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Effect of penetration enhancers on flurbiprofen permeation through rat skin

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Abstract

To increase the skin permeation rate of flurbiprofen, fatty acids and urea were added in propylene glycol vehicle containing 1% flurbiprofen. The enhancing effects of these compounds on the skin permeation of flurbiprofen were evaluated using Keshary-Chien diffusion cells fitted with excised rat skins. Unsaturated fatty acids increased the skin permeation rate of flurbiprofen 6.5–17.5 fold compared to the control vehicle without enhancer, while saturated fatty acids did not show any significant increase. Although the addition of urea in the vehicle decreased the skin permeation rate of flurbiprofen, the mixture of oleic acid and urea showed a significantly higher permeation rate than oleic acid alone. It was coincident with the results obtained with the plasma concentrations of flurbiprofen determined after the transdermal application of propylene glycol vehicle containing them. AUC and C_{max} of the vehicle containing the mixture were increased 2.3 and 2.5 fold, respectively, whereas each parameter of the vehicle containing oleic acid only was increased 1.7 fold compared to those of the control vehicle.

Keywords: Flurbiprofen; Skin permeation; Fatty acids; Urea; Pharmacokinetics

1. Introduction

Flurbiprofen, a potent nonsteroidal anti-inflammatory drug, has been used extensively for the treatment of rheumatoid arthritis and its related disorders (Brogden et al., 1979). Although flurbiprofen has potent pharmacological activities with oral administration, it has also unwanted problems such as systemic side effects and gastrointestinal irritation (Brogden et al., 1979; Teixeira et al., 1984). Considering the fact that flurbiprofen is usually used for a long period, it is desirable to reduce these side effects while maintaining its therapeutic blood concentration. Among several attempts to achieve this goal, transdermal preparations, such as gels, ointments and creams, have been intensively studied (Kitagawa et al., 1993; Kyuki et al., 1984; Masumoto et al., 1982). However, it was difficult to get an effective blood concentration by transdermal delivery of flurbiprofen due to its intrinsically poor skin permeability, although it has a relatively good permeability among the nonsteroidal anti-inflammatory drugs frequently used (Yano et al., 1986). Therefore, it is indispensable to employ

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penetration enhancers to increase the skin permeation rate of flurbiprofen in order to maintain an effective blood level. Several penetration enhancers, especially pyrrolidone derivatives, were evaluated for this purpose. However, their enhancing effects were not sufficient for practical use (Sasaki et al., 1991; Akhter and Barry, 1985).

The purpose of this study is to evaluate various fatty acids and urea as penetration enhancers for the skin permeation of flurbiprofen in propylene glycol (PG) vehicle in order to achieve an adequate delivery of flurbiprofen through skin.

2. Materials and methods

2.1. Materials

The following compounds were used as received without further purification: flurbiprofen, PG, myristic acid, lauric acid, capric acid, palmitoleic acid, oleic acid, linolenic acid, linoleic acid, arachidonic acid, urea, monosodium phosphate and disodium phosphate (Sigma Chemical Co.), HPLC grade acetonitrile and methanol (Merck Co.), and cyclohexane (Fisher Scientific Co.). Oxaprozin was generously provided by Il-Dong Pharmaceutical Co., S. Korea. Water was distilled, deionized and filtered in house.

2.2. Preparation of vehicles

The vehicles were prepared by dissolving appropriate amounts of the drug and the enhancers directly in PG. The enhancers used in this study were myristic acid, lauric acid, capric acid, palmitoleic acid, oleic acid, linolenic acid, linoleic acid, arachidonic acid and urea. The concentrations of flurbiprofen and enhancer in PG were fixed to 1% and 5%, respectively, except for the concentration of urea which was varied as 5% and 10% to determine any concentration dependence of urea. A control PG vehicle containing 1% flurbiprofen and no penetration enhancer was used as a reference. The percentages used in the study were based on weight.

2.3. Skin permeation of flurbiprofen through excised rat skins

Rat skins were harvested from male Sprague-Dawley rats weighing 280 ± 20 g. After careful removal of the hair on the dorsal area using an electric clipper (Daito Electric Co., Japan, Model 808), a 5 cm × 5 cm patch of skin was excised from each sacrificed rat and subcutaneous fat and other extraneous tissues were trimmed. The excised rat skins were stored at −20°C prior to use. They were used within 1 week after the skin harvest.

The extent and rate of skin permeation of flurbiprofen from applied vehicles were determined using Keshary-Chien diffusion cells fitted with excised rat skins. The effective diffusion area was 5.1 cm^2. The receptor compartment was filled with pH 7.4 phosphate buffer (0.01 M) and its temperature was maintained at 37 ± 0.5°C using a thermostatic water pump (Haake, Model F-4391) during the experiment. After 3 ml of the vehicle was applied under occlusion on the epidermal surface, 0.2 ml of the receptor medium was withdrawn at 2, 4, 6, 8, 9, 10, 11 and 12 h, and replaced immediately with an equal volume of fresh phosphate buffer.

The amounts of flurbiprofen permeated into the receptor medium were quantitated by a slight modification of an HPLC method developed in our laboratories (Chi et al., 1994). The HPLC system consisted of an isocratic pump (Spectra-Physics, Model 8810), a manual injector (Rheodyne, Model 7125), a UV/Vis detector (Spectra-Physics, Model SC100) set at 254nm and an integrator (Dionex, Model 4270). The column used was a C_{18} column (μ Bondapak, 3.9 mm × 300 mm, 10 μm particle size, Waters Assoc.). The mobile phase was a mixture of pH 7.0 phosphate buffer (0.02 M) and acetonitrile in the volume ratio of 74:26 and the flow rate was 1.0 ml/min. After the receptor medium was mixed with an equal volume of the internal standard solution (oxaprozin 50 μg/ml in mobile phase), 50 μl of the mixed sample was injected onto the column.

After plotting the cumulative amounts of flurbiprofen permeated through rat skins as a function of time, permeation parameters were cal-

culated using the following equations (Barry, 1983):

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

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

where, Js is the permeation rate at steady-state (μg/cm^2/h), A is the area of skin (cm^2) through which the permeation of the drug takes place, $(dQ/dt)_{ss}$ is the amount of drug passing through the skin per unit time at steady-state (μg/h), C is the drug concentration in the vehicle (μg/ml), K is the partition coefficient of drug (skin/vehicle), h is the effective path length (cm), D is the (apparent) diffusion coefficient of the drug (cm^2/h) and T_L is the lag time (h).

2.4. Percutaneous absorption of flurbiprofen using rats

Four male Sprague-Dawley rats weighing 350 ± 20 g were used as a group for the study of percutaneous absorption of flurbiprofen to evaluate the enhancing effect of selected penetration enhancers (mixture of oleic acid and urea, oleic acid alone and control). Food and water were not restricted during the study. One day before the experiment, the jugular vein of each rat was cannulated with a Silastic® tubing (Dow Corning) and a polyethylene tubing (INTRAMEDIC®, Clay Adams) under light ether anesthesia.

The rats were lightly anesthetized with ether prior to dosing. The hair of dorsal area was removed carefully with an electric clipper, 500 μl of control and each test vehicles containing 1% flurbiprofen was uniformly applied on the dorsal area of 3 cm × 3 cm with gentle rubbing. After the application of vehicles, a blood sample of 250 μl was collected at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h postdose from jugular vein of the rat. Collected rat blood samples were immediately transferred into 0.25 ml polypropylene tubes containing a small amount of heparin and centrifuged at 7000 rpm for 3 min to obtain plasma. The plasma was stored at −20°C prior to analysis. Flurbiprofen in rat plasma was quantitated with the HPLC method developed in our laboratories (Chi et al., 1994).

The area under the plasma concentration-time curve (AUC) was determined to compare the amount of drug absorbed through the skin after the transdermal application of two test vehicles and a control vehicle. AUC from 0 to 6 h was calculated using the trapezoidal rule, AUC from 6 to 24 h using the log trapezoidal rule and AUC after 24 h using C_T/λ, where, C_T is the plasma concentration at 24 h postdose and λ is the elimination rate constant of terminal phase.

2.5. Statistics

Each experiment was repeated 4–8 times and their mean value with standard error was presented. Student's t-test was performed to see any significant difference in permeation or pharmacokinetic parameters between the control vehicle and test vehicles containing penetration enhancers.

3. Results and discussion

3.1. Effect of unsaturated fatty acids on skin permeation of flurbiprofen

Unsaturated fatty acids have been used as potent enhancers for many drugs (Yamada and Uda, 1987; Niazy, 1991; Green et al., 1988; Kim aet al., 1993). Cooper (1984) reported the structure-activity relationship clearly for the enhancement of skin permeation of salicylic acid by PG and fatty acids system. The enhancing effect of unsaturated fatty acids on the skin permeation of flurbiprofen through rat skins was determined using PG vehicle containing a series of unsaturated fatty acids at the concentration of 5%. The cumulative amounts of flurbiprofen permeated through excised rat skins from the vehicles at predetermined time intervals are shown in Fig. 1 and the permeation parameters calculated using the profiles are presented in Table 1. The permeation rate of flurbiprofen for the control vehicle was increased 5.8–17.5 times with the addition of unsaturated fatty acids. Linolenic acid showed the

most potent enhancing effect, followed by oleic, palmitoleic, linoleic and arachidonic acid, in that order. Generally, unsaturated fatty acids which showed large increase of partition coefficient of flurbiprofen were powerful enhancers.

The increase of lag time by unsaturated fatty acids of same carbon number was proportional to the increase of double bond numbers in the molecular structure. The numbers of double bonds in the structure of oleic and linoleic acids are one and two, and their lag times were 4.5 h and 5.5 h, respectively. The lag time of linolenic acid, which has three double bonds in structure, was 8.8 h, the longest lag time among the employed penetration enhancers. The more kinked shape in structure of fatty acids, with the increase of cis double bond number, makes it difficult to insert themselves into the lipid matrices of skin, which resulted in even longer lag time than the control vehicle. However, once they are packed in the skin, higher skin flux of the drug can be obtained due to the wider channel made.

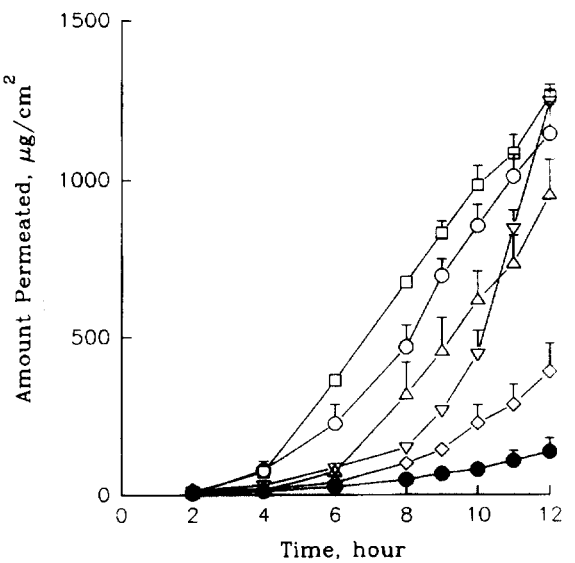

Fig. 1. Effect of unsaturated fatty acids in PG vehicle containing 1% flurbiprofen on the drug permeation through rat skins. Key: ●, control; ○, oleic acid 5%; □, palmitoleic acid 5%; △, linoleic acid 5%; ▽, linolenic acid 5%; ◇, arachidonic acid 5%. n = 4–8 (Mean ± S.E.).

3.2. Effect of saturated fatty acids on skin permeation of flurbiprofen

Although saturated fatty acids have been successfully used as penetration enhancers for several drugs (Ogiso and Shintani, 1990; Green et al., 1988), they did not show potent enhancing effects compared to the unsaturated fatty acids for some drugs such as salicylic acid (Cooper, 1985) and nicardipine (Davidson et al., 1986). To study the effect of saturated fatty acids on the skin permeation of flurbiprofen, capric acid, lauric acid and myristic acid were incorporated into 1% flurbiprofen-PG vehicle and the skin permeation of drug was measured using excised rat skins. The permeation profiles of flurbiprofen from these vehicles containing individual saturated fatty acids are shown in Fig. 2 and the permeation parameters calculated from these profiles are also presented in Table 1. As shown in Fig. 2, saturated fatty acids did not show any significant enhancing effect on the permeation of flurbiprofen through rat skins compared to the control PG vehicle. The increase of the permeation rate of capric acid, lauric acid and myristic acid was only 1.1–1.8 times. Lauric acid has been known to have a pronounced effect on the skin permeation of several compounds (Ogiso and Shintani, 1990; Barry, 1987; Kim et al., 1993), possibly due to an optimal balance of partition coefficient and affinity to the skin of hydrophobic groups of lauric acid (Ogiso and Shintani, 1990). However, on the skin permeation of flurbiprofen, lauric acid did not show any significant enhancing effect compared to the unsaturated fatty acids of 16–20 carbons, which may be attributed to the difference in lipid solubility and structure between unsaturated and saturated fatty acids. The melting points of saturated fatty acids studied are in the range of 31–59°C, which are much higher than those of unsaturated fatty acids, −50–4°C. Consequently, saturated fatty acids are expected to have lower solubility (Yalkowsky, 1983). Saturated fatty acids of linear shape and low solubility have less capability to disrupt the lipid packing of stratum corneum and to insert themselves into the lipid bilayers than kinked unsaturated fatty acids of high solubility.

Table 1
Permeation parameters of flurbiprofen through excised rat skins after the transdermal application of 1% flurbiprofen-PG vehicles containing various fatty acids and/or urea at the concentration of 5%, otherwise described

Penetration enhancers	Permeation parameters[a]			
	T_L (h)	J_s (μg/cm^2/h)	D $\times$ 10^3 (cm^2/h)	K $\times$ 10^1
None (Control)	6.8	22.7	0.76	0.54
	(0.3)[b]	(1.7)	(0.02)	(0.02)
Urea	3.8*	8.1	1.39*	0.11*
	(0.2)	(1.2)	(0.07)	(0.02)
Urea 10%	2.7*	3.2	1.54*	0.03*
	(0.1)	(0.5)	(0.02)	(0.01)
Palmitoleic acid	3.4*	147.5*	2.79*	0.25
	(0.2)	(4.3)	(0.18)	(0.22)
Oleic acid	4.5*	132.0*	1.06*	2.20*
	(0.3)	(6.5)	(0.04)	(0.28)
Linoleic acid	5.5*	118.2*	2.72*	0.75
	(0.2)	(7.7)	(0.29)	(0.46)
Linolenic acid	8.8*	397.2*	0.56*	12.4*
	(0.2)	(16.1)	(0.01)	(0.57)
Arachidonic acid	6.8	62.5*	3.67*	1.31*
	(0.1)	(1.9)	(0.18)	(0.04)
Capric acid	5.7	24.0	3.50*	0.13*
	(0.4)	(1.3)	(0.38)	(0.02)
Lauric acid	4.6*	40.1	2.76*	0.28*
	(0.1)	(1.1)	(0.12)	(0.01)
Myristic acid	6.8	31.2	4.77*	0.13*
	(0.3)	(1.1)	(0.32)	(0.01)
Oleic acid and urea	6.1*	220.7*	0.78	4.44*
	(0.1)	(4.3)	(0.08)	(0.36)

[a]T_L, lag time; D, diffusion coefficient; J_s, steady-state permeation rate; K, partition coefficient (skin/vehicle). [b]S.E. (n = 4–8). *significantly different from the control ($P < 0.05$).

3.3. *Effect of urea on skin permeation of flurbiprofen*

To study the penetration enhancing effect of urea on flurbiprofen permeation through rat skins, the skin permeation of flurbiprofen from 1% flurbiprofen-PG vehicles containing 5% and 10% urea, was determined using excised rat skins. The permeated amounts of flurbiprofen through excised rat skin as a function of time up to 12 h are presented in Fig. 3. As shown in this figure and in Table 1, the addition of urea in the vehicle decreased the permeation rate of flurbiprofen, which depends upon the concentration of urea in the vehicle. Even though urea 5% and 10% in PG vehicle increased diffusion coefficient of flurbiprofen approximately 2 times compared to the control PG vehicle, it was compensated by the 5–17 fold decrease of partition coefficient of the drug, which resulted in a decrease of the overall permeation rates of flurbiprofen. However, lag time was significantly shortened with the addition of urea.

It has been known that urea causes two changes in the barrier function of the skin through increase of the hydration of the stratum corneum and inducement of keratolysis of skin after prolonged contact (Hadgraft, 1984). This mechanism makes urea a possible penetration enhancer for a few drugs (Ritschel and Sprockel, 1988). However, urea did not play a role as an enhancer for the skin permeation of hydrophobic molecules like 5-fluorouracil (Williams and Barry, 1989), naloxone (Aungst et al., 1986), indomethacin (Sugibayashi et al., 1988), ketoprofen (Kim et al.,

1993) and flurbiprofen in this study, since the increased water content in lipids of skin by urea may inhibit the penetration of hydrophobic molecules. Nevertheless, urea is, still, a valuable penetration enhancer to shorten lag time, because of its rapid action on the structured lipids of skin (Beastall et al., 1986).

3.4. Effect of mixture of oleic acid and urea on skin permeation of flurbiprofen

The possibility of interaction between enhancers and flurbiprofen was also evaluated in this study. Oleic acid, as a representative for fatty acid, and urea were added into 1% flurbiprofen-PG vehicle at the concentration of 5% each, and the skin permeation of flurbiprofen from these vehicles was determined using excised rat skins. The skin permeation profiles of flurbiprofen are also presented in Fig. 3. Even though urea decreased the permeation rate of flurbiprofen through excised rat skins as explained previously, the mixture of oleic acid and urea at the same concentration levels showed 1.7-fold higher permeation rate than oleic acid only and 9.7-times

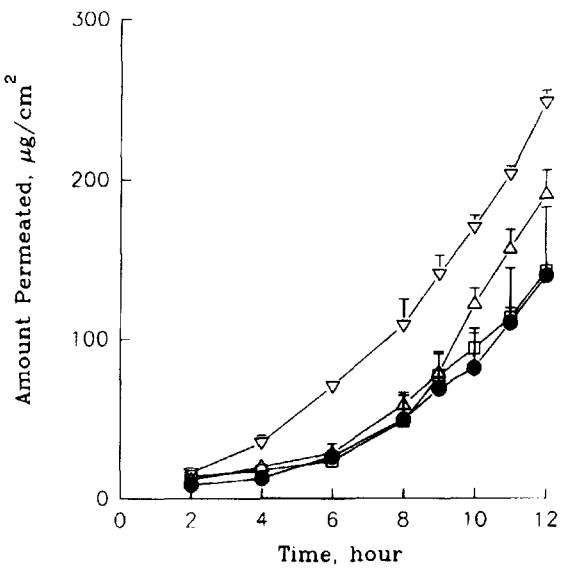

Fig. 2. Effect of saturated fatty acids in PG vehicle containing 1% flurbiprofen on the drug permeation through rat skins. Key: ●, control; □, capric acid 5%; △, myristic acid 5%; ▽, lauric acid 5%. n = 4–8 (Mean ± S.E.).

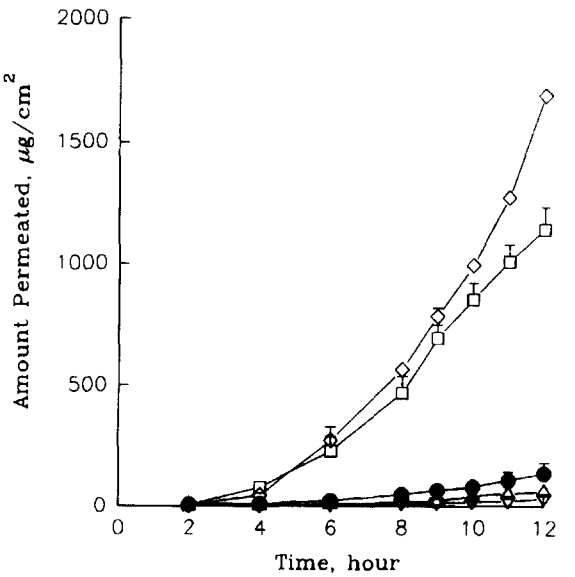

Fig. 3. Effect of oleic acid and/or urea in PG vehicle containing 1% flurbiprofen on the drug permeation through rat skin. Key: ●, control; □, oleic acid 5%; △, urea 5%; ▽, urea 10%; ◇, mixture of oleic acid 5% and urea 5%. n = 4–8 (Mean ± S.E.).

higher than the control vehicle. Since the increase of permeation rate of flurbiprofen with the addition of the mixture was only due to the partition coefficient between skin and vehicle, not the diffusion coefficient, as shown in Table 1, it can be supposed that there were molecular interactions, possibly weak hydrogen bonding among molecules of flurbiprofen, urea and oleic acid. In the evaluation of fatty acids as penetration enhancers, Ogiso and Shintani (1990) confirmed the reaction between fatty acids and the drug, propranonol. Similarly, the skin permeation of an acidic drug was promoted with several basic compounds (Büyüktimkin et al., 1993). Based on their explanation, it could be deduced that flurbiprofen was pulled to stratum corneum by weak molecular interaction exist among molecules when oleic acid was embedded into stratum corneum.

3.5. Percutaneous absorption of flurbiprofen in rats

After 1% flurbiprofen-PG vehicle containing oleic acid or the mixture of oleic acid and urea

was applied transdermally on dorsal skin of rats, their pharmacokinetic characteristics including bioavailability were determined and compared to the control vehicle without enhancer. The plasma concentration-time profiles of flurbiprofen after transdermal application of the control and each of the two test vehicles are shown in Fig. 4. The maximum concentrations of flurbiprofen(C_{max}) after the application of test vehicles containing oleic acid alone and the mixture were 1.7- and 2.5-times higher than that of the control vehicle, respectively, in the same rank order as results of previous skin permeation studies. As presented in Table 2, the AUCs obtained from the vehicle containing oleic acid alone and the mixture of oleic acid and urea were also 1.7-times and 2.3-times higher than the control vehicle, respectively, which indicates the increased extent of flurbiprofen permeation through the rat skin from the vehicle with these penetration enhancers. The time to reach maximum concentration(T_{max}) after the application of two test vehicles was approximately 2.0 h, while T_{max} of the control vehicle was 4.3 h.

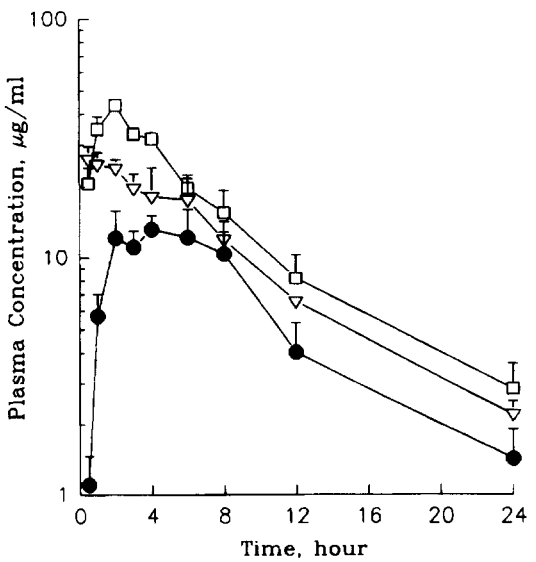

Fig. 4. Plasma concentration-time profiles of flurbiprofen after the transdermal application of 1% flurbiprofen-PG solutions containing penetration enhancers. Key: ●, control; ▽, oleic acid 5%; □, mixture of oleic acid 5% and urea 5%. $n = 4$ (Mean ± S.E.).

Table 2
Pharmacokinetic parameters in rats after transdermal application of 1% flurbiprofen-PG vehicles containing 5% oleic acid only and a mixture of 5% oleic acid and 5% urea

Penetration enhancers	AUC (μg·h/ml)	T_{max} (h)	C_{max} (μg/ml)
None (control)	157.0 ± 29.6*	4.3 ± 1.1	17.5 ± 1.1
Oleic acid	262.8 ± 32.9*	1.9 ± 0.8*	29.4 ± 2.9*
Oleic acid and urea	357.1 ± 43.2*	1.8 ± 0.3*	43.9 ± 1.4*

[a]Mean ± S.E. ($n=4$). *significantly different from the control ($P < 0.05$).

In the skin permeation studies, the lag time was also in the order of above T_{max} values.

From the above results, the mixture of urea and unsaturated fatty acid was found to be effective penetration enhancer for the skin permeation of flurbiprofen. In order to develop a transdermal preparation of flurbiprofen using this mixture, we will further evaluate milder systems than fatty acid/PG system which was known to be irritating in humans (Robinson et al., 1991).

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