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Preparation and Evaluation of Pranoprofen Gel for Percutaneous Administration

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ABSTRACT The percutaneous delivery of nonsteroidal anti-inflammatory drug (NSAID) has the advantages of avoiding the hepatic first pass effect and delivering the drug to the inflammation site at a sustained, concentrated level over an extended period of time. Hydroxypropyl methylcellulose (HPMC) and poloxamer 407 were used in an attempt to develop new topical formulations of pranoprofen. The effects of the drug concentration (0.04, 0.08, 0.12, 0.16, and 0.20%) on the rate of drug release from HPMC-poloxamer 407 gels were examined using a synthetic cellulose membrane at 37 ± 0.5°C. The rate of drug permeation increased significantly with increasing drug concentration in the gels until the concentration reached 0.16%, and increased slightly thereafter. The effects of temperature on the rate of drug release from the 0.16% pranoprofen gels were evaluated at 32, 37, and 42°C. The rate of drug release from the 0.16% pranoprofen gels increased with increasing temperature with activation energy (Ea) of 8.88 kcal/mol. Various penetration enhancers, such as nonionic surfactants and fatty acids, were incorporated in the gel formulation in an attempt to increase the level of drug permeation. Among the enhancers used, octanoic acid had the strongest enhancing effects with an enhancement factor of 3.09. The anti-inflammatory effect of the pranoprofen gel was evaluated using a rat paw-edema model. The 0.16% pranoprofen gel containing octanoic acid as an enhancer reduced the edema size by approximately 73% compared with that of the control group. These results highlight the feasibility of a topical gel formulation of pranoprofen containing an enhancer.

KEYWORDS Pranoprofen gels, Penetration enhancer, Gender, Swelling, Anti-inflammatory effects

INTRODUCTION

Pranoprofen is a potent NSAID that is widely used for the acute and long-term management of rheumatoid arthritis and osteoarthritis (Gennaro, 1995). However, alternative administration routes need to be considered in order to avoid the systemic side effects and gastric disorders that often occur after oral administration.

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The percutaneous delivery of NSAIDs has the advantages of avoiding the hepatic first pass effect and being able to deliver the drug at a sustained level over an extended period of time. NSAIDs administered percutaneously act mainly at the joints and related regions, and the drug can be concentrated at the inflammation site. Therefore, new formulations with suitable bioadhesive properties need to be developed. Percutaneous drug delivery allows the controlled delivery of drugs. The self-placement of a dosage form is possible because of their excellent accessibility. Moreover, the dosage form can be removed at any time. HPMC has been used to control the release of drugs from several pharmaceutical systems on account of its nontoxic nature, swelling properties, and ability to accommodate high levels of the drug. Poloxamer 407, which is a nontoxic copolymer with an average molecular weight of 11,500, contains 70% hydrophilic ethylene oxide units and 30% hydrophobic propylene oxide units. An aqueous 20–30 (w/w) % solution of this compound is a clear liquid at refrigerator temperatures (Schmolka, 1972; Chen-Chow & Frank, 1981; Miyazaki, 1984; Shin et al., 2000; Shin & Kim, 2000). Upon warming to room temperature, the solution forms a gel by undergoing a sol-gel transition. As a result of this reversible thermal gelation process, the drug-containing solution turns into a gel with slow release characteristics.

Despite several advantages of a transdermal delivery system over oral delivery, the excellent barrier function of the skin has allowed only a limited number of drugs to be administered using this system. The effects of various classes of transdermal penetration enhancers, such as the surfactants, glycols, and chelators, have been reported (Angust & Rogers, 1989; Ishida et al., 1981; Rhee et al., 1999; Sinha & Kaur, 2000; Mohamed, 2001) to affect the diffusion properties of drugs in the semisolid vehicles particularly when the rate of drug release at the application site is likely to limited by the diffusion of the drug (Larrucea, 2001). Various enhancers have been used with the aim of improving the drug permeability, including nonionic surfactants, glycols, fatty acids, and propylene glycols (Shin et al., 2005).

This study investigated the feasibility of a dermal delivery for pranoprofen by examining its in vitro release characteristics and anti-inflammatory effects. To optimize the pranoprofen gel formulation, the effects of the drug concentration, temperature, and penetration enhancer on the release of the drug were evaluated. The anti-inflammatory effects of the pranoprofen gels containing an enhancer were evaluated using a rat paw-edema model, and the inhibitory effect on edema was investigated.

MATERIALS AND METHODS

Materials

The pranoprofen was supplied by Kolon Pharm. Co. Ltd. (South Korea). The hydroxypropyl methylcellulose was obtained from Dow Chemical Co. Ltd. The poloxamer 407 was purchased from BASF Co. (Germany), and the carrageenan was purchased from Sigma Chemical Co. (St. Louis, MO). The nonionic surfactants, such as polyoxyethylene 2-stearyl ether, polyoxyethylene 2-oleyl ether, and polyoxyethylene 23-lauryl ether, were obtained from Sigma Chemical Co. (St. Louis, MO). The anhydrous ethyl alcohol was HPLC grade supplied by J. T. Baker Inc. All the other reagents were of analytical grade and used without further purification.

Preparation of HPMC-poloxamer Gels Containing Pranoprofen

The HPMC-poloxamer gel that showed suitable bioadhesion (Shin et al., 2005) was prepared. Briefly, 2 g of HPMC was dissolved in hot water to make a 35 g solution. 20 g of poloxamer 407 was dissolved in water in a refrigerator overnight to make a 55 g solution. Pranoprofen (0.16 g) was added to the above two polymer solutions with vigorous stirring, and water was added to make 100 g of the gel.

Permeation of Pranoprofen from the HPMC-Poloxamer Gels

The permeation of pranoprofen from the HPMC-poloxamer gels was determined using a 20% PEG solution as the receptor. A synthetic cellulose membrane was mounted on the receptor compartment of the diffusion cell. Two grams of the prepared HPMC-poloxamer gels containing pranoprofen was placed in intimate contact with the cellulose membrane and the donor cap was covered with parafilm and clamped. The sampling port was sealed with parafilm in order to prevent evaporation of the receptor

medium. The receptor solution was maintained at 37°C using a circulating water bath and stirred with a magnetic stirring bar. The donor compartment was maintained at an ambient temperature of 25 ± 1°C. The effect of the drug concentration on its release from the gels was examined using drug concentrations of 0.04%, 0.08%, 0.12%, 0.16%, and 0.2% (w/w). The effects of temperature on the rate of drug release were determined at 32°C, 37°C, and 42°C in a circulating water bath. The whole receptor medium were withdrawn at predetermined intervals and replaced immediately with the same amount of fresh receptor medium.

HPLC Determination of Pranoprofen

The pranoprofen concentration was determined using high performance liquid chromatography (HPLC, Waters 501). The column was a μ-Bondapak C_{18} (Waters). The mobile phase was a combination of 0.03 M ammonium acetate in methyl alcohol:water (30:70), and the column temperature was maintained at ambient. A flow rate of 1.0 mL/min yielded an operation pressure of ~1200 psi. The UV detector was operated at a wavelength of 247 nm. Under these conditions, the retention time of pranoprofen was 7.7 min.

Mathematical Models for Drug Release

Higuchi proposed two equations to describe the kinetics of drug release based on the state of the drug in the vehicle: released from the solution and released from suspensions. The drug release rates were examined using the simplified Higuchi diffusion Eq. (1), which depicts the drug release from one side of a semisolid layer containing the dissolved drug.

$$q = 2C_0(D_t / \pi)^{1/2} \quad (1)$$

where q is the amount of the drug released into the receptor medium per unit area of exposure, C_0 is the initial drug concentration in the vehicle, D is the apparent diffusion coefficient of the drug, and t is the time elapsed since the start of drug release.

In the case of passive diffusion, Fick's law can be used to model the steady-state flux through the unit area of the membrane,

$$J = P(C_d - C_r) \quad (2)$$

where J is the flux per unit area, P is the permeability coefficient, and C_d, and C_r are the concentrations in the donor and receptor solutions, respectively. (C_d–C_r) can be replaced by C_d in the case that sink conditions are maintained on the receptor side.

$$J = PC_d \quad (3)$$

The permeability coefficient, P, is constant for a given drug under the same experimental conditions, and there should be a linear relationship between the flux and the donor concentration.

Skin Preparation

A male rat (Sprague Dawley rat strain) was sacrificed by snapping the spinal cord at the neck. The hair of the abdominal area was carefully removed using electric clippers. A square section of the abdominal skin was excised, and the adhering fat and other visceral debris in the skin were removed carefully from the undersurface with tweezers (Durrhein, 1980; Shin et al., 1999). The excised skin was used immediately.

Effect of the Enhancer on the Permeation of Pranoprofen from the HPMC-Poloxamer Gels Through the Rat Skin

The excised abdominal skin was mounted in a diffusion cell. The 0.16% pranoprofen gel was mixed with the 5% (w/v) enhancer. The enhancing effects of various enhancers were compared. The following enhancers were used: the nonionic surfactants, such as polyoxyethylene-2-oleyl ether, polyoxyethylene-2-stearyl ether, polyoxyethylene-23-lauryl ether, and the fatty acids, such as octanoic acid, oleic acid. The amount of the drug permeated was determined by HPLC.

Analysis of the Permeation Data

The cumulative amount of the drug permeated was plotted as a function of time, and the flux was calculated from the steady-state part of the curve. All the means are presented with their standard deviation (mean ± S.D.). An unpaired student's *t*-test was used to compare the controls and enhancer group. A p value <0.01 was considered significant.

The effectiveness of the penetration enhancer was determined by comparing the pranoprofen flux in the presence or absence of an enhancer. The effectiveness was defined as the enhancement factor (EF), which was calculated using the following equation:

$$\text{EF} = (\text{flux of samples containing an enhancer}) / (\text{flux of control sample})$$

Anti-inflammatory Effects of the Pranoprofen Gels Containing an Enhancer on Carrageenan-induced Paw-edema in Rats

The percentage inhibition of swelling in the rat was determined using the Levy method (Levy, 1969). The anti-inflammatory effects of pranoprofen on carrageenan-induced paw-edema in rats were determined using a mercury plethysmometer. Male Sprague-Dawley rats weighing 125–160 g were used for the experiments. The animals were allowed access to food and water ad libitum.

The anti-inflammatory effects of the pranoprofen gel were evaluated by applying the gel containing 0.16% pranoprofen on the right hind paw of the rats. The control group was treated with normal saline. After 3 hr, 0.1 mL of a 1% carrageenan solution in physiological saline or 0.1 mL of normal physiological saline as the control were injected intradermally in the right hind paw of the rats. The edema volume was measured using a plethysmometer (Ugo Bacile, Model 7150) 3 hr after the carrageenan injection. The extent of swelling (%) was calculated from the difference in the volume between immediately and 3 hr after the carrageenan injection (at least six rats per group).

$$\text{Swelling}(\%) = \frac{V - V_1}{V_1} \times 100 \quad (4)$$

Where, V is the volume 3 hr after the carrageenan injection in the sole of the foot and V_i is the volume immediately after the injection (Shin et al., 2000).

$$\text{Inhibition of swelling}(\%) = 1 - \frac{\text{Swelling \% of the group treated}}{\text{Swelling \% of the control}} \times 100 \quad (5)$$

RESULTS AND DISCUSSION

Effect of Pranoprofen Concentration on Drug Release

The effect of the pranoprofen concentration (0.04, 0.08, 0.12, 0.16, and 0.20%) on the rate of drug release across the synthetic cellulose membrane was examined from the prepared HPMC-poloxamer gels at 37 ± 0.5°C. The permeation of the drug followed Fick's law and showed concentration-dependent passive diffusion. The rate of drug permeation increased linearly with increasing drug concentration in the gels until the concentration reached 0.16%, and increased slightly thereafter (Fig. 1). In the diffusion process, there could be two steps—one is diffusion through the gel, the other is diffusion through the membrane/skin. The diffusion measurements obtained would be a combination of both the processes.

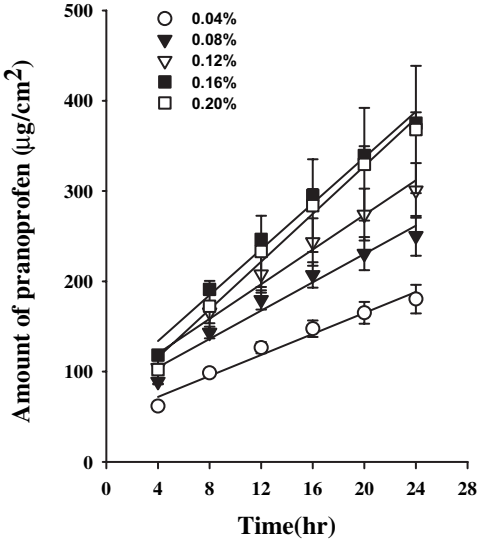

FIGURE 1 Effect of Pranoprofen Concentration in the HPMC-Poloxamer Gel on Drug Release Through Cellulose Membrane.

Hence, above a certain concentration, there may be limitations in the amount of drug that can diffuse out of the gel to the skin. On the other hand, at the low concentration, it would be expected that diffusion through the membrane/skin would be the rate-determining step.

Effect of Temperature on Drug Release

The effect of temperature on the release of pranoprofen from the gel formulations was evaluated at 32, 37, 42°C. All the experiments were performed at least in triplicate. Fig. 2 shows the temperature dependency of drug release.

The relationship between the diffusion coefficient and temperature is as follows:

$$D = D_0 \ e^{-Ea/RT} \tag{6}$$

An Arrhenius relationship was observed between the natural logarithm of the apparent diffusivity (D) and the reciprocal of absolute temperature (T), as shown in Fig. 2. The activation energy (E_a) and pre-exponential term were obtained from the slope and intercept.

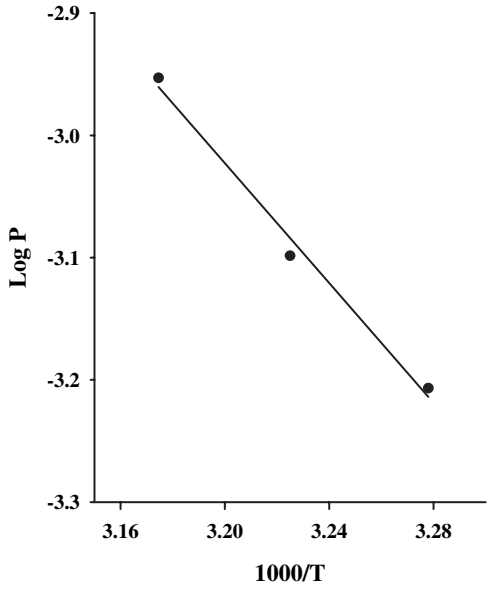

FIGURE 2 **Effect of Temperature on Drug Release From The 0.16% Pranoprofen Gel.**

The permeability coefficient is then defined as follows:

$$P = \frac{\text{Flux}}{\text{Solubility}} \tag{7}$$

$$P = P_0 . e^{\frac{-E_a}{RT}} \tag{8}$$

$$\text{Log}\, P = \text{Log}\, P_0 - \frac{E_a}{R \cdot 2.303 \cdot 1000} \frac{1000}{T} \tag{9}$$

$$\text{Slope} = -\frac{E_a}{R \cdot 2.303} \cdot \frac{1}{1000} \tag{10}$$

$$\begin{aligned} Ea &= -\text{Slope} \times R \times 2.303 \times 1000\,\text{cal} \\ &= -\text{slope} \times 1.987 \times 2.303\,\text{kcal} \end{aligned} \tag{11}$$

The activation energy of drug permeation from the 0.16% pranoprofen gel (E_a), which was calculated from the slope of log P vs. $1000/T$ plots, was 8.88 kcal/mol (Fig. 2).

In Vitro Skin Permeation Study with Various Biological Factors

In vitro skin permeation studies with various skin conditions, such as age, gender, and skin site, were performed to determine the effect of the rat skin condition on drug permeation.

Effect of the Rat Age on Pranoprofen Permeation from the HPMC-Poloxamer Gels

The abdominal skins of old rats and young rats were used to determine the effect of age on the permeation of pranoprofen from the HPMC-poloxamer gels. The rats were classified according to the number of weeks after birth (6, 8, and 12 weeks). As shown in Fig. 3, the rate of pranoprofen permeation was higher in the young rat skin than the old rat skin.

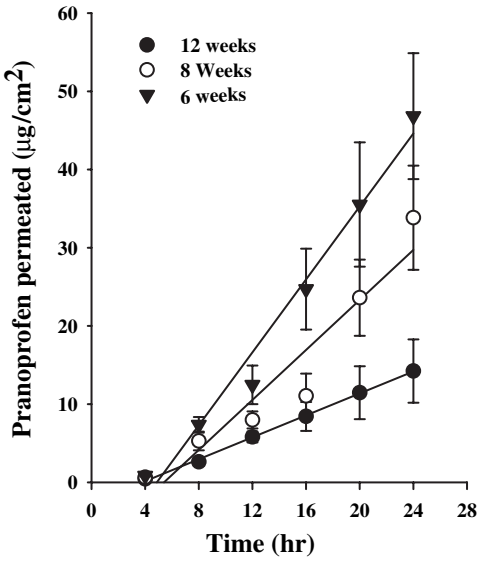

FIGURE 3 Permeation of Pranoprofen through the Male Skin According to Rat Age.

Effect of the Gender on Pranoprofen Permeation from the HPMC-Poloxamer Gels

The in vitro permeation of pranoprofen gel was examined using the skin from male and female rats (12 weeks). The aim was to determine if there were any gender effects on the permeation of pranoprofen. There was a higher rate of pranoprofen permeation in males than in females (Fig. 4).

Effect of the Skin Site on Permeation of Pranoprofen from the HPMC-Poloxamer Gels

The dorsal and abdominal skins of male rats were used to determine if there were any site effects (12 weeks). The results showed that the abdominal skin was more permeable than the dorsal skin (Fig. 5).

Permeation of Pranoprofen from the HPMC-Poloxamer Gels Containing Various Enhancers Across the Rat Skin

The effect of various enhancers on the permeation of pranoprofen across the rat skin was investigated. The level of drug permeation was increased by incorporating penetration enhancers, such as nonionic surfactants and fatty acids in the gel formulation at a concentration of 5%. The enhancer might affect the fluidity of the stratum corneum allowing the drugs to permeate better through the rat skin (Shin et al., 2001).

Table 1 shows the permeation data of pranoprofen from the gels in the presence and absence of enhancers.

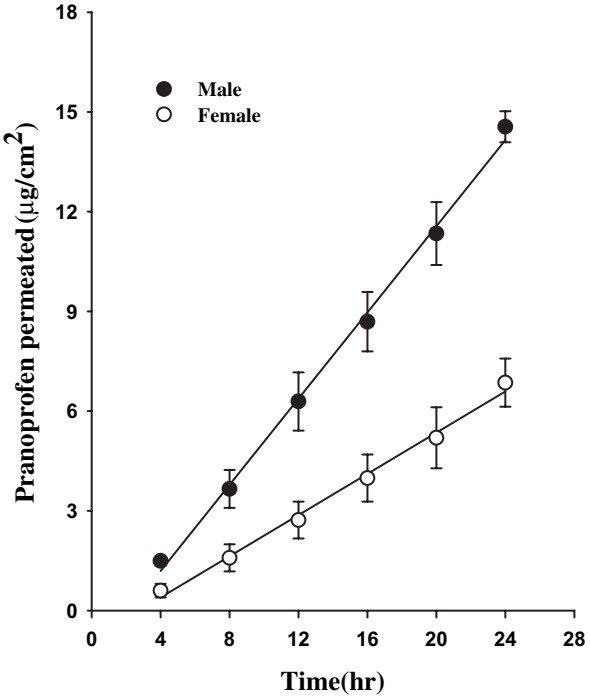

FIGURE 4 Permeation of Pranoprofen through the Rat Skin According to Gender.

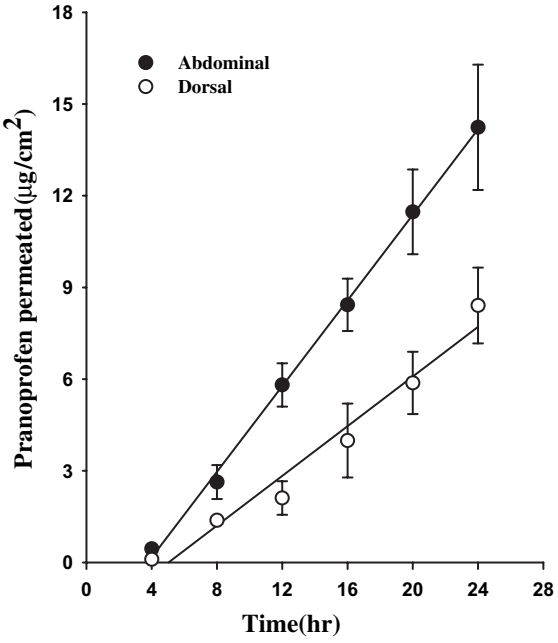

FIGURE 5 Permeation of Pranoprofen through the Male Skin According to the Skin Site.

TABLE 1 **Effect of Enhancers on the Permeation of Pranoprofen from the Gels through the Rat Skin**

	Enhancer	Permeation rate ($\mu/cm^2/hr$)	EF
Control	No-enhancer	0.5 8 ± 0.04	1
Nonionic surfactants	Polyoxyethylene-23-lauryl ether	1.18 ± 0.11	2.03
	Polyoxyethylene-2-stearyl ether	0.22 ± 0.02	0.38
	Polyoxyethylene-2-oleyl ether	1.2 9 ± 0.11	2.23
Fatty acids	Octanoic acid	1.7 9 ± 0.11	3.09
	Oleic acid	1.12 ± 0.10	1.93

Among the various enhancers used, octanoic acid had the highest enhancing effect with an enhancement factor of 3.09.

Anti-inflammatory Effects of the of Pranoprofen Gels Containing an Enhancer on Carrageenan-induced Paw-edema in Rats

The percentage inhibition of swelling in the rat was determined using the Levy method (Levy, 1969). The anti-inflammatory effects of pranoprofen on carrageenan-induced paw-edema in rats were determined using a mercury plethysmometer. The control group was treated with normal saline.

A pranoprofen gel containing octanoic acid as the enhancer showed significant inhibition of swelling compared with the control group. The pranoprofen gel containing the enhancer reduced the edema size by 73% compared with gel with no enhancer (Fig. 6).

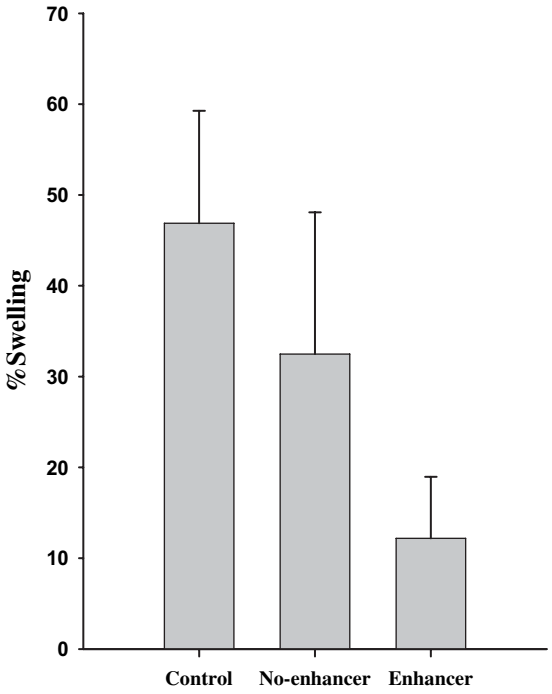

FIGURE 6 **Anti-inflammatory Effects of 0.16% Pranoprofen Gels Containing an Enhancer Using Rat Paw Swelling Methods.**

CONCLUSION

This study examined the percutaneous absorption of pranoprofen from HPMC-poloxamer gels. The drug release rate increased with increasing drug concentration and temperature. The activation energy of drug permeation from the 0.16% pranoprofen gel was 8.88 kcal/mol. The rate of pranoprofen permeation through the rat skin was higher in the young, male, and abdominal skin. Among the various enhancers used, octanoic acid had the highest enhancing effects with an enhancement factor of 3.09 compared with that of the pranoprofen gel containing no enhancer. The pranoprofen gels containing an enhancer reduced the level of swelling by approximately 73% compared with that of the control group. The HPMC-poloxamer gel containing a penetration enhancer is a promising modality for the controlled delivery of pranoprofen.

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