J. Kor. Pharm. Sci., Vol. 24, No. 3, S27-S32 (1994)

Skin Permeation of Flurbiprofen through Excised Rat Skin from Poloxamer 407 Gel

Hyung-Jun Gil, Woo-Young Lee and Sang-Cheol Chi†

College of Pharmacy, Sung Kyun Kwan University, Suwon, Kyunggi-Do 440-746, Korea

(Received August 24, 1994)

In order to reduce systemic side effects following oral administration, flurbiprofen was formulated as transdermal gels consisting of the drug, poloxamer 407 and ethanol in buffer solutions. The effect of formulation variables in the preparation of flurbiprofen gels on skin permeation of the drug was evaluated using Keshary-Chien diffusion cells fitted with excised rat skins. The permeation rate of flurbiprofen through rat skin was directly proportional to initial drug concentration (between 0.1% and 1.0%) in the gel while it was inversely proportional to poloxamer 407 concentration (between 17.5% and 25%). The skin permeation of flurbiprofen was substantially influenced by the gel pH between 3 and 7, exhibiting a maximum at pH 4. The concentration effect of ethanol on the permeation of the drug was negligible in the concentration range of 10~20%.

Keywords—Flurbiprofen, Gel, Poloxamer 407, Skin permeation

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used for the treatment of rheumatoid arthritis and related conditions, but they are accompanied with systemic side effects and gastrointestinal irritation after oral adminstration. Since these drugs are administered repeatedly over a prolonged period, it is desirable to reduce these side effects while maintaining therapeutic blood level at disease sites. A transdermal preparation, which will bypass the stomach and yield high concentration at the local site underneath the skin, would be the dosage form of choice to achieve this goal. However, in spite of an intensive interest in research for the development of clinically useful transdermal preparations of NSAIDs, only a few products have been introduced in the market.

Flurbiprofen, one of the most potent NSAIDs, possesses several desirable properties necessary for a formulation as a transdermal aqueous preparation. These properties include relatively high solubility in water compared to other NSAIDs,[1] adequate permeability through the skin[2] and a high potency.[3] In our laboratory, flurbiprofen was successfully formulated as a transdermal gel using poloxamer 407 and the drug release properties of the gel were evaluated using membraneless drug diffusion cells.[4] Poloxamer 407, which has several useful properties as a gel base,[5] was used in the formulation of flurbiprofen gel. In the present study, Keshary-Chien diffusion cells fitted with excised rat skins were used to investigate the effects of formulation variables on skin permeation of flurbiprofen. The formulation variables studied were concentrations of the polymer, the drug and ethanol, and gel pH.

Materials and Methods

†To whom correspondence should be addressed.

Materials

The following chemicals and solvents were used as received without further purification: flurbiprofen, potassium phosphate monobasic, sodium phosphate dibasic and citric acid (Sigma Chemical Co., U.S.A.), poloxamer 407 (BASF Wyandotte Corp., Germany), ethanol (James Burrough Ltd., U.K.) and HPLC grade acetonitrile (Baxter Healthcare Corp., U.S.A.). Water was distilled, deionized and filtered in house.

Preparation of Flurbiprofen Gels using Poloxamer 407

The poloxamer 407 gels of flurbiprofen shown in Table I were prepared with a slight modification of the "cold" method first described by Schmolka.[6]

Preparation of Excised Rat Skin

Rat skins were obtained from male Sprague-Dawley rats weighing 200~240 g. After careful removal of hair on the dorsal area using a hair clipper (Thrive, Model 900), a skin area of approximately 5 cm×6 cm was excised from each sacrificed rat and the excised skin sections were stored at −20℃ prior to use. They were used within 1 week after the skin preparation.

Measurement of Skin Permeation of Flurbiprofen

The extent and rate of skin permeation of flurbiprofen from the applied gels were determined using Keshary-Chien diffusion cells fitted with excised rat skins. The receptor medium was pH 7.4 phosphate buffer (0.01 M). The skin surface was exposed to ambient temperature, while the temperature of the receptor medium was maintained at 37 ± 0.5℃ with a circulating water bath (Haake, Model F4391). Prior to starting an experiment, the frozen skin specimens were thawed at room temperature and carefully rinsed with warm water. The skins were soaked in pH 7.4 phosphate buffer (0.01 M) at 37℃ for 30 min and mounted on diffusion cells. After uniformly applying 3 g of the gel on the skin surface (5.07 cm^2) on the donor side, 0.2 m*l* of the receptor medium was withdrawn at 30 mins and hourly up to 10 hrs from the sampling port using a microsyringe. The sample removed was immediately replaced with an equal volume of fresh phosphate buffer at 37℃. Each experiment was performed in triplicate and their mean value with standard deviation was presented.

Table I—*Formulations of Flurbiprofen Gel used for the Skin Permeation of Flurbiprofen through Excised Rat Skin*

Ingredients	Formulations			
	A	B	C	D
Fluribiprofen	1*	0.1−1	1	1
Poloxamer 407	17.5−25	20	20	20
Ethanol	10	10	10−20	10
Buffer**	qs to 100	qs to 100	qs to 100	qs to 100

* W/W%

** 0.02 M buffer (pH 4, otherwise mentioned) consisting of citric acid and sodium phosphate dibasic

Determination of Flurbiprofen in the Receptor Medium

The amount of flurbiprofen permeated into the receptor medium was determined with a modification of the HPLC method developed in our laboratory.[7] The HPLC system consisted of an isocratic pump (Spectra-Physics, Model 8810), a manual injector (Rheodyne, Model 7125), a UV detector (Spectra-Physics, Model SC 100) set at 254 nm and an integrator (Dionex, Model 4270). The column used was a C_{18} column (μ-Bondapak 3.9×300 mm, 10μm particle size, Waters). The mobile phase was a mixture of pH 7.0 phosphate buffer (0.02 M) and acetonitrile in the volume ratio of 74 : 26. The flow rate was 1.4 m*l*/min and the column temperature was ambient.

Analysis of Data from Skin Permeation Studies

The cumulative amounts of flurbiprofen permeated per unit area of the skin were plotted as a function of time. From the linear portion of the plot after a certain time elapsed, the permeation

rate at steady-state was calculated and compared among the different formulations of flurbiprofen gels.

Results and Discussion

Effect of Poloxamer 407 Concentration on Skin Permeation of Flurbiprofen

The effect of poloxamer 407 concentration on drug permeation through excised rat skin was determined with Formulation A in Table I. Only poloxamer 407 concentration was varied as 17.5, 20, 22.5 and 25% in gel formulations consisted of 1% flurbiprofen, 10% ethanol and pH 4 buffer. Fig. 1 shows the cumulative amounts of flurbiprofen permeated through the skin upon application of these gels as a function of time. For each of the gels, the amount of flurbiprofen permeated during the first 2 hr was negligible, due to initial resistance of skin to drug permeation. Thereafter, more drug molecules permeated and the rate became constant over time, so called steady-state permeation rate.

Fig. 2 shows that the skin permeation rate of flurbiprofen decreased from 18.96 to 8.84 $\mu g/cm^2$ /hr as poloxamer 407 concentration in the gel increased from 17.5% to 25%. This decrease may be due to a reduction in the amount of free drug molecules, in the aqueous phase, available for permeation through skin. It is expected that, at higher poloxamer 407 concentrations, more micelles are formed within the gel which would entrap more drug molecules. The increased entrapment of drug in the micelles lowers the amount of free drug in the aqueous phase of the gel, causing a decrease in the permeation of flurbiprofen through the skin.

Effect of Initial Drug Concentration on Skin Permeation of Flurbiprofen

The effect of initial drug concentration on the skin permeation of flurbiprofen from the gel was evaluated with Formulation B in Table I in which only the amount of flurbiprofen was varied while those of poloxamer 407 and ethanol were fixed to 20% and 10%, respectively. As presented in Fig. 3, the permeation profiles from these gels shows a lag time followed by a linear segment. As the concentration of flurbiprofen changed from 0.1 to 1%, the skin permeation rate of the drug

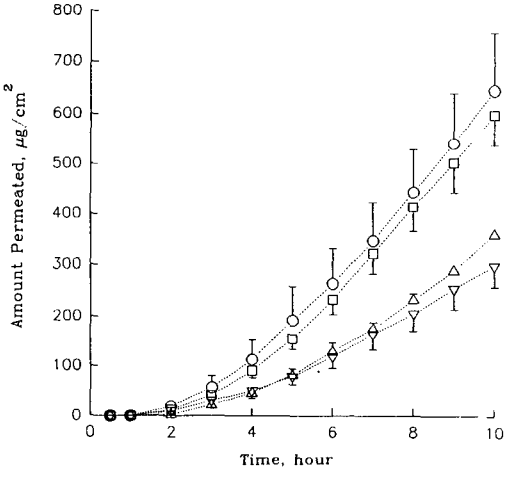

Figure 1—Permeation profiles of flurbiprofen through excised rat skin from 1% flurbiprofen gels containing 10% ethanol and different amount of poloxamer 407.
Key : ○; 17.5%, □; 20%, △; 22.5%, ▽; 25%.

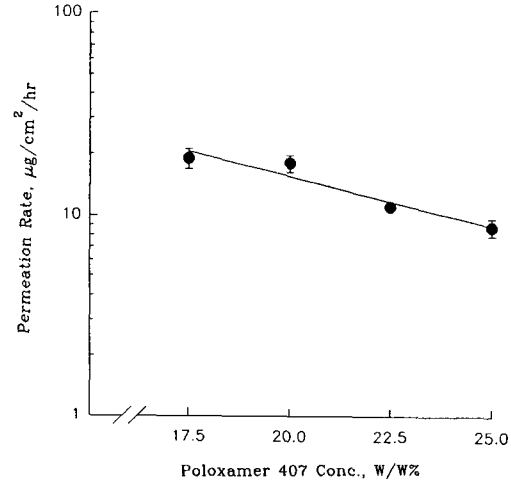

Figure 2—Effect of poloxamer 407 concentration on drug permeation rate through excised rat skins from 1% flurbiprofen gels containing 10% ethanol.

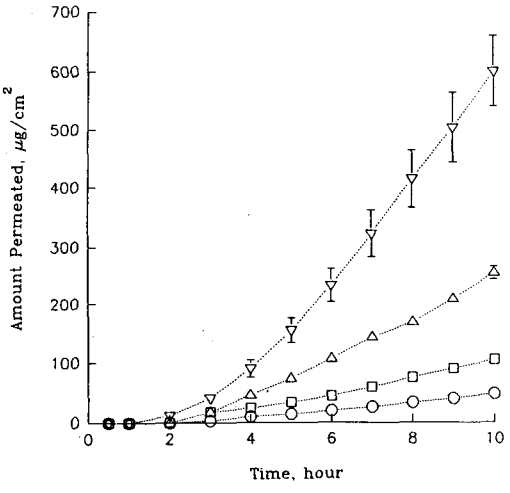

Figure 3—Permeation profiles of flurbiprofen through excised rat skin from 20% poloxamer 407 gels containing 10% ethanol and different amount of flurbiprofen.
Key : ○; 0.1%, □;0.2%, △; 0.5%, ▽; 1.0%.

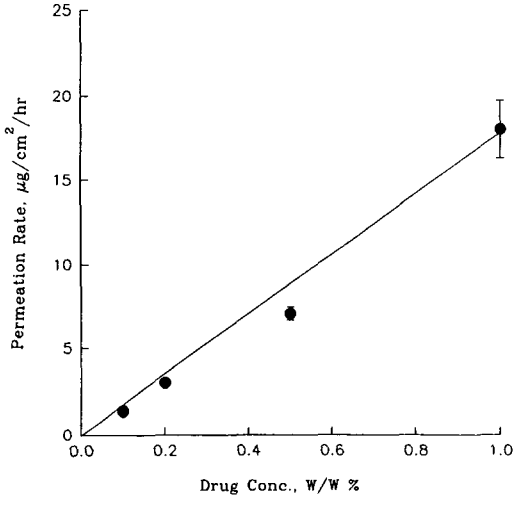

Figure 4—Effect of initial drug concentration on drug permeation rate through excised rat skins from 20% poloxamer 407 gels containing 10% ethanol.

increased from 1.39 to 18.01 μg/cm²/hr. The plot of skin permeation rate against the initial drug concentration was almost linear as shown in Fig. 4. Although a nonlinear relationship between permeation rate and drug concentration was often observed for the percutaneous absorption of

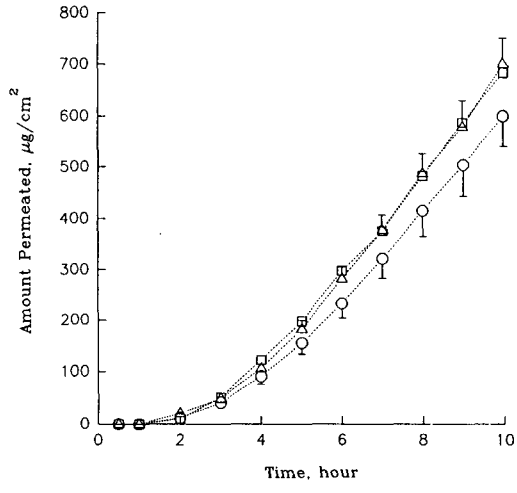

Figure 5—Permeation profiles of flurbiprofen through excised rat skin from 1% flurbiprofen gels containing 20% poloxamer 407 and different amount of ethanol.
Key : ○; 10%, □; 15%, △; 20%.

drugs from vehicles, the increase in the initial drug concentration, generally, results in a linear increase in the permeation rate of the drug, as long as the drug is completely dissolved in vehicle.

Effect of Ethanol Concentration on Skin Permeation of Flurbiprofen

Ethanol has been commonly used in transdermal preparations of NSAIDs as a cosolvent to increase the solubility of the drug in the vehicle. However, in this study, ethanol was added to the gels to evaluate its enhancing effect on skin permeation of flurbiprofen in the gel. The permeation of flurbiprofen through excised rat skin was determined at ethanol concentrations of 10, 15 and 20% in 1% flurbiprofen gel containing 20% poloxamer 407 (Formulation C in Table I). Flurbiprofen did not dissolve completely at the concentration lower than 10% and the formulation did not gel properly at room temperature at the concentration higher than 20%. The cumulative amounts of the drug permeated through the skin from the gels containing different ethanol contents are shown in Fig. 5 and the permeation rates

Table II—*Effect of Ethanol Concentration in the Gel on the Permeation of Flurbiprofen through Excised Rat Skin from 20% Poloxamer 407 Gel Containing 1% Flurbiprofen*

Ethanol Conc. (% W/W)	Flux (μg/cm²/hr)	K[a]
10	18.01 ± 2.97[b]	0.26 ± 0.06[b]
15	19.66 ± 8.32	0.29 ± 0.07
20	19.91 ± 3.53	0.31 ± 0.05

[a]partition coefficient

[b]mean ± S.D.

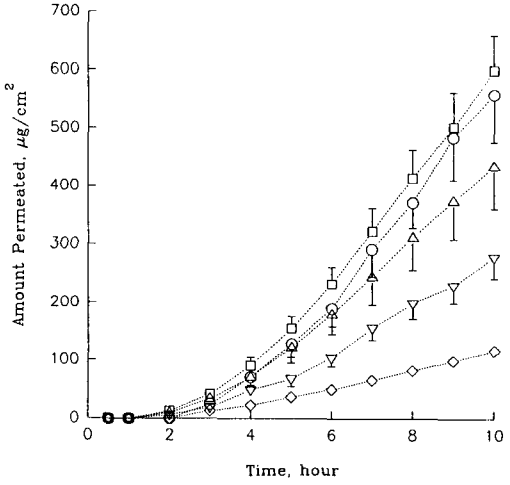

Figure 6—Permeation profiles of flurbiprofen through excised rat skin from 1% flurbiprofen gels containing 20% poloxamer 407 and 10% ethanol at different pH.
Key : ○; 3.0, □; 4.0, △; 5.0, ▽; 6.0, ◇; 7.0

determined from these profiles are presented in Table II including the partition coefficient calculated with lag-time method.[8] There was no significant change in the permeation rate among the ethanol concentrations employed. The partition coefficient of flurbiprofen between the skin and the gel did not change significantly, neither. It indicates that the concentration effect of ethanol on skin permeation of flurbiprofen was negligible in the concentration range employed.

Effect of Gel pH on Skin Permeation of Flurbiprofen

The percutaneous absorption of weak acidic or basic compounds is known to be affected by the pH of the vehicle due to the pH effect on ionization of these compounds.[9, 10] The effect of gel pH on the permeation of flurbiprofen through excised rat skin was evaluated using Formulation D in Table I, of which pH was adjusted to 3, 4, 5, 6 and 7.

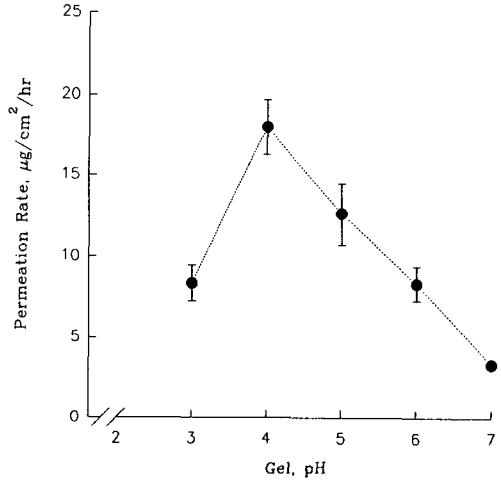

Figure 7—Effect of gel pH on drug permeation rate through excised rat skins from 1% flurbiprofen gels containing 20% poloxamer 407 and 10% ethanol.

As shown in Fig. 6, the linear increase of flurbiprofen permeation through rat skin was observed following a lag time for all of the gels studied. The plot of permeation rate versus gel pH in Fig. 7 demonstrates that the permeation rate of flurbiprofen was pH dependent, reaching a maximum value of 18.01 μg/cm²/hr at pH 4, which is almost identical to the pKa of the drug, 4.22.[11] The permeation rate was 5.4 times faster at pH 4 than at pH 7. Chi also showed, in the permeation studies of ketoprofen through rat skin from poloxamer 407 gels, that a maximum skin permeation rate occurred at the pH close to the pKa of the drug.[5]

Acknowledgements

This research was supported by Korea Science

and Engineering Foundation, Contract No. 91-0500-07.

References

1) C.D. Herzfeldt and R. Kummel, Dissociation constants, solubilities and dissolution rates of some selected nonsteroidal antiinflammatories, *Drug Devel. Ind. Pharm.*, **9**, 767-793 (1983).
2) T. Yano, A. Nakagawa, M. Tsuji and K. Noda, Skin permeability of various non-steroidal antiinflammatory drugs, *Life Sci.*, **39**, 1043-1050 (1983).
3) R.N. Brogden, R.C. Heel, T.M. Speight and G.S. Avery, Flurbiprofen : A review of its pharmacological properties and therapeutic use in rheumatic diseases, *Drugs*, **18**, 417-438 (1979).
4) H.J. Gil, H. Kim and S.C. Chi, Release of flurbiprofen from poloxamer 407 gel, *Arch. Pharm. Res.* accepted for publication (1994).
5) S.C. Chi, Biopharmaceutic and pharmacokinetic studies of ketoprofen topical gel preparations using Pluronic F-127, *Ph.D. Dissertation*, University of Georgia (1989).
6) I.R. Schmolka, Artificial skin I. Preparation and properties of Pluronic F-127 gels for treatment of burns, *J. Biomed. Mater. Res.*, **6**, 571-582 (1972).
7) S.C. Chi, H. Kim and S.C. Lee, High performance liquid chromatographic analysis of flurbiprofen in rat plasma, *Anal. Lett.*, **27**, 377-389 (1994).
8) B.W. Barry, *Dermatological Formulations*, Marcel Dekker, Inc., New York, U.S.A., pp. 49-94 (1983).
9) Y.H. Tsai and S.I. Naito, Changes in site and size of application of indomethacin ointment and percutaneous absorption in rabbits, *Int. J. Pharm.*, **10**, 125-131 (1982).
10) F. Marcus, J.L. Colaizzi and H. Barry, **III**, pH effects on salicylate absorption from hydrophilic ointment, *J. Pharm. Sci.*, **59**, 1616-1620 (1970).
11) B.D. Anderson and R.A. Conradi, Predictive relationships in the water solubility of salts of a nonsteroidal anti-inflammatory drug, *J. Pharm. Sci.*, **74**, 815-820 (1985).