Drug Development and Industrial Pharmacy, 26(4), 409–414 (2000)

RESEARCH PAPER

In Vitro Release Studies of Piroxicam from Oil-in-Water Creams and Hydroalcoholic Gel Topical Formulations

Morteza Rafiee-Tehrani* and Ali Mehramizi

School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

The importance of piroxicam, a therapeutic anti-inflammatory drug, is well known. Because of gastrointestinal disorders, dermatological dosage forms are recommended most. In our first studies, oil-in-water (O/W) creams of piroxicam (1% concentration) were prepared using glyceryl monostearate (GMS), stearic acid, and triethanolamine as additive ingredients. In our second studies, hydroalcoholic transparent gel formulations of this drug in a 0.5% concentration were prepared using hydroxypropylcellulose (HPC) as the gelling agent. The release of piroxicam from all formulations via dialysis through a cellulose membrane into phosphate buffer pH 6.8 at 37°C was studied. The effects of additives such as propylene glycol and 2-propanol on the drug release were also investigated. The release profiles from the standpoint of diffusion-controlled processes, as well as zero-order and first-order kinetics, were evaluated, and relevant parameters, such as diffusion coefficient, permeability coefficient, and partition coefficient, were calculated. The release obeys both the diffusion mechanism and first-order kinetics. The drug release from gel formulations containing 10%, 20%, and 30% propylene glycol was decreased due to the enhancement of viscosity. However, the limpidity of these formulations was improved. Moreover, the release of drug from gel formulations containing 15% and 20% of 2-propanol was increased. These results show that a hydroalcoholic gel formulation with HPC is a more suitable preparation of piroxicam when compared with an O/W cream formulation.

Key Words: *Hydroalcoholic gel; In vitro release; O/W cream; Piroxicam; Topical.*

* To whom correspondence should be addressed. North Karegar Avenue, Postal Code 14, P.O. Box 14395-459, Tehran, Iran. Telephone: 0098-21-8009440. Fax: 0098-21-659958.

INTRODUCTION

Piroxicam is a potent nonsteroidal anti-inflammatory drug (NSAID) often used for the treatment of acute and chronic rheumatoid arthritis or osteoarthritis (1). Piroxicam is well absorbed following oral administration (2,3). Although the usual oral dose of piroxicam is well tolerated by patients, several side effects have been reported, including gastrointestinal disturbances, dizziness, and headache, as well as peptic ulcer (4–6). Recently, the efficacy of piroxicam used topically has been reported (7,8). The hydrogel, modified hydrophilic base, and emulsion base formulations, as well as supersaturated solutions of piroxicam, were developed and studied by some investigators (8–10). The effects of various additives like dimethyl sulfoxide (DMSO) and ethanol on the release behavior of chlorpheniramine maleate and naproxen from topical bases have been reported by some investigators (11,12).

The purposes of the present study were (*a*) to formulate an oil-in-water (O/W) cream and hydroalcoholic gel containing piroxicam, (*b*) to determine the in vitro release of the drug from these formulations, and (*c*) to investigate the influence of various additives on the drug release.

EXPERIMENTAL

Equipment

The following equipment was used: ultraviolet (UV) spectrophotometer 160 A (Shimadzu, Tokyo, Japan); pH meter (Corning, UK); and Franz diffusion cell (developed at Tehran University).

Materials

Piroxicam (Pfizer Corp., New York, NY); hydroxypropylcellulose (HPC; Hercules, London); 2-propanol, propylene glycol, ethanol, hard paraffin, soft paraffin, liquid paraffin, cetyl alcohol, triethanolamine, stearic acid, glyceryl monostearate, glycerin, NaOH, methyl paraben, propyl paraben, benzyl alcohol (Merck, Darmstadt, Germany); and cellulose membrane (Spectrum Medical Industries, Inc., CA) were used. All chemicals were either analytical or pharmaceutical grade and were used as received.

Methods

Sample Preparation

Gel Samples

The HPC was dispersed in hot water with continuous stirring until uniformly dispersed, and the solution was allowed to cool to 50°C. The other ingredients (e.g., ethanol, benzyl alcohol) were premixed and added to the batch with continuous stirring. The piroxicam then was dissolved in water with the aid of a small amount of sodium hydroxide solution (1 N) and was mixed with other substances in the formulation.

Oil-in-Water Cream Samples

All the aqueous phase material and the oil phase ingredients were placed in separate stainless steel containers and heated above 70°C. The water phase then was added to the oil phase under continuous agitation.

The semisolid emulsions (O/W) were then cooled to approximately 40°C, and the piroxicam, previously dissolved in water with the aid of small amounts of sodium hydroxide solution (1 N), was incorporated. Other additives included in the formulation were also added at this stage. The batch was mixed to reach ambient temperature. The samples were then kept in airtight aluminum tubes.

Analytical Method

All samples were analyzed for piroxicam content spectrophotometrically using a wavelength of 354 nm.

Content Uniformity

All samples were analyzed for piroxicam content prior to diffusion studies. Only samples with piroxicam contents within 100% ± 10% were used for diffusion studies.

pH Measurement

The pH of all samples in the 1% concentration were measured by pH meter. All gel formulations showed a pH range of 5.9–6.1; however, the O/W creams exhibited a higher pH range, between 6.7 and 6.9.

Stability Studies

All cream samples were refrigerated at 40°C for 48 hr, and the physical aspects and homogeneity of the samples were investigated; no change was observed.

All cream samples were stored at 40°C for 48 hr. The physical properties of the samples were not altered.

Limpidity Studies

The limpidity of all gel samples was measured spectrophotometrically (transmittance) at 610 nm. Gels are

classified in four categories, from limpid (T% greater than 80%) to very opaque (T% less than 22%). All gel samples prepared were limpid.

In Vitro Drug Release Studies

A 4-g sample of each formulation was accurately weighed and placed in the donor part of the Franz diffusion cell, and a semipermeable cellulose membrane with a molecular weight cutoff point of 1000, which previously was immersed in receptor phase for 1 hr, was placed over the mouth of the acceptor post. The cell body was filled to overflowing with a degassed phosphate buffer, pH 6.8, as the receptor phase and maintained at a constant temperature of 37°C ± 1°C by means of water jacket in each cell. The donor part containing the sample was then placed over the semipermeable membrane, and diffusion was allowed to take place. The receptor phase was stirred thoroughly by a constantly spinning bar magnet at 100 rpm. Intervals of 15, 30, 45, 60, 90, 150, and 180 min were chosen as sampling times, and samples were analyzed for piroxicam content spectrophotometrically at 354 nm. A 50-ml aliquot was removed and was replaced with an equal volume of receptor phase.

RESULTS AND DISCUSSION

Kinetics of In Vitro Release Studies

A simplified Higuchi diffusion equation (13,14) for drug release from one side of a semisolid layer in which the drug is completely dissolved is described as follows:

$$M = Q = 2C_0(Dt/\pi)^{1/2} \quad (1)$$

where M or Q is the amount of drug released into the receptor phase per unit area of exposure (mg/cm^2), C_0 is the initial drug concentration in the vehicle (mg/ml), D is the (apparent) diffusion coefficient of drug (cm^2/sec), t is time after the application (sec), and π is a constant.

According to the Higuchi theory, Eq. 1 is valid if (*a*) the percentage released is less than 30% of the total drug in the vehicle, (*b*) only a single drug species is present in the vehicle, (*c*) the diffusion coefficient is invariant with respect to time or position within the vehicle layer, (*d*) only the drug diffuses out of the vehicle, and (*e*) the drug reaching the receptor side is removed rapidly. The experimental conditions in the present study appeared to match the above assumptions favorably in most formulations. However, in other formulations, the release of drug seems to be according to first-order of kinetics.

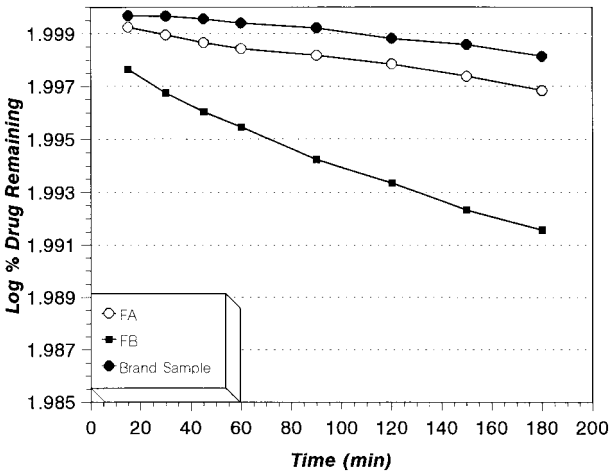

Figure 1. Drug release profile of selected formulations of piroxicam 1% cream (FA, FB) and brand sample according to first-order kinetics.

In Vitro Release Studies

Oil-in-Water Cream Samples

The release rates of piroxicam from 1% creams were determined and plotted according to the first-order kinetics and Higuchi equation (Figs. 1 and 2). Each data point represents the mean of 6 determinations. The method was validated, and the coefficient of variation (calculated

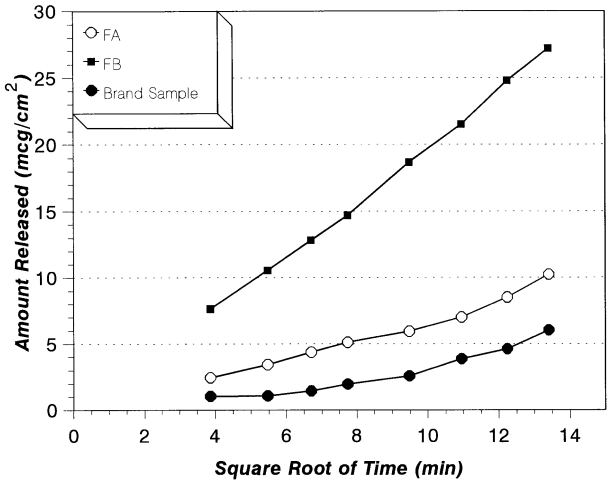

Figure 2. Drug release profiles of selected formulations of piroxicam 1% cream (FA, FB) and brand sample according to Higuchi equation.

from the standard deviation of the mean percentage of drug release versus time) varied from 0.47% to 8.74% within all data sets. For the sake of clarity, the standard deviations of the means are not presented in figures showing the mean piroxicam release profiles. The amount of drug was constant in two different cream formulations. Surprisingly, the release of drug was faster in one of the prepared formulations compared to the brand sample. Drug release from O/W 1% cream seems to fit first-order kinetics. These results are contrary to those in the report of Babar et al. (8), who found such release according to the Higuchi equation. The diffusion coefficient, permeability coefficient, and partition coefficient of selected piroxicam cream preparations and a brand sample (Felden®) are shown in Table 1.

Gel Samples

Cosolvents were used in various topical formulations to aid the solubilization of the active substances in the vehicle. In this study, propylene glycol and 2-propanol were added as cosolvents to increase the solubility of piroxicam in the aqueous phase selectively rather than in the micellar portion of the gel. The effect of 2-propanol on the release of piroxicam was studied using the gel with 0.5% piroxicam in 1.5% HPC and varying the 2-propanol concentration (15% or 20%) (Fig. 3). In all of these formulations, 2-propanol concentration (15% or 20%) was first substituted for 10% of the water content and then for 5% or 10% of the ethanol, respectively. Over the range of 2-propanol concentration used, the diffusion coefficient of piroxicam calculated from the Higuchi diffusion equation increased linearly from 7.4×10^{-8} cm^2/sec for the gel without 2-propanol to 11.6×10^{-8} cm^2/sec for the gel containing 20% of 2-propanol. The enhanced drug release in the presence of 2-propanol could be due to the decreased viscosity of piroxicam gel. These results are in agreement with a previous investigation performed by

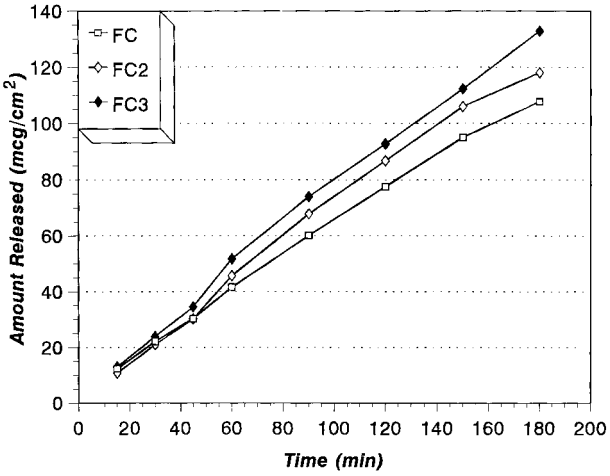

Figure 3. Effect of 2-propanol (2-p) concentration on piroxicam release from 0.5% gel: FC (gel without 2-p), FC_2 (gel + 15% 2-p), FC_3 (gel + 20% 2-p).

Chi and Jun (15), who demonstrated that the enhancement of ethanol in ketoprofen gel formulations increased the release of drug from the gel due to decrease of viscosity. Moreover, the relative increase in the release was probably due to the fact that, at these concentrations, 2-propanol augmented the solubility of the drug in the gel, causing an increase in the thermodynamic activity and enhanced permeation.

The effect of various concentrations of propylene glycol on the release of piroxicam from a gel formulation was also investigated. The concentration of HPC (1.5%) and the drug (0.5%) remained constant; however, the amount of ethanol in the vehicle was substituted with an equal volume of propylene glycol (10%, 20%, and 30%) (Fig. 4). Over the range of propylene glycol concentration used, the diffusion coefficient of piroxicam decreased linearly from 6.590×10^{-8} cm^2/sec for the gel

Table 1

Values of Diffusion, Permeability, and Partition Coefficient as Calculated from In Vitro Data of Selected Piroxicam Cream Formulations and Brand Sample (Felden, Pfizer)

Formulation	Diffusion Coefficient D, ($D \times 10^{10}$) cm^2/sec	Permeability Coefficient P, ($P \times 10^{7}$) cm/sec	Partition Coefficient KP
Felden	0.370	0.512	8.296
FA	0.784	0.728	5.575
FB	3.157	1.922	3.652

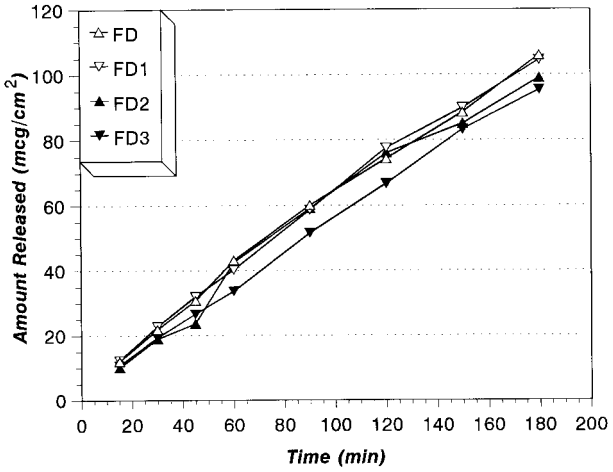

Figure 4. Effect of propylene glycol (PG) concentration on piroxicam release from 0.5% gel: FD (gel without PG), FD_1 (gel + 10% PG), FD_2 (gel + 15% PG), FD_3 (gel + 20% PG).

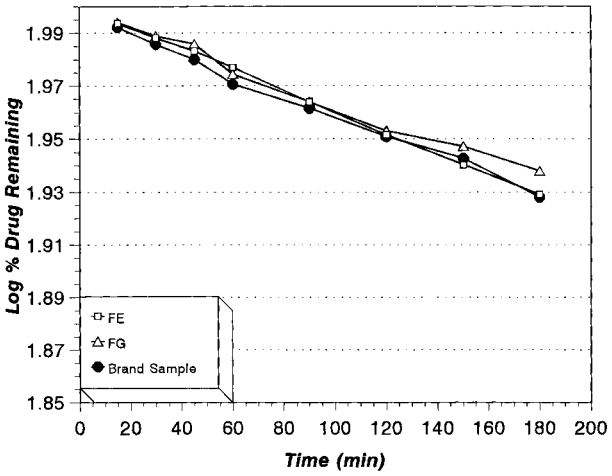

Figure 6. Drug release profiles of selected formulations of piroxicam 0.5% gel (FE, FG) and brand sample according to first-order kinetics.

without propylene glycol to 4.980×10^{-8} cm^2/sec for the gel containing 30% propylene glycol (Fig. 5). The inhibition effect observed in drug release from the gel containing propylene glycol might be due to the increase of viscosity of piroxicam gel. However, the addition of propylene glycol in gel formulations caused the improvement of the limpidity of the gels when was measured by spectrophotometer at 610 nm.

The release rates of piroxicam from hydroalcoholic selected gel formulations containing different amounts of water, ethanol, and propylene glycol were plotted according to the first-order kinetics (Fig. 6) and Higuchi equation (Fig. 7). The amount of piroxicam (0.5%) and HPC (1.5%) was kept constant in all these selected preparations. Drug release from all these formulations appeared to fit the Higuchi equation ($r > 0.99$) and to correspond to a diffusion model shown in Eq. 1. These results are in agreement with the findings of other investigators (8), who have shown that the release of piroxicam from a hydrogel formulation obeys the Higuchi equation. The diffusion coefficient, permeability coefficient, and parti-

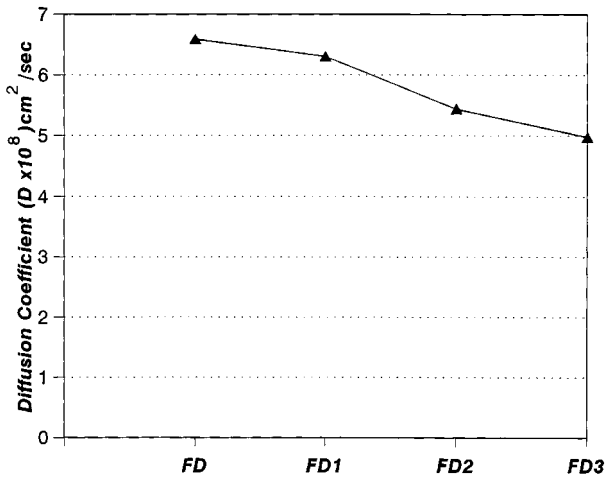

Figure 5. Apparent diffusion coefficients of piroxicam in the gel containing 0.5% piroxicam as a function of propylene glycol concentration.

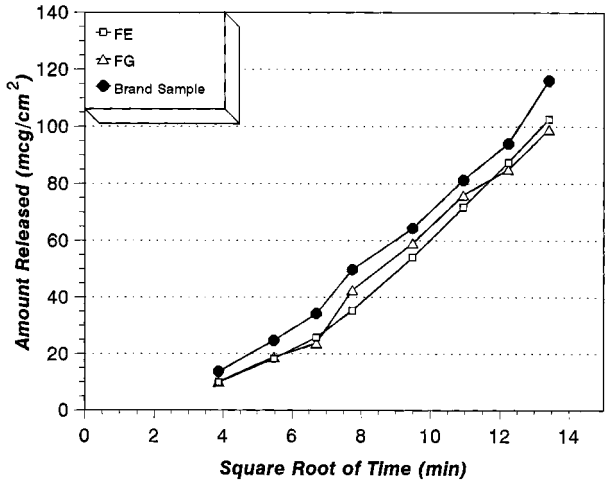

Figure 7. Drug release profiles of selected formulations of piroxicam 0.5% gel (FE, FG) and brand sample according to Higuchi equation.

Table 2

Values of Diffusion, Permeability, and Partition Coefficient as Calculated from In Vitro Data of Selected Piroxicam Gel Formulations and Brand Sample (Gelden, Pfizer)

Formulation	Diffusion Coefficient D, ($D \times 10^8$) cm^2/sec	Permeability Coefficient P, ($P \times 10^6$) cm/sec	Partition Coefficient KP
Gelden	5.520	1.929	0.210
FE	5.440	1.898	0.209
FG	7.093	2.203	0.188

tion coefficient of selected piroxicam gel formulations, as well as the brand sample (Gelden®) are shown in Table 2.

CONCLUSIONS

Diffusion studies were used to evaluate the in vitro release of piroxicam from different topical vehicles, and they were meaningful in screening formulations for relative availability of this drug.

The gel formulations obeyed the diffusion method; however, the O/W creams of piroxicam showed a better fit with first-order of kinetics. The effect of additives on drug release from gel preparations showed that the presence of 2-propanol enhanced the release of piroxicam from the gel formulations by decreasing the apparent gel viscosities. However, propylene glycol decreased the release of drug, but improved the limpidity of the gel formulations. The general rank order of piroxicam release from the vehicles was gel formulation > O/W cream formulation.

ACKNOWLEDGMENT

This study would not have been possible without invaluable excellent technical assistance of our colleagues Dr. T. Toliat and Ms. Mehri Sharif.

REFERENCES

1. R. J. Flower, *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, 9th ed., Macmillan, New York, 1996, pp. 640–641.
2. D. C. Hobbs and T. Twomey, J. Am. Pharm., 270 (1979).
3. E. Wiseman and D. C. Hobbs, Am. J. Med., 72, 9 (1982).
4. D. Narashima Reddy, U. V. Singh, S. Pandey, and N. Udupa, Indian J. Pharm. Sci., 54(4), 152 (1992).
5. R. N. Brogden, R. C. Heel, T. M. Speight, and G. S. Avery, Drugs, 22, 165 (1981).
6. Pfizer Laboratories, *Product Information: Felden®*, Author, New York, 1984.
7. S. Santoyo, A. Arellano, P. Ygartua, and C. Martin, Pharm. Acta Helv., 71(2), 141 (1996).
8. A. Babar, U. D. Solanki, A. J. Cutie, and F. M. Plakogiannis, Drug Dev. Ind. Pharm., 16(3), 523 (1990).
9. S. Tayel and A. Osman, Egypt. J. Pharm. Sci., 36(1–6), 11 (1995).
10. M. A. Pellett, M. S. Roberts, and J. Hadgraft, J. Controlled Release, 151, 91 (1997).
11. A. Babar, R. D. Bhandari, and F. M. Plankogiannis, Drug Dev. Ind. Pharm., 17(8), 1027 (1991).
12. M. S. Rahman, A. Babar, N. K. Patel, and F. M. Plankogiannis, Drug Dev. Ind. Pharm., 16(4), 651 (1990).
13. T. Higuchi, J. Soc. Cosm. Chem., 11, 85 (1960).
14. T. Higuchi, J. Pharm. Sci., 50, 874 (1961).
15. S. C. Chi and H. W. Jun, J. Pharm. Sci., 80(3), 280 (1991).