40); △: PGMC-DGME (60 : 40); ■: 3% capric acid in PG.

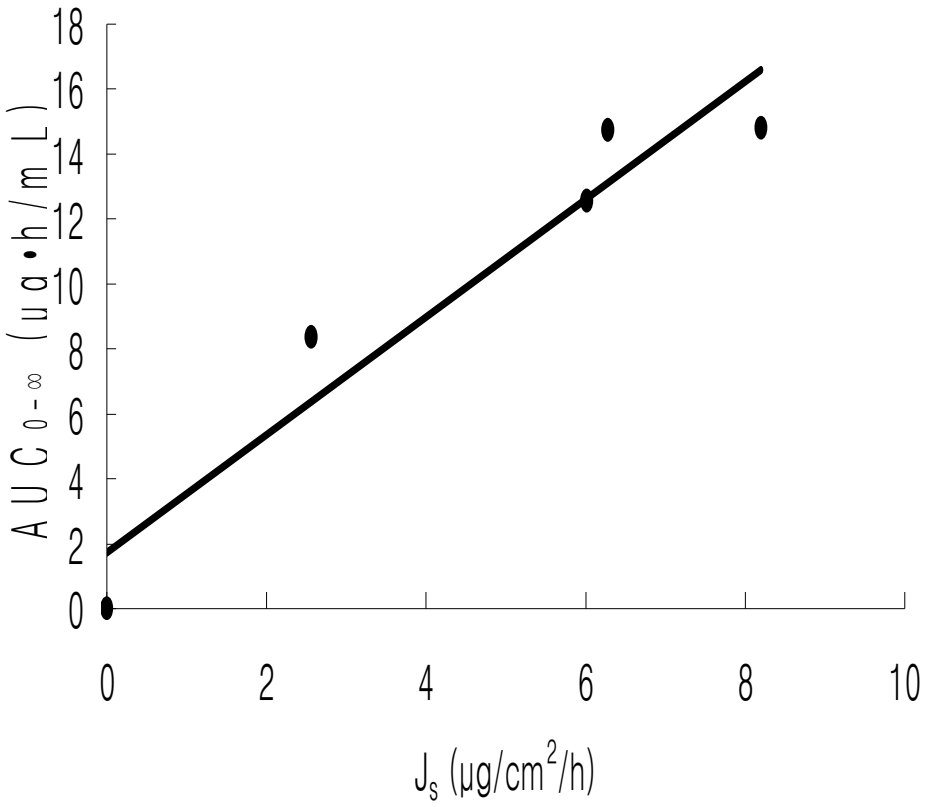

Fig. 10. Relationship between *in vitro* permeation flux (J_s) through excised hairless mouse skins and *in vivo* $AUC_{0-\infty}$ in rats for four ketorolac transdermal systems with a correlation coefficient of 0.9576.

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