Arch Pharm Res Vol 29, No 10, 928-933, 2006

Archives of Pharmacal Research
http://apr.psk.or.kr

Enhanced Transdermal Delivery of Pranoprofen from the Bioadhesive Gels

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(Received July 11, 2006)

Percutaneous delivery of NSAIDs has advantages of avoiding hepatic first pass effect and delivering the drug for extended period of time at a sustained, concentrated level at the inflammation site that mainly acts at the joint and the related regions. To develop the new topical formulations of pranoprofen that have suitable bioadhesion, the gel was formulated using hydroxypropyl methylcellulose (HPMC) and poloxamer 407. The effects of temperature on drug release was performed at 32°C, 37°C and 42°C according to drug concentration of 0.04%, 0.08%, 0.12%, 0.16%, and 0.2% (w/w) using synthetic cellulose membrane at 37±0.5°C. The increase of temperature showed the increased drug release. The activation energy (Ea), which were calculated from the slope of lop P versus 1000/T plots was 11.22 kcal/mol for 0.04%, 10.79 kcal/mol for 0.08%, 10.41 kcal/mol for 0.12% and 8.88 kcal/mol for 0.16% loading dose from the pranoprofen gel. To increase the drug permeation, some kinds of penetration enhancers such as the ethylene glycols, the propylene glycols, the glycerides, the non-ionic surfactants and the fatty acids were incorporated in the gel formulation. Among the various enhancers used, propylene glycol mono laurate showed the highest enhancing effects with the enhancement factor of 2.74. The results of this study suggest that development of topical gel formulation of pranoprofen containing an enhancer is feasible.

Key words: Pranoprofen, Gels, Penetration enhancer, Permeation, Hydroxypropyl methylcellulose, Poloxamer

INTRODUCTION

Pranoprofen, a potent NSAID (nonsteroidal anti-inflammatory drug), has been widely used for the acute and long-term management of rheumatoid arthritis and osteoarthritis (Gennaro, 1995). To avoid the systemic side effects and gastric disorders that could be occurred after oral administration, alternative routes of administration have been considered.

Percutaneous delivery of NSAIDs has advantages of avoiding hepatic first pass effect and delivering the drug for extended period of time at a sustained level. Percutaneously administered NSAID mainly acts at the joint and the related regions, and the drug can be concentrated at the inflammation site. Various topical or transdermal formulations such as creams, ointments, patches and gels are being developed to deliver the drug *via* skin. Percutaneous drug delivery has some advantages of providing the controlled delivery of drugs. In case of their application such as ointments, creams, it is difficult to expect their effects, because wetting, movement and contacting easily remove them. We need to develop the new formulations that have suitable bioadhesion. The percutaneous administration of bioadhesive gels has good accessibility and can be applied, localized and removed easily. Because of its excellent accessibility, self-placement of a dosage form is possible. Moreover, the dosage form can be removed at any time. Hydroxypropyl methylcellulose (HPMC) was used to control drug release from several pharmaceutical systems because of its non-toxic nature, swelling properties. Poloxamer 407, non-toxic copolymer with average molecular weight of 11,500, contains 70% hydrophilic ethylene oxide units and 30% hydrophobic propylene oxide units. Aqueous solution from 20 to 30 (w/w) % of this compound is a clear liquid at refrigerator temperature. It forms a gel on warming to room temperature by undergoing a sol-gel transition. As a result of this reverse thermal gelation, the drug-containing solution turns into a

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gel and has slow release characteristics (Schmolka, 1972; Miyazaki *et al.*, 1984; Shin *et al.*, 2000; Shin and Kim, 2000).

In spite of many advantages of transdermal delivery system over oral delivery, only a limited number of drugs have been used to develop the system due to the excellent barrier function of the skin. The effect of various classes of transdermal penetration enhancers such as the surfactants, the glycols, and the chelators have been studied (Angust *et al.*, 1989; Ishida *et al.*, 1981; Shin *et al.*, 2005) to determine the diffusion properties of drugs in the semisolid vehicles especially when the release of drugs at the application site is likely to be rate-limited by the diffusion of drug.

To increase the drug permeation, some kinds of penetration enhancers such as the ethylene glycols, the propylene glycols, the glycerides, the non-ionic surfactants and the fatty acids were incorporated in the gel formulation. To optimize the pranoprofen gel formulation, the effects of drug concentration, temperature, and penetration enhancer on drug release were evaluated.

MATERIALS AND METHODS

Materials

Pranoprofen was supplied by Kolon Pharm. Co., Ltd. (Korea). Hydroxypropyl methylcellulose was obtained from Dow chemical Co. Ltd. (U.S.A.), poloxamer 407 was from BASF Co. (Germany), and carrageenan was purchased from Sigma Chemical Co. (U.S.A.). The propylene glycols such as propylene glycol mono caprylate, propylene glycol mono laurate, propylene glycol laurate, the glycerides such as caprylocaproyl macrogol-8 glycosides, oleyl macrogol-6 glycosides, and the glycols such as tetraethylene glycol (TEG) and diethylene glycol (DEG) were purchased from Sigma Chemical Co. (U.S.A.). All reagents of analytical grade were used without further purification. Anhydrous ethyl alcohol was HPLC grade from J. T. Baker Inc. (U.S.A.).

Measurement of viscosity

The viscosity of each gel was measured by viscometer equipped with a sensor system MV II (HAAKE, Germany). The sensor was inserted into a gel sample in MV II cup and adjusted to a rate of shear of 1.8 (sec^{-1}). It took approximately 45s to equilibrate the sample. The viscosity of sample was then determined by multiplying the observed reading by the shear rate.

Measurement of bioadhesive forces

Adhesive forces were determined by measuring the maximum detachment force using Auto Peeling Tester (C.K. Trading Co. South Korea). To compare the bioadhesive forces of HPMC gels relatively, rat intestines were used. Cyanoacrylate adhesive was used to fix the intestine of rats to both the upper and lower supports. The HPMC-poloxamer gels were placed on the mucosa attached to the both supports (contact surface area, 0.5 cm^2). After attaching the gel to intestine mucosa, the force (contact pressure, 50 gf) was applied for five minutes. The detachment procedure was carried out at a speed of 150 mm/min until the complete detachment of the components was achieved. The force required to completely separate two compartments was recorded as adhesion forces, which was designated as gram force (gf).

Preparation of HPMC-poloxamer 407 gels

The various concentrations of HPMC K 100M and poloxamer 407 were dissolved in water with gentle stirring. The solution was left in a refrigerator overnight to complete polymer dissolution and water was added to make a final 10 g.

Preparation of HPMC-poloxamer gels containing pranoprofen

Two grams of HPMC was dissolved in hot water to make 35 g. Twenty grams of poloxamer 407 was dissolved in 55 g of water and left overnight in a refrigerator to complete dissolution. 0.16% pranoprofen was added to the poloxamer solution with vigorous stirring and combined with HPMC solution and water was added to make final 100 g.

Determination of drug solubility in various concentrations of PEG

An excess amount of pranoprofen was added to the various percentage of PEG solution and shaken vigorously at 37°C for 24 h. The concentration of pranoprofen was determined by HPLC after proper dilution.

Permeation of pranoprofen from the HPMC-poloxamer gels

The flux of pranoprofen from the HPMC-poloxamer gels was determined using the 20% PEG solution as a receptor. The synthetic cellulose membrane was mounted on the receptor compartment of the diffusion cell. Two grams of prepared HPMC-poloxamer gels containing pranoprofen was placed in intimate contact with the cellulose membrane and the donor cap was covered with a parafilm and clamped. The sampling port was sealed with a parafilm to prevent the evaporation of the receptor medium. Twenty percent PEG solution was used as receptor solution. The receptor solution was maintained at 37°C by a circulating water bath and stirred by a magnetic stirring bar. The donor compartment was maintained at ambient temperature of 25±1°C. The effects of temperature

on drug release was performed at 32°C, 37°C and 42°C according to drug concentration of 0.04%, 0.08%, 0.12%, 0.16%, and 0.2% (w/w) by thermostated water bath. The total samples (20ml) from the receptor compartment were withdrawn at predetermined intervals to maintain a sink condition, and immediately replaced by the same amount of fresh PEG solution.

HPLC determination of pranoprofen

The concentration of pranoprofen was assayed by HPLC methods. The column was μ-Bondapak C_{18} (Waters, U.S.A.), the mobile phase was a combination of 0.03M ammonium acetate in methyl alcohol: water (30:70), and 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 the wavelength of 247 nm. Under these conditions, pranoprofen peak appeared at the retention time of 7.7 min.

Data treatment for drug release studies

Two mathematical equations were proposed by Higuchi to describe the kinetics of drug release based on the state of drug in the vehicle: release from solutions and release from suspensions. In the present study, the drug release rates were evaluated according to the simplified Higuchi diffusion equation (1), depicting the drug release from one side of a semisolid layer in which the drug is dissolved.

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

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

In case of passive diffusion, the steady-state flux through unit area of a membrane is given by Fick's law,

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

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

$$J = P\, C_d \quad (3)$$

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

In vitro skin permeation study

Skin preparation

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

Effect of an enhancer on the permeation of pranoprofen from the HPMC-poloxamer gels through rat skin

The excised abdominal skin was mounted in a diffusion cell. And other conditions were same as above experimental method. The 0.16% pranoprofen gel was mixed with the 5% (w/v) enhancer. Two different types of the enhancer were used to compare the effects. The enhancer used were the glycols such as diethylene glycol, tetraethylene glycol, and the propylene glycols such as propylene glycol mono caprylate, propylene glycol mono laurate, propylene glycol laurate, and the glycerides such as oleyl macrogol-6 glycerides, caprylocaproyl macrogol-8 glycerides. The enhancer might affect the fluidity of stratum corneum structure and drugs could be permeated better through the rat skin. The amount of drug permeated was determined by HPLC.

Analysis of permeation data

The cumulative amount of the permeated drug was plotted versus time, and the flux was calculated from the steady-state part of the curve. The effectiveness of penetration enhancer was determined by comparing the flux of pranoprofen in the presence and absence of enhancer.

It was defined as the enhancement factor (EF). EF was calculated using the following equation:

EF = (flux of samples containing an enhancer) / (flux of control sample)

RESULTS AND DISCUSSION

Effects of poloxamer 407 concentration at 2% HPMC gels on the bioadhesive forces and viscosity

To establish the optimal formula of bioadhesive polymers, the determination of bioadhesive forces is frequently required. If we could identify the relationship between the bioadhesive forces and viscosity, the convenient, time saving determination of viscosity might be available instead of the bioadhesive determination. The rheological properties of bioadhesive gels have been investigated by several authors (Tur and Ch`ng, 1998; Shin *et al.*, 2000; Cho *et al.*, 1997; Prasad *et al.*, 1979), although there is still debate regarding the relationship between these properties and

bioadhesive performances. The previous study (Shin *et al.*, 2000) suggested that the relationship between the viscosity of carbopol gel system and bioadhesion may facilitate optimization of mucoadhesive performance, leading to the development of more effective bioadhesive dosage forms

If the bioadhesive gels are applied on the body of 37°, it is convenient to apply at the fluid state and turns into the viscous gels state, showing the bioadhesiveness. It has been known that poloxamer exists in the solution state at a refrigerator temperature and in the gel state on warming to room temperature (Cho *et al.*, 1997). Searching for thermo-gelling gels, the addition of poloxamer 407 into the HPMC gels were tried for the reverse thermal gelation properties.

The viscosities of 2% HPMC gels containing 0%, 5%, 10%, 15%, and 20% poloxamer 407 were 44.8, 0.75, 2.28, 139, and 227 Pa's, respectively (Fig. 1). As the viscosity of the system increases, the bioadhesive forces increased. The previous study (Cho *et al.*, 1997) showed that as the temperature and/or poloxamer concentration increased, the viscosity increased in the 15, 20, and 25% solution of poloxamer, however, the 10% solution of poloxamer did not form a gel remaining relatively constant, regardless of increasing temperature. The surface tension profiles of poloxamer 407 according to poloxamer concentration showed the two marked inflection points at concentrations of 0.003% and 17.5% (w/w). This range of concentration is close to the critical micelle concentration range of conventional alkyl polyoxyethylene ethers (Cho *et al.*, 1997; Prasad *et al.*, 1979). It is suggested that such changes are a consequence of interaction between poly (oxyethylene) chains of adjacent micelles.

There were close relationships between the concentration of HPMC in gel and the bioadhesive forces (Fig. 1). In this study, 2% HPMC based bioadhesive polymer gels containing the 20% poloxamer 407 could be formulated and its physicochemical characteristics were evaluated.

Solubility of pranoprofen

The aqueous solubility should be increased to maintain sink condition during the permeation studies. The solubility of pranoprofen could be improved by addition of a water-miscible hydrophilic polymer like PEG 400 into the aqueous solution as a solubilizer for pranoprofen. By adding PEG, the solubility of pranoprofen increased, which showed maximum solubility at 20% PEG solution (Fig. 2).

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 experiments were carried out at least in triplicate. The dependency of drug release on temperature is shown in Fig. 3.

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

$$D = D_0 e^{-Ea/RT} \quad (4)$$

A linear relationship was observed between the natural logarithm of apparent diffusivity (D) and the reciprocal of

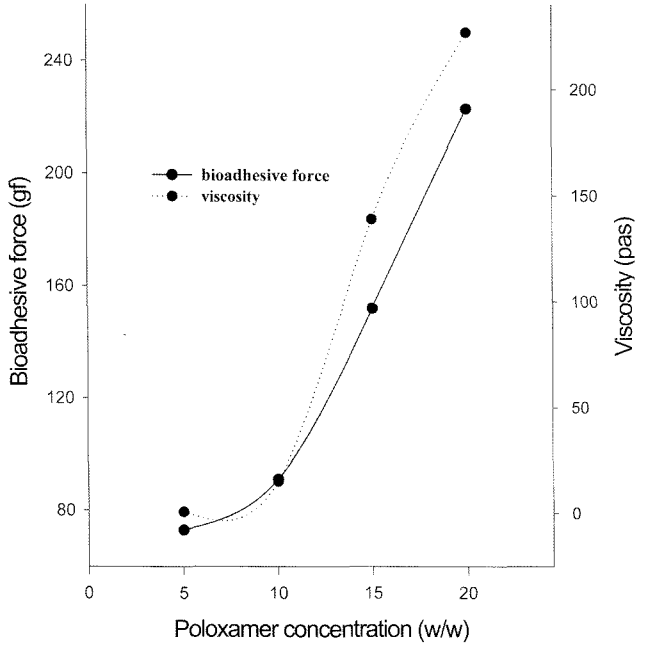

Fig. 1. Effects of poloxamer 407 concentration at 2% HPMC K 100 M gels on the bioadhesive forces and the viscosity

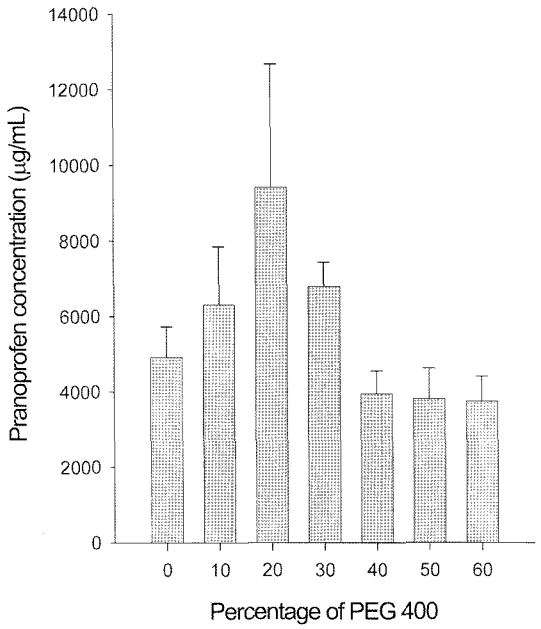

Fig. 2. Solubility of pranoprofen in various concentration of PEG 400 solution

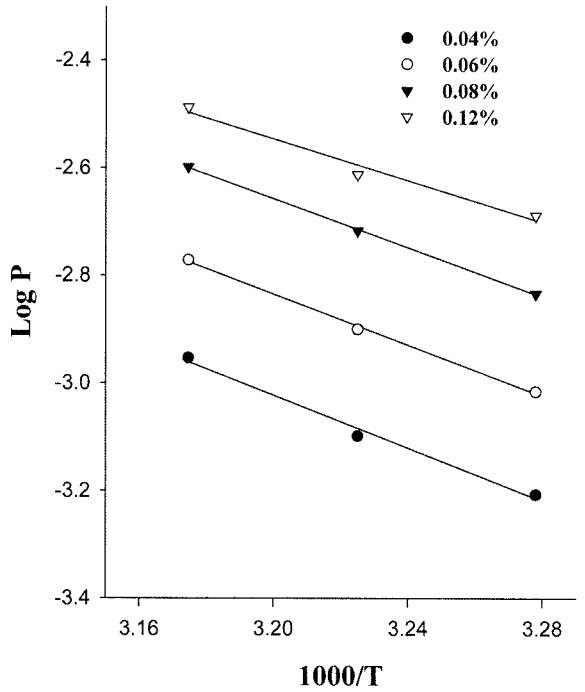

Fig. 3. Effect of temperature on pranoprofen release from the HPMC-poloxamer gels containing various loading dose

temperature (T) as shown in Fig. 3. The slope was used to calculate the activation energy (Ea) for drug diffusion. The intercept was used to calculate the pre-exponential term.

The Permeability coefficient is then defined by:

$$P=\frac{Flux}{Solubility} \quad (5)$$

$$P=P_0 \cdot e^{\frac{E_a}{RT}} \quad (6)$$

$$LogP=LogP_0-\frac{E_a}{R\cdot 2.303\cdot 1000}\cdot 1000 \quad (7)$$

As expected from Equation 9, a plot of log P versus 1000/T yields a straight line.

$$Slope=-\frac{E_a}{R\cdot 2.303}\cdot\frac{1}{1000} \quad (8)$$

$$Ea=-Slope\times R\times 2.303\times 1000cal$$
$$=-slope\times 1.987\times 2.303kcal \quad (9)$$

The activation energy which was measured from the slope of log P versus 1000/T plots (Fig. 3) were 11.22 kcal/mol for 0.04% concentration, 10.79 kcal/mol for 0.08% concentration, and 10.41 kcal/mol for 0.12% concentration, 8.88 kcal/mol for 0.16% concentration from HPMC-poloxamer gels (Table I).

Table I. The activation energy and log P versus 1000/T

Drug concentration	log P vs 1000/T	Ea (activation energy) (kcal/mol)
0.04%	2.45	11.22
0.08%	2.36	10.79
0.12%	2.27	10.41
0.16%	1.94	8.88

Table II. Enhancement factor according to various enhancers

	Enhancer	Permeation rate ($\mu g/cm^2/h$)	EF
Control	No-enhancer	0.58±0.04	1
Glycols	Diethyleneglycol	1.01±0.08	1.72
	Tetraethylene glycol	1.55±0.11	2.67
Glycerides	Caprylocaproyl macrogol-8 glycosides	0.86±0.07	1.48
	Oleyl macrogol-6 glycosides	1.56±0.11	1.95
Propylene glycols	Propylene glycol mono caprylate	0.96±0.08	1.66
	Propylene glycol mono laurate	1.59±0.12	2.74
	Propylene glycol laurate	0.59±0.06	1.01

Permeation of pranoprofen from the HPMC-poloxamer gels containing various enhancers across the rat skin

To increase the drug permeation, some kinds of penetration enhancers such as the ethylene glycols, the propylene glycols, the glycerides were incorporated in the gel formulation at concentration of 5%. The effect of enhancers on the permeation of pranoprofen across the rat skin was investigated.

Table II represents the permeation data of pranoprofen from the gels in the absence and presence of enhancers. Among the various enhancers used, propylene glycol mono laurate showed the highest enhancing effects with the enhancement factor of 2.74.

CONCLUSION

The present investigation on the percutaneous absorption of pranoprofen from the HPMC-poloxamer gels showed following results.

1. The activation energy of release was 11.27 kcal/mol for 0.04% concentration, 10.79 kcal/mol for 0.08% concentration, and 10.41 kcal/mol for 0.12% concentration, 8.89 kcal/mol for 0.16% concentration.

2. Among the enhancers used such as the ethylene glycols, the propylene glycols, the glycerides, propylene glycol mono laurate showed the best enhancement. Enhancement factor of the pranoprofen gels containing propylene glycol mono laurate was 2.74 comparing the pranoprofen gels containing no-enhancer.

3. For the enhanced transdermal delivery of pranoprofen, the HPMC-poloxamer gels containing penetration enhancer could be developed.

ACKNOWLEDGEMENTS

This study was financially supported by research fund of Chonnam National University in 2003

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