Arch. Pharm. Res. Vol. 17, No. 4, pp. 240-243, 1994

Release of Flurbiprofen from Poloxamer 407 Gel

Hyung-Jun Gil, Hyun Kim and Sang-Cheol Chi

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

(Received January 24, 1994)

Release rates of flurbiprofen from transdermal gels made of poloxamer 407 were evaluated using a membraneless diffusion cell in order to study the effects of formulation variables on flurbiprofen release such as poloxamer 407 (17.5-25%), drug (0.1-1.0%), ethanol (10-20%), PG or PEG 300 (5-15%) concentrations and gel pH (3-7). Isopropyl myristate was employed as a receptor medium for the drug released from the gel. The diffusion coefficient of flurbiprofen decreased linearly as the amount of poloxamer 407 and the drug in the gel increased. The release rate of flurbiprofen was gel pH-dependent and the diffusion coefficient of the drug in the gel increased as the pH of the gel increased. The addition of more ethanol in the gel increased the drug release, resulting from the increase of the thermodynamic activity of the drug in the aqueous phase of the gel. However, the concentration effects of PG and PEG 300 on the release rate of flurbiprofen were negligible over the concentration range used.

Key words: Flurbiprofen, Poloxamer 407, Gel, Release, Formulation

INTRODUCTION

Flurbiprofen is a potent nonsteroidal antiinflammatory drug (NSAID) and widely used for the treatment of rheumatoid arthritis and its related conditions (Brogden *et al.*, 1979). However, the oral administration of its conventional dosage forms has caused systemic side effects and gastrointestinal irritation (Sasai *et al.*, 1986). Recently, several NSAIDs such as indomethacin (Fujimura *et al.*, 1985), ketoprofen (Kyuki *et al.*, 1985), diclofenac (Tsuji *et al.*, 1985) and piroxicam (Schiantarelli *et al.*, 1982) have been formulated as transdermal preparations and they offer the advantages of delivering the drugs directly to the disease site and producing high local drug concentrations while reducing systemic blood levels and gastric irritations when applied directly onto the inflamed site. However, they have some problems such as skin irritation due to the high portion of organic solvents in the preparations and limited percutaneous absorption due to the drugs themselves as well as formulation additives. In our laboratories, transdermal gel formulations of flurbiprofen were prepared using poloxamer 407 as a gel forming agent to overcome the problems of existing NSAIDs transdermal preparations. In the present study, effects of formulation variables of the gel on the drug release from poloxamer 407 were evaluated with the membraneless diffusion cell technique using isopropyl myristate (IPM) as a receptor medium.

Correspondence to: Sang-Cheol Chi, College of Pharmacy, Sung Kyun Kwan University, Suwon, Kyunggi-Do 440-746, Korea

MATERIALS AND METHODS

Materials

The following chemicals and solvents were used as received without further purification: Flurbiprofen, IPM, polyethylene glycol(PEG) 300, propylene glycol(PG), potassium phosphate monobasic, sodium phosphate dibasic, 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.). Oxaprozin was generously supplied by Il-Dong Pharmaceutical Co..

Preparation of Gels and Measurement of Their Physical Properties

The poloxamer 407 gels of flurbiprofen were prepared according to the formula shown in Table I and by a slight modification of the "Cold" method first described by Schmolka (1972).

When necessary, the viscosity and pH of the gels were measured with a digital viscometer (Brookfield Engineering Laboratories, U.S.A., Model DV-II) and a pH meter (Fisher Scientific Co., U.S.A., Model Accumet

Table I. Formulations used in the preparation of flurbiprofen gels

Ingredients	Formulations			
	A	B	C	D
Flurbiprofen	1[a]	0.1-1	1	1
Poloxamer 407	17.5-25	20	20	20
Ethanol	10	10	10-20	–
PG or PEG 300	–	–	–	5-15
Water	qs to 100	qs to 100	qs to 100	qs to 100

[a]W/W%

925), respectively.

Determination of Solubility of Flurbiprofen

To determine the solubility of flurbiprofen in vehicles in which only poloxamer 407 was not added, an amount of the drug well in excess of its predicted solubility was suspended in the vehicle and it was shaken at 25°C for 2 days. The suspension was filtered with a 0.45 μm syringe filter (Acrodisc, Gelman Science, U.S.A.) and diluted properly. The concentration of flurbiprofen was analyzed using the HPLC condition described by Kim and Chi (1992).

In Vitro Drug Release Studies

The release of flurbiprofen from poloxamer 407 gels was studied using the membraneless diffusion cell designed by Chi and Jun (1991). IPM was employed as the receptor medium for flurbiprofen releasing from the gel. The receptor medium was continuously stirred at the rate of 100 rpm and maintained at 37°C. At the predetermined time intervals of 0.25, 0.5, 1, 2, 3, 4, 5 and 6 hrs, 0.2 ml of the receptor medium was withdrawn and immediately replaced with an equal volume of fresh IPM. Flurbiprofen released into the receptor medium was quantitated with the HPLC method developed by Kim and Chi (1992). All the experiments were performed in triplicate runs and the mean values were presented.

Treatment of Data for Drug Release Studies

The release rates of flurbiprofen from the gels of various formulations were evaluated based on Higuchi's diffusion equation (Higuchi, 1961).

$$Q=2C_o\left(\frac{D\times t}{\pi}\right)^{1/2} \quad (1)$$

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

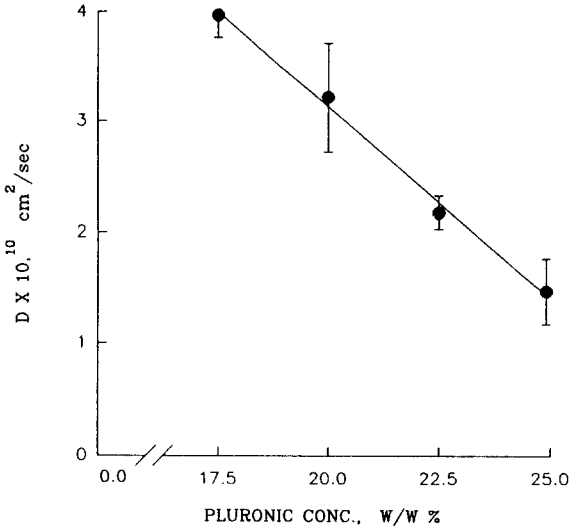

Fig. 1. Diffusion coefficients of flurbiprofen in the gel containing 1% drug and 10% ethanol as a function of poloxamer 407 concentration.

RESULTS AND DISCUSSION

Effect of Poloxamer 407 Concentration on Drug Release

The release rates of flurbiprofen from gels containing different poloxamer 407 amounts were determined using Formulation A in Table I. Only the poloxamer 407 concentration was varied at 17.5, 20, 22.5 and 25% in the formulation consisting of 1% flurbiprofen, 10% ethanol and water. When the amounts of the drug released from each gel were plotted against the square root of time, excellent linearities ($r>0.999$) were obtained, indicating that the release kinetics of flurbiprofen from these gels followed the Higuchi's diffusion model. Similarly, the release kinetics from all other gels made with different formulations in Table I complied to the Higuchi's diffusion model.

The diffusion coefficients of flurbiprofen in the gels containing 1% drug and different poloxamer 407 amounts were calculated using Equation (1) and are shown in Fig. 1. The diffusion coefficients of flurbiprofen decreased linearly as the polymer concentration increased in the gel. The diffusion coefficient depends upon the resistance of drug movement through the vehicle. Therefore, as the diffusion coefficient of the drug decreased, less drug would be released into the receptor medium. On the other hand, in contrast with the linearly declining mode of this study, others (Chi and Jun, 1991; Chen-Chow and Frank, 1981; Gilbert *et al.*, 1986) observed exponentially declining diffusion coefficients for ketoprofen and benzoic acid derivatives, as the poloxamer concentrations increased. This difference in the mode of decrease of diffusion coeffi-

Table II. Effect of gel pH on solubility and diffusion coefficient of flurbiprofen in 20% poloxamer 407 gels containing 1% drug and 10% ethanol

	pH				
	3	4	5	6	7
Solubility[a] ($\times 10^5$, g/ml)	3.1	14.4	23.9	130.9	701.6
Diffusion coefficient ($\times 10^{10}$, cm^2/sec)	0.63	0.84	1.67	3.37	8.37

[a]Solubility of flurbiprofen in 10% ethanol of different pH

cient might be attributed to the difference in active ingredients and additives as well as poloxamer concentrations in the gels.

Effect of Gel pH on Drug Release

The effect of gel pH on flurbiprofen release from the gel was evaluated using a 1% flurbiprofen gel containing 20% poloxamer 407 and 10% ethanol. The gel pH was adjusted to pH 3, 4, 5, 6 and 7 using different buffer solutions (0.02 M) made of citric acid and sodium phosphate dibasic.

The diffusion coefficients of flurbiprofen in the gels at five different pH values were calculated based on the plots of the cumulative amount of the drug released from the gels at these pH values against the square root of time, and presented in Table II.

Since flurbiprofen is a weak acid with a pKa of 4.22 (Anderson and Conradi, 1985), its solubility in 10% ethanol increased from 3.1×10^{-5} to 7.0×10^{-3} g/ml as the pH was changed from 3 to 7 due to the ionization of the drug. Nevertheless, the amounts of unionized flurbiprofen in 10% ethanol should remain the same over the pH range studied. However, the diffusion coefficient of flurbiprofen also increased more than 10 times with increasing gel pH from 3 to 7, despite the fact that the amount of unionized drug in the aqueous phase of the gel should be constant and only the unionized form of the drug could be released into the receptor medium. The increase in the diffusion coefficient of flurbiprofen at high pH may be due to the highly increased amount of the ionized form of flurbiprofen at these pH values. Ionized flurbiprofen quickly equilibrates to the unionized form as this form becomes depleted in the aqueous phase.

Effect of Initial Drug Concentration on Drug Release

The effect of the initial drug concentration in the gel on flurbiprofen release was evaluated with Formulation B in Table I in which only the amlunts of flurbiprofen was varied from 0.1 to 1.0% while the amounts of poloxamer 407 and ethanol were fixed to 20% and 10%, respectively.

Table III. Effect of initial drug concentration on the diffusion coefficient of flurbiprofen in 20% poloxamer 407 gel containing 10% ethanol and on the viscosity and pH of the gels

	Flurbiprofen, W/W%			
	0.1	0.2	0.5	1
Amount released during 6 hrs (mg/cm^2)	0.992	1.502	2.376	3.516
Diffusion coefficient ($\times 10^{10}$, cm^2/sec)	31.2	19.3	6.19	3.22
Viscosity at 37℃ ($\times 10^{-5}$, cps)	1.22	1.32	1.46	1.84
Gel pH	6.06	5.75	5.44	5.24

Table III shows the amount of the drug released during 6 hrs and the diffusion coefficient of flurbiprofen calculated based on the Higuchi Equation. According to Higuchi (1961), diffusion coefficient should be independent of the initial drug concentration as long as the latter is below the solubility of the drug in the vehicle. In Table III, however, the diffusion coefficient of flurbiprofen decreased from 31.2×10^{-10} to 3.22×10^{-10} cm^2/sec as the flurbiprofen concentration increased from 0.1 to 1.0% although the drug was completely dissolved in the gel. Therefore, the drug release might have been also influenced by other factors besides the drug concentration in poloxamer 407 gels. Barry (1983) reported that the drug concentration-dependence of diffusion coefficients occurs commonly in situations where the diffusant affects the properties of the diffusion medium. The dependence of drug release from vehicle on drug loading was also reported with lidocaine (Chen-Chow and Frank, 1981) and ketoprofen (Chi and Jun, 1991). As presented in Table III, the gel pH decreased from 6.1 to 5.2 as the flurbiprofen concentration in the gel increased from 0.1 to 1.0%. the decrease in the gel pH could result in the lower diffusion coefficient of the drug as explained previously. In addition to the pH change, the higher viscosity of the gel with the increase of drug amount in the gel could have attributed to the decrease of the diffusion coefficient of flurbiprofen. The vsicosity of the gels increased 1.3 times as the drug concentration changed from 0.1 to 1.0% as shown in Table III, probably due to the increase in the size of micelles in the gel.

Effect of Cosolvents on Drug Release

Ethanol, PG and PEG 300 have been used as typical cosolvents for water-insoluble drugs in various topical preparations. In this study, they were also added as cosolvents to selectivity increase the solubility of flurbiprofen in the gel. Their concentration effects on the release of flurbiprofen was studied using Formulation C and D in Table I. The concentration of ethanol was

Table IV. Effect of cosolvents on solubility of flurbiprofen in waster and drug diffusion coefficient in 1% flurbiprofen gel containing 20% poloxamer 407

Cosolvents	Conc.	Diffusion coefficient ($\times 10^{10}$, cm^2/sec)	Solubility ($\times 10^5$, g/ml)
Ethanol	10%	3.22	4.14
	15%	4.98	5.09
	20%	8.72	8.52
PG	5%	2.61	4.09
	10%	3.48	4.22
	15%	3.37	4.41
PEG 300	5%	0.67	3.11
	10%	0.84	3.97
	15%	0.85	6.76

varied from 10, to 15 and 20%, and that of PG or PEG 300 from 5, to 10 and 15%, while the amounts of flurbiprofen and poloxamer 407 were fixed to 1% and 20%, respectively.

The diffusion coefficients of flurbiprofen in the gel containing different cosolvent were also calculated based on the plot of the amounts of flurbiprofen released from the gels containing different amounts of cosolvents against the square root of time. Table IV shows the calculated diffusion coefficients and the solubility of flurbiprofen in water containing each cosolvent at different concentration levels. When flurbiprofen is dissolved completely in the gel, the drug exists both in the aqueous phase and inside the micelles formed by poloxamer 407. The addition of more ethanol increased the solubility of the drug preferentially in the aqueous phase of the gel as a result of the cosolvent effect. The enhanced drug release in the presence of more ethanol in the gels was probably due to this increased thermodynamic activity of flurbiprofen in the aqueous phase of the gel, considering the fact that the diffusion coefficient of flurbiprofen was proportional to the solubility of the drug in water containing different perecentage of ethanol.

The gels containing PG resulted in higher drug release than those containing PEG 300, even though the solubilities of flurbiprofen in 5, 10 and 15% PG or PEG 300 were not significantly different from each other. Unlike ethanol, however, the concentration effects of PG and PEG 300 on the release of flurbiprofen from the gels were negligible over the concentration range used in the study.

ACKNOWLEDGMENTS

This research was supported by Korea Science and Engineering Foundation, Contract No. 91-0500-07.

REFERENCES CITED

Anderson, B. D. and Conradi, R. A., Predicitive relationships in the water solubility of salts of a nonsteroidal anti-inflammatory drug. *J. Pharm. Sci.*, 74, 815-820 (1985).

Barry, B. W., Dermatological Formulation, Marcel Dekker, New York, 1983.

Brogden, R. N., Heel, R. C., Speight, T. M. and Avery, G. S., Flurbiprofen: A review of its pharmacological properties and therapeutic use in rheumatic diseases. *Drugs*, 18, 418-438 (1979).

Chen-Chow, P.-C. and Frank, S. G., In vitro release of lidocaine from Pluronic F-127 gels. *Int. J. Pharm.*, 8, 89-99 (1981).

Chi, S.-C. and Jun, H. W., Release rates of ketoprofen from Poloxamer gels in a membraneless diffusion cell. *J. Pharm. Sci.*, 80, 280-283 (1991).

Fujimura, H., Hiramatsu, Y., Tamura, Y., Maekawa, K. and Yokota, H., Pharmacological studies of ketoprofen ointment. *Yakuri to Chiryo*, 13, 4115-4127 (1985).

Gilbert, J. C., Hadgraft, J., Bye, A. and Brookes, L. G., Drug release from Pluronic F-127 gels. *Int. J. Phram.*, 32, 223-228 (1986).

Higuchi, T., Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci.*, 50, 874-875 (1961).

Kim, H. and Chi, S.-C., Quantitation of flurbiprofen in isopropyl myristate by high performance liquid chromatography. *J. Kor. Pharm. Sci.*, 22, 63-68 (1992).

Kyuki, K., Tsurumi, K. and Fujimura, H. Anti-inflammatory activity of ketoprofen cream in topical application. *Oyo Yakuri*, 29, 969-976 (1985).

Sasai, Y., Nagata, M., Ogawa, N., Gondo, S., Yano, T., Saita, M. and Tsuji, M., Absorption, metabolism and systemic effects after cutaneous application of KPG-200 in healthy volunteers. *Yakuir to Chiryo*, 14, 2273-2284 (1986).

Schiantarelli, P., Cadel, S., Acerbi, D. and Pavesi, L., Antiinflammatory activity and bioavailability of percutaneous piroxicam. *Arzneim.-Forsch.*, 32, 230-235 (1982).

Schmolka, I. S., Artificial skin I. Preparation and properties of Pluronic F-127 gels for treatment of burns. *J. Biomed. Mater. Res.*, 6, 571-582 (1972).

Tsuji, M., Saita, M., Yano, T., Noda, K., Hibi, M. and Sakashita, M., Preclinical laboratory studies on ketoprofen gel ointment. *Kyushu yakugakkai Kaio*, 39, 13-25 (1985).