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The Stability of Piroxicam in Propylene Glycol

Young-Shin Shin, Young-Hee Shin, and Chi-Ho Lee†
College of Pharmacy, Pusan National University, Pusan 609-390, Korea
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프로필렌글리콜에서의 피록시캄의 안정성

신영신·신영희·이치호†
부산대학교 약학대학
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The stability and solubility of piroxicam in propylene glycol (PG), polyethylene glycol (PEC), and PG-water cosolvents have been studied by using high performance liquid chromatography. The degradation rate followed an apparent first-order kinetic and the reaction rate constants at 70, 80, and 90 °C were determined. From these rate constants, the activation energy and the rate constant of piroxicam at 25 °C in pure PG calculated by Arrhenius equation were 23.34 kcal/mole and 7.0×10^{-4} day^{-1}, respectively. Both of PG and PEG increased the solubility of the drug, but PEG was more effective.

Keywords—piroxicam, stability, solubility, propylene glycol, propylene glycol-water cosolvents, polyethylene glycol, Arrhenius plots.

Piroxicam is structurally new antiinflammatory agent that has proved highly potent in animals after oral[1], rectal[2], and percutaneous[3-5] administrations. This agent may be characterized physico-chemically as lipophilic, moderately strong acid (pKa = 6.3)[6] and when the sample was kept in a brown colored-glass in the dark at 20 and 40 °C for two years, no change in color, small, taste and shape of crystals could be observed at either temperature. Thin layer chromatogram and high performance liquid chromatogram did not show any degradation products[7,8].

Piroxicam is all extensively bound to plasma protein, and its half-lives in plasma vary from a few hours to several days. Its high antiinflammatory potency in animals is reflected in clinical trials in which oral dose of as little as 20 mg per day has been shown to control the symptoms of arthritis in man[9-12]. This level of potency shows that small amount of piroxicam applied topically produce antiinflammatory effects superior to those of existing topical agents[7-9]. Japanese patent for piroxicam formulation of ointment showed that the formulation was effective and stable.

Piroxicam itself, generally, has been determined spectrophotometrically and chromatographically[1,9]. The former procedure is relatively nonspecific because the degradation products of piroxicam retain the ultraviolet chromophores of the intact drug[13]. A HPLC method for the quantitation of piroxicam in pharmaceuticals has been already reported but each of them has some faults for stability indicating assays[14]. Topical formulations of piroxicam contain PG or PEG as a dispersing or solubilizing agent. However, the stability of piroxicam in PG or PEG has not been reported.

The present study was undertaken to investigate piroxican stability in PG, 50% PG-water, 70% PG-water cosolvents and PEG by HPLC method. Also the solubility of piroxicam in PG, PEG, and

†To whom correspondence should be addressed.

PG-water cosolvents were determined.

EXPERIMENTAL

Materials

Ammonium phosphate, phosphoric acid, polyethylene glycol 400, and distilled water (HPLC grade) were obtained from Wako Pure Chemical Co. Piroxicam was purchased from Sigma Chemical Co. Propylene glycol was obtained from Fluka AG Chemicals and methanol (HPLC grade) was purchased from Merck Co.

Apparatus

A high performance liquid chromatograph equipped with an universal injector (model U6K, Waters Ass.), a microparticulate reversed-phase C_{18} column (Young-In, cat. No. Y365272), a fixed-wavelength UV detector (model 481, Waters Ass.), a solvent delivery system (model 510, Waters Ass.), and a data module (model 730, Waters Ass.) was used for quantification.

Piroxicam Formulations

Piroxicam was dissolved in PG, 50 v/v% and 70 v/v% PG in water cosolvents, and PEG by agitation at ambient temperature. The concentration of piroxicam formulated into solutions was from 0.005 to 0.06 w/v%. All of these formulations were listed in Table I.

Assay of Piroxicam

In the case of Nos. I and II among formulations listed in Table I, 2 m*l* of 1N HCl were added to 200 μl of each sample and these mixtures were extracted with 5 m*l* of 1,2-dichloroethane by agitating for 3 min at ambient temperature. Then, 3 m*l* of organic phase was back extracted with 3 m*l* of sodium bicarbonate buffer (pH 9.0)[15-17].

Table I—*Piroxicam Formulations.*

Formulation number	Vehicles	Piroxicam concentration (μg/m*l*)	pH
I	50 v/v% PG in water	50	7.0 ± 0.1
II	70 v/v% PG in water	50	7.0 ± 0.1
III	100% PG	250	–

For formulation No. III, 100 μl was taken and acidified with 2 m*l* of 1N HCl. The mixture was extracted with 5 m*l* of 1,2-dichloroethan by agitating for 3 min. 2 m*l* of organic phase from the extract was back extracted with 5 m*l* of sodium bicarbonate buffer (pH 9.0). These extracts were used as samples for HPLC assay of piroxicam.

100 μl of each sample solution were injected into the liquid chromatograph. The system was operated at ambient temperature with a flow rate of 1.5 m*l*/min, and the detector was set at 340 nm with a sensitivity of 0.02 AUFS. The mobile phase consisted of methanol-0.05M ammonium phosphate buffer-0.05M phosphoric acid (3:1:1). Piroxicam concentrations were calculated from the peak heights relative to the standard curve constructed from the peak height versus the known concentrations (0.5-3.0 μg/m*l*) of piroxicam in sodium bicarbonate buffer (pH 9.0). The standard stock solution (100 μg/m*l* in 0.1N NaOH solution) was stable at 4 °C in dark place for at least one month.[18]

Solubility Determination of Piroxicam

The solubility of piroxicam was determined in PG or PEG. A suitable amount of PG or PEG was introduced in 20 m*l* prescription ampules containing 500 mg of piroxicam. These ampules were closed by melting a portion of the glass of the neck with a fine jet of flame and submerged in a constant water bath being shaken at 45 strokes per min for 8 days. Preliminary study showed that this period of time was sufficient to ensure saturation at 30 ± 0.1 °C. After equilibrium had been attained, each of the solutions from ampules was transfered to a syringe and filtered using a 0.45 μm Milipore filter. Filtrates were diluted with sodium bicarbonate buffer (pH 9.0) and assayed by HPLC. The solubilities of piroxicam were determined at least six times for each solvent and the average value was taken. The experimental variation was ±3% in replicate samples.

Stability Test of Piroxicam

Each solution of Formulations listed in Table I was filled in 36 ampules of 2 m*l* -capacity and sealed by melting a portion of the glass in a flame.

These ampules were immerged in constant water bath fixed at 70, 80, and 90 ± 0.5 °C for four days. Every 24 hours, three ampules were withdrawn from a water bath and the concentrations of piroxicam were estimated by measuring the absorbance at 340 nm with UV detector HPLC.

Semilogarithmic plots of piroxicam concentrations remaining in the solutions as a function of time were used to obtain the degradation rate constants. Moreover, these rate constants were used to predict the stability of piroxicam at room temperature.

RESULTS AND DISCUSSION

Linearity and Precision of Calibration Curve

The ideal stability test would measure the undegraded drug and all possible degraded products without prior separation. A chromatographic technique such as HPLC generally comes closest to meet this criteria, and piroxicam formulations were assayed by HPLC procedure in order to check their stabilities. Linearity of this method and reproducibility were determined at each fortification level of the calibration curve. The relative standard deviation based on six times injections of standard solution was 0.496%. Assay recovery was determined by comparing the response from known amounts of piroxicam with processes fortified each of formulation samples. For the purpose of assessing assay specificity, spectrum of piroxicam was compared with spectrum of PG in sodium bicarbonate buffer. As shown in Fig. 1, the retention time of piroxicam was different from that of PG and so PG as a solvent did not much interfere with piroxicam measurement.

As shown in Fig. 2, the linear calibration curve was constructed by plotting peak heights versus the corresponding piroxicam concentrations and the correlation coefficient was 0.998. The reproducibility was determined by repeated injections of a standard solution and the relative standard deviation was less than 0.6%.

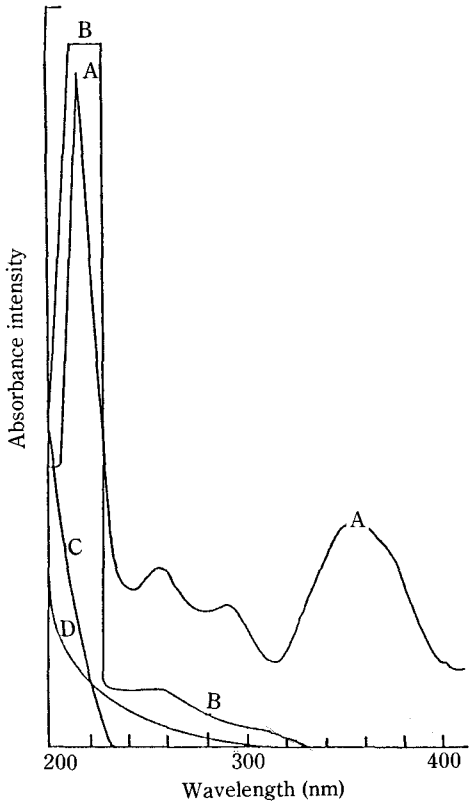

Figure 1—Ultraviolet spectra of piroxicam in the presence of PG or PEG.
Key: A, piroxicam in sodium bicarbonate buffer; B, PG in sodium bicarbonate buffer; C, sodium bicarbonate buffer and D, PEG in sodium bicarbonate buffer

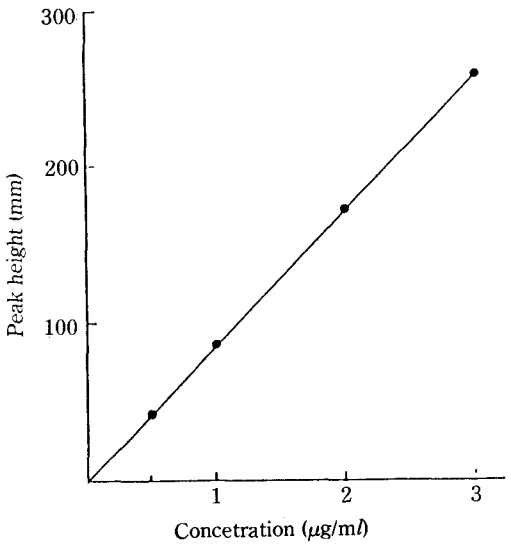

Figure 2—Standard calibration curve of piroxicam in sodium bicarbonate buffer at 340 nm (y = 85.9x + 0.5, r = 0.998).

Solubility of Piroxicam

The solubility of piroxicam increased with increasing the proportion of PG or PEG. Moreover, it was known that PEG was more effective than PG in solubilizing piroxicam as shown in Table II. From these results, it was suggested that the lipophilicity of vehicles was related to the solubility of piroxicam.

Stability of Piroxicam

Semilogarithmic plots of piroxicam concentration remaining as a function of time for each of all formulations at the fixed pH 7.0 ± 0.2 during the storage for the solubility test were shown in Figs. 3-6. As known from these figures, piroxicam of

Table II—*Solubilities of Piroxicam in Various Vehicles at 30°C.*

Vehicles	Number of sample	Concentration (μg/ml)	Relative standard deviation (%)
Water	6	44.6	2.9
50% PG in water	6	550	2.6
60% PG in water	6	660	2.5
70% PG in water	6	870	2.2
80% PG in water	6	1,030	1.8
90% PG in water	6	1,300	1.75
Pure PG	6	1,900	1.3
50% PEG in water	6	2,400	2.0
60% PEG in water	6	3,100	2.1
70% PEG in water	6	3,900	1.8
80% PEG in water	6	5,500	1.3
90% PEG in water	6	10,500	1.2
Pure PEG	6	16,700	1.1

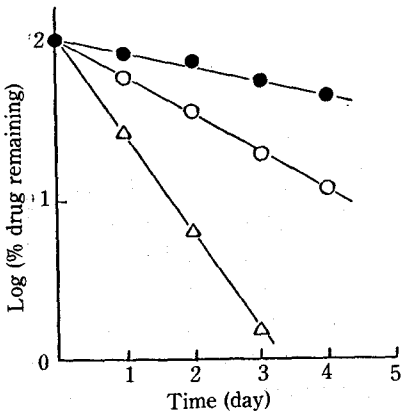

Figure 3—Pseudo first-order plots of piroxicam in pure PG at various temperatures.
Key: ●, 70°C; ○, 80°C and △, 90°C

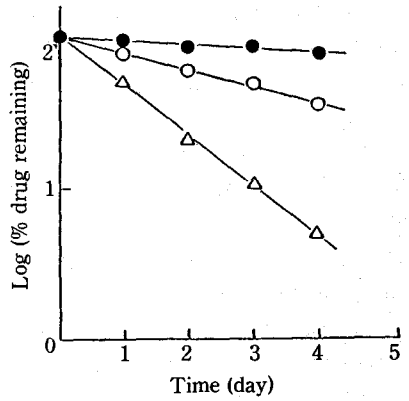

Figure 4—Pseudo first-order plots of piroxicam in 50% PG-water solution at various temperatures.
Key: ●, 70°C; ○, 80°C and △, 90°C

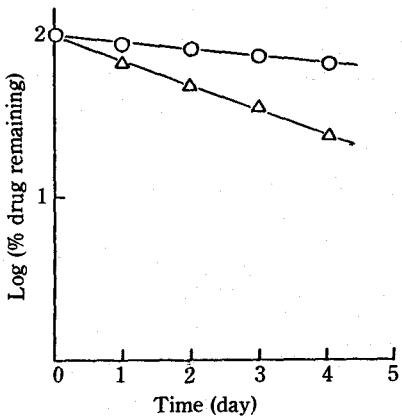

Figure 5—Pseudo first-order plots of piroxicam in 70% PG-water solution at 80°C (○) and 90°C (△).

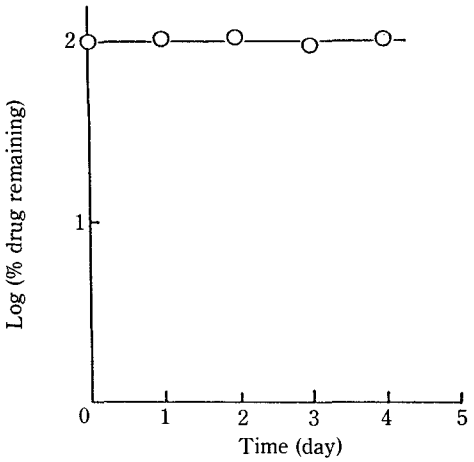

Figure 6—Stability plots of piroxicam in pure PEG at 80 °C.

the formulations was decomposed very slowly and he data from the stability studied followed an apparent first-order. Among four formulations, piroxicam was the most unstable in pure PG solution and in contrast with this, the most stable in pure PEG. The degradation rate constants (k) were listed in Table III.

In order for the rate constants to be of use in formulations of pharmaceutical products, it was necessary to evaluate the temperature dependency of the stability. Arrhenius equation[19] permitted the prediction of the stability of piroxicam at ordinary shelf temperature from data obtained under accelerated conditions of testing. Fig. 7 represented a plots of log k values obtained at three elevated temperatures versus 1/T. Since the plots were linear, the prediction of stability at shelf temperature was possible by extrapolating the curve to the lower temperature. The activation

Table III—*Stability Parameters for Piroxicam Formulations.*

Formulation number	Rate constant (k, day^{-1}) 70°C	80°C	90°C	E_a (kcal/mole)	Predicted shelf-life ($T_{10\%}$, day)
I	0.0263	0.104	0.337	30	1,069
II	—	0.043	0.148	31.67	—
III	0.0924	0.237	0.609	23.34	389

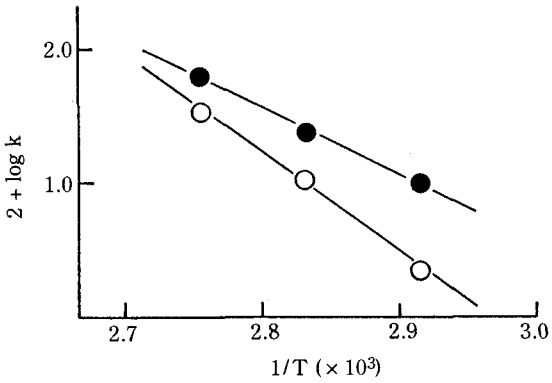

Figure 7—Arrhenius plots for the degradation of piroxicam in PG (●) and 50% PG-water solution (○).

energy and the times ($T_{10\%}$) required for 10% of piroxicam to degrade were listed in Table III.

The activation energy of piroxicam was 23.34 kcal/mole in pure PG and 30 kcal/mole in 50% PG-water cosolvent. It was known from these results that the stability of the drug in PG-water cosolvent was more temperature-dependent than in pure PG, but k value in pure PG was greater than that in PG-water cosolvents. That is, piroxicam was more stable in PG-water cosolvents than in pure PG. The effect of water on the stability of piroxicam in PG-water cosolvents was not well understood. The degradation mechanism of piroxicam needs to be thoroughly investigated as a further work.

CONCLUSION

The stability and solubility of piroxicam in pure PG, PEG and PG-water cosolvents were investigated by HPLC, and the following results were obtained;

1. Both of PG and PEG increased the solubility of piroxicam but PEG was more effective than PG in solubilizing piroxicam than PG.

2. Piroxicam was unstable in pure PG and its degradation rate constant at 25 °C was 7×10^{-4} day^{-1}.

3. Piroxicam was more stable in 70% PG in water than 50% PG in water, and piroxicam was not degraded in PEG at 80 °C for 4 days.

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