Pharmacokinetic Profiles of Two Branded Formulations of Piroxicam 20mg in Healthy Korean Volunteers by a Rapid Isocratic HPLC Method

Hyun Ho Song1,2, Kwang Sik Choi1, Chan-Wha Kim3, Young Ee Kwon1,*

1Bioequivalence Division of Korea Drug Test Laboratory, Seoul (Republic of Korea)
2Graduate School of Life Sciences and Biotechnology, Korea University, Seoul (Republic of Korea)

Abstract

The aim of this study was to develop and validate for determination of piroxicam in human plasma by new rapid HPLC method and to compare the relative bioavailability of two branded formulations of piroxicam in healthy Korean volunteers. The analysis running time of piroxicam was just 2 minutes using C18 column (100 x 4.6 mm, 5 µm) with variable wavelength detector (at 355 nm). This HPLC method was validated by examining the precision and accuracy for inter- and intra-day analysis. A randomized, open-label, single dose, 2-period crossover method was performed in 28 subjects. For analysis of pharmacokinetic properties, the blood samples were drawn at 0, 1, 2, 3, 4, 5, 6, 12, 24, 48, 96 and 168 hours after dosing. The standard curve was linear (R² = 0.9999) over the concentration range of 0.1 - 6 µg/mL. The relative standard deviation (R.S.D.) and accuracy were 0.2 - 6.1% and 95.4 - 104.0%. After single dose of piroxicam 20 mg, the plasma pharmacokinetic parameters, Cmax, Tmax, t1/2 and AUC were 2.15 ± 0.25 µg/mL, 2.44 ± 1.15 h, 46.84 ± 8.73 h and 107.42 ± 27.25 µg·h/mL in the test drug.

No significant differences were found based on analysis of variance, with mean values and 90% CIs of test/reference ratio for these parameters as follows: Cmax was 0.9351-1.0377; AUC0-168 was 0.9510-1.0752. The developed method was successfully applied to bioequivalence study of two branded piroxicam capsules in 28 healthy Korean. The results of pharmacokinetics showed two branded piroxicam 20 mg formulations were bioequivalent, based on the regulatory definition.

Keywords: Bioequivalence; HPLC; Meloxicam; Pharmacokinetics; Piroxicam

Introduction

Piroxicam [4-hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide] (Figure 1) is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs). It has been used in the treatment of rheumatoid arthritis, osteoarthritis and other inflammatory disorders in humans (Brogden et al., 1984; Cerretani et al., 1993). The mechanism of piroxicam, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition (Gadek-Michalska et al., 2008).

Piroxicam is well absorbed following oral administration. Piroxicam binds strongly to plasma protein (>99%) and reached a maximum concentration within three to five hours after oral medication. For the relief of rheumatoid arthritis and osteoarthritis, the recommended dose is 20 mg given orally once per day. Because of the long half-life (about 50 hours) of piroxicam, steady-state blood levels are not reached for 7-12 days (Woolf et al., 1989). The Cmax values were reported as 1.5 to 2 µg/mL when the healthy volunteers were administered 20 mg piroxicam as single dose (Dadashzadeh et al., 2002; Rasetti-Escargueil et al., 2005).

Metabolism of piroxicam occurs by hydroxylation at the 5 position of the pyridyl side chain and conjugation of this product; by cyclodehydration; and by a sequence of reactions involving hydrolysis of the amide linkage, decarboxylation, ring contraction and N-demethylation. Piroxicam and its biotransformation products are excreted in urine and feces (Dixon et al., 1990).

Several high-performance liquid chromatography (HPLC) methods have been developed for piroxicam determination in human or rat plasma for pharmacokinetic study (Amanlou et al., 1997; Boudinot et al., 1988; Dixon et al., 1984; Gillilan et al., 1989; Macek et al., 1987; Milligan, 1992; Richardson et al., 1986; Riedel et al., 1983; Saeed et al., 1989). Nevertheless, there

Figure 1: Chemical structures of piroxicam and meloxicam as an internal standard.
is a need to improve these methods in terms of ease of sample handling and analysis time. A lot of generic products of piroxicam are used in worldwide, but there is no bioequivalence data about a large group of human.

The aim of the present study was to develop a rapid, simple, economic and sensitive HPLC isocratic method for the quantitative determination of piroxicam in human plasma and to compare the pharmacokinetic profile of the test drug (Piroxicam Crown® capsule, Crown Pharm. Co., Ltd., Seoul, Republic of Korea) and the reference drug (Comcam® capsule, Daelim Pharm. Co., Ltd., Seoul, Republic of Korea) for bioequivalence study after a single oral dose of 20 mg piroxicam.

**Subjects, Materials and Methods**

**Subjects and Study Design**

This single-dose, randomized, open-label, 2-period crossover study was conducted at Soonchunhyang University Hospital (Cheonan, Republic of Korea) with 28 volunteers. Healthy adult male and female Korean volunteers were enrolled. The study was performed according to the criteria of bioavailability and bioequivalence study of the Regulatory guideline of Korea Food and Drug Administration (KFDA). The institutional review board at Korea Drug Test Laboratory (Seoul, Republic of Korea) approved the protocol prior to the start of this study. The study protocol was approved by the KFDA. Twenty eight healthy Korean subjects (22 men and 6 women), a mean age of 22.1 ± 3.7 years, a mean body weight of 63.8 ± 6.5 kg, and a mean height of 170.4 ± 7.6 cm were enrolled in this study.

All subjects provided the written informed consent prior to the commencement of the study. The subjects’ medical histories were documented and a physical examination was conducted. Inclusion eligibility was based on the successful completion of a clinical health evaluation that consisted of a personal interview, a complete physical examination (blood pressure, pulse, weight, height, temperature, respiratory rate), and diagnostic testing that included a 12-lead electrocardiogram. Laboratory testing included a complete blood count, metabolic and hepatic tests, urinalysis, pregnancy test (for female subjects), and serologic tests for glucose, blood urea nitrogen, creatinine as well as syphilis, hepatitis B and HIV antibodies. Volunteers were excluded if they had any physical disorder based on medical history, physical examination, and the above clinical and laboratory analyses or had received any prescription or over-the-counter medication within 2 weeks prior to or during the study period.

**Drug Administration and Sampling**

Each subject was administered 20 mg of piroxicam orally a Comcam®capsule (Daelim Pharm. Co., Ltd. Seoul, Republic of Korea) and a Piroxicam Crown® capsule (Crown Pharm. Co., Ltd., Seoul, Republic of Korea) with 240 ml of water, using a standard 2 X 2 cross-over model in randomized order after an overnight fast. The subjects were maintained in the fasting state for 4 h after administering the drug. Blood samples were obtained using an 18-G x 1.16-in (1.3 x 30 mm), indwelling angiocatheter (Becton Dickinson Korea Co., Ltd., Gyeongbuk, Republic of Korea), which was inserted into the subjects’ fore-arm vein and collected into a 7.5 mL heparinized tube (Becton Dickinson). Before collection of each blood sample, 1 mL of blood sample was drawn from angiocatheter and discarded. To ensure patency, 0.5 mL of lithium heparin (25 IU/mL) was injected into the angiocatheter after each blood sample was drawn. The venous blood samples (10 mL) were obtained before (0 hour; baseline) and at 1, 2, 3, 4, 5, 6, 12, 24, 48, 96 and 168 hours after drug administration. The blood samples were transferred to poly propylene centrifuge tubes and the plasma samples were separated using centrifugation at 1,000 g for 10 min at room temperature (25 °C), followed by direct transfer into microcentrifuge tubes (MCT-200-C, Axyen, California, USA) and stored frozen at -70 °C until analysis. After washout period (24 days), the 28 subjects returned to the hospital and the blood sample analysis was repeated in the second period in the same manner to complete the crossover design.

The amount of food and water intake and physical activity for each individual subject were standardized during the sampling days. Xanthine-containing food or beverages and fruit juices were not allowed for 24 hours before and during the entire sampling days. Blood pressure, heart rate and adverse events were monitored during the blood sampling and also on follow-up study.

**Assay Methodology**

**Preparation of Standard solution and Samples for Assays**

The standard reagent of piroxicam, Piroxicam Crown® capsule (piroxicam 20 mg, test drug) and Comcam® capsule (piroxicam 20 mg, reference drug) were donated from Crown Pharm. Co., Ltd. (Seoul, Republic of Korea). A stock solution of piroxicam (100 μg/mL) and meloxicam (10 μg/mL) as internal standard (I.S.) were prepared by dissolving them in 30% methanol. The secondary standard solutions of piroxicam were prepared by diluting the stock solutions with 30 % methanol. The working standard solutions of piroxicam were produced by diluting the secondary solutions with blank human plasma. The seven calibration standards of piroxicam (final concentrations: 0.1, 0.2, 0.5, 1, 2, 4 and 6 μg/mL) were prepared independently. The working I.S. solution (10 μg/mL) was prepared by diluting the stock solution with 30 % methanol. All solutions were stored at 4 °C until needed. Five hundred microliters of plasma or the calibration standards, 100 μL of I.S. solution (meloxicam, 10 μg/mL) and 30 μL of 60 % perchloric acid were added to a microcentrifuge tube (MCT-200-C, Axyen, California, USA). After vortex mixing for 5 min, each sample was centrifuged at 14,000 rpm for 10 min (Micro 17TR, Hanil instrument, Incheon, Korea). And then, the upper layer was transferred to a new tube and a 50 μL of aliquot was injected into the HPLC system for analysis.

**Assay Procedure**

The matrix effect was estimated by extracting blank human plasma from 6 different sources, reconstituting the final sample in injecting solvent containing a known amount of the piroxicam and meloxicam (I.S.), analyzing the reconstituted samples and then comparing the peak areas of the piroxicam and I.S. The low limit of quantification (LLOQ) was defined as a reproducible lowest possible concentration, linear with the calibration curve having a coefficient of variation (CV) below 20 % and accuracy between 80 and 120 % of the theoretical value. The linearity of calibration curve for piroxicam was conducted in
the range 0.1 - 6 µg/mL in the plasma samples. The calibration curve was obtained by plotting the area ratios of piroxicam and I.S. as a function of the piroxicam concentration using least-squares linear regression analysis (no weighing factor). The regression line was used to calculate the respective concentrations of piroxicam samples from healthy volunteers.

The accuracy and precision of inter- and intra-day assay were determined by replicate analysis of five sets of samples spiked with seven different concentrations of piroxicam (0.1 – 6 µg/ml) within 1 day or on 5 consecutive days. The precision and accuracy was determined to be the coefficient of variation (CV), and the accuracy is expressed as the relative standard deviation (R.S.D). The whole study was conducted in accordance with FDA guideline.

**Instruments and Chromatographic Conditions**

The HPLC system consisted of an Agilent 1100 series Quaternary Pump (G1311A), an Agilent 1100 series Autosampler (G1329A) and an Agilent 1100 series variable wavelength detector (Agilent-technologies, Waldbronn, Germany). Agilent chemstation data system (Rev.B.02.01_SR1 [260]) was used as the data software. The analytical column was an XBridge™ C18 column (particle size: 5.0 µm, 4.6 x 100 mm, Waters Co. Ltd., Milford, USA). The detection wavelength was a 355 nm. The column temperature was maintained at 40 °C using a Thermostatted Column Compartment (G1316A). The mobile phase contained a mixture of acetonitrile-5 mM ammonium formate (45:55, v/v). 5 mM Ammonium formate contained formic acid (7 mL/L) and triethylamine (10 mL/L) and the mixture of mobile phase pH values was 3.35. The flow rate of mobile phase was 1.8 mL/min.

**Pharmacokinetic Study and Statistical Evaluation**

The pharmacokinetic parameters of piroxicam were estimated using non-compartmental methods with BA calc 2007 (Lee et al., 2000). The actual blood sampling times were used, and the maximum plasma concentration (Cmax) and the time to reach Cmax (Tmax) were observed values. The area under the plasma concentration-time curve (AUC) was calculated using the linear trapezoidal rule. The elimination rate constant (ke) was obtained as the slope of the linear regression of the log-transformed concentration-time curve data in the terminal phase. The half-life (t1/2) was calculated as ln 2/ke.

For the purpose of bioequivalence analysis, a two-way ANOVA (analysis of variance) was performed using the K-BE Test 2007 1.1.0 program at a significant level of 0.05. The test and reference treatments of each study were compared with respect to relevant pharmacokinetic variables using an analysis of variance with subject, treatment, and period effects with the raw data. Bioequivalence of the test treatment to the reference treatment was evaluated on the basis of the confidence intervals for the "test/reference" mean ratios of these raw variables in relation to the bioequivalence range of 80–125 % for the raw data.

**Results**

**Specificity of Human Plasma Samples**

Reproducible chromatographic separation between piroxicam and meloxicam (I.S.) were established after tests in various chromatographic conditions by injecting the protein precipitated plasma samples. Under the experimental conditions, reproducible chromatographic separations were obtained at acetonitrile -5 mM ammonium formate buffer (pH 3.35 adjusted with triethylamine and formic acid) (45:55, v/v). The protein precipitation and HPLC assay resulted in a symmetrical peak shape and good baseline resolution of piroxicam and meloxicam. Figure 2 showed the representative chromatograms for human blank plasma (Figure 2A), blank human plasma spiked with 0.1 µg/mL (LLOQ) of piroxicam and 10 µg/mL of meloxicam (Figure 2B), and blank plasma spiked with 4 µg/mL of piroxicam and 10 µg/mL of meloxicam (Figure 2C). The retention time of piroxicam and I.S. was approximately 1.3 and 1.7 min, respectively, and the total running time for each sample was 2 min. No interfering endogenous peaks were detected in chromatogram. Fluctuations in retention times occurred due to changes in temperature and column performance within 0.1 min.

**Sensitivity and Linearity for Determination of Piroxicam**

The low limit of quantification (LLOQ) was determined as a concentration of drug giving a signal-to-noise ratio greater than...
10 with accuracy between 80 and 120% and with a precision
R.S.D. (%) less than 20%. The linearity of detector response
was assessed for precipitated plasma standards over the range
of 0.1 – 6 µg/ml. The calibration curve of piroxicam exhibits an
excellent linearity and a correlation coefficient. The mean (±S.D.)
regression equation from five replicated calibration curves was
\[ y = 0.4437 \pm 0.0016 \times + 0.0032 \pm 0.0053 \] \( (y = \text{ratio of peak area}, x = \text{piroxicam concentration}) \) with the \( R^2 = 0.9999 \) or 1.0000.

**Precision and Accuracy of Assays**

Table 1 provided a summary of the accuracy and precision at
0.1, 0.2, 0.5, 1, 2, 4, and 6 µg/ml as a piroxicam concentration
in human plasma. The inter-day accuracy and precision ranged
from 99.0 ± 1.42 to 102.6 ± 3.93 %, and between 0.2 and 6.1 %,
respectively, for continuous 5 days. The intra-day accuracy and

d| Concentration (µg/ml) | Precision, CV\(^a\) (%) | Accuracy\(^b\) (%) |
|----------------------|------------------------|------------------|
| Inter-day            |                        |                  |
| 0.1 (LLOQ)           | 6.1                    | 101.1 ± 6.66     |
| 0.2                  | 3.7                    | 102.6 ± 3.93     |
| 0.5                  | 1.1                    | 101.7 ± 1.15     |
| 1                    | 1.4                    | 99.2 ± 1.42      |
| 2                    | 1.6                    | 99.0 ± 1.61      |
| 4                    | 0.5                    | 100.4 ± 0.54     |
| 6                    | 0.2                    | 99.9 ± 0.19      |
| Intra-day            |                        |                  |
| 0.1                  | 4.9                    | 95.4 ± 5.10      |
| 0.2                  | 2.0                    | 101.2 ± 2.06     |
| 0.5                  | 2.0                    | 104.0 ± 2.10     |
| 1                    | 1.9                    | 98.5 ± 1.90      |
| 2                    | 1.9                    | 99.5 ± 1.86      |
| 4                    | 0.8                    | 100.2 ± 0.83     |
| 6                    | 0.6                    | 100.0 ± 0.62     |

Each inter- and intra-day calibration was performed 5 times. Inter-
day calibration was performed one time per one day for continuous
5 days. Intra-day calibration was performed 5 times using different
human plasma. The values of precision, CV\(^a\) (%) and accuracy\(^b\) (%) were presented relative standard deviation of 5 times tests.

\(^a\)Coefficient of variations
\(^b\)Values are reasonable for 15 % deviation of the standard from nominal

**Table 1:** The validation results of inter- and intra-day precision and accuracy of piroxicam in human plasma.

| PK parameter     | Test\(^a\)  | Reference\(^b\) |
|------------------|-------------|-----------------|
| \( C_{\text{max}} \) (µg/ml) | 2.15 (0.25)\(^c\) | 2.20 (0.36) |
| \( T_{\text{max}} \) (h) | 2.44 (1.15) | 2.62 (1.10) |
| \( t_{1/2} \) (h) | 46.84 (8.73) | 48.56 (12.78) |
| \( AUC_t \) (µg·h/ml) | 107.41 (27.25) | 106.81 (22.47) |
| \( AUC_{\infty} \) (µg·h/ml) | 121.42 (31.33) | 123.07 (24.55) |
| \( k_e \) (h\(^{-1}\)) | 0.0139 (0.0030) | 0.0141 (0.0027) |
| \( \text{AUC}_t / \text{AUC}_{\infty} \) (%) | 88.46 (4.99) | 86.82 (7.92) |

\(^c\)Trademark: Piroxicam Crown\(^a\) capsules (20 mg x 1C, Crown Pharm. Co., Ltd., Seoul, Republic of Korea)
\(^b\)Trademark: Comcam\(^a\) capsules (20 mg x 1C, Daelim Pharm. Co., Ltd., Seoul, Republic of Korea)
\(^d\)Values are mean (SD)

**Table 2:** Pharmacokinetic parameters of piroxicam in plasma of 28 healthy Korean volunteers after a single oral administration of 20 mg piroxicam.

**Figure 3:** Chromatograms of (A) 0, (B) 4, and (C) 48 h after a single oral dose of 20 mg piroxicam.

**Table 3:** The results of statistical evaluation of bioequivalence study.

**Bioequivalence Study**

This method was applied to the determination of piroxicam in
human plasma samples for bioequivalence study of two
piroxicam formulations. Twenty eight healthy volunteers were
administered 20 mg of piroxicam in capsule formulations. Plasma samples were obtained during 168 h after piroxicam administration. Figure 3 shows the change of the plasma concentration of piroxicam at 0 h, 4 h and 48 h after oral administration of 20 mg single dose.

The pharmacokinetic parameters are summarized in Table 2. The $C_{\text{max}}$, $T_{\text{max}}$, $t_{1/2}$, and $AUC_{0-12}$ values of piroxicam 20 mg were similar in test and reference formulations as 2.15 ± 0.25 vs 2.20 ± 0.36 µg/mL, 2.44 ± 1.15 vs 2.62 ± 1.10 h, 46.84 ± 8.73 vs 48.56 ± 12.78 h and 107.41 ± 27.25 vs 106.81 ± 22.47 µg·h/mL, respectively. These results showed no statistically significant difference between the two formulations with a $p$-value greater than 0.05 on analysis of variance for these parameters after log-transformation of the data. The 90% confidence intervals (CIs) for the log transformation of the data were within the acceptance range of log 0.8 to log 1.25 at $\alpha = 0.05$ (Table 3). The major pharmacokinetic parameters, $C_{\text{max}}$ and $AUC_{0-12}$ met the criteria set by KFDA for bioequivalence indicating that generic drugs are bioequivalent to branded drugs. Mean plasma concentration-time curves of two branded piroxicam formulations are shown in Figure 4.

**Discussion**

We established a simple and rapid analytical method for the determination of piroxicam in human plasma using HPLC method with UV detection. A one-step protein precipitation provided a simple, rapid and economic procedure. This method showed excellent sensitivity, reproducibility, specificity and velocity. The total running time is only 2 min. Therefore, this HPLC analysis method can be useful method and applied to routinely monitor the concentration of piroxicam.

In a randomized, open label, two-way and crossover bioequivalence study of two formulations of piroxicam 20 mg was performed to demonstrate that generic drugs and branded drugs are statistically bioequivalent. In this population of healthy Korean adults, the test and reference formulations were found to be bioequivalent based on the regulatory definition. The method has been successfully used to provide the bioequivalent study of piroxicam in human plasma and the result of bioequivalent test of two branded 20 mg piroxicam formulations were considered bioequivalent.

According to the previous reported paper, the pharmacokinetic parameters of against male Caucasian 16 healthy volunteers (aged 18 – 30 years) are follows. The $C_{\text{max}}$, $T_{\text{max}}$, $t_{1/2}$ and $AUC_{0-12}$ values of piroxicam 20 mg capsule formulation were 1900.31 ± 96.20 ng/mL, 5.22 ± 0.73 hours, 53.11 ± 4.54 hours and 113250.31 ± 10877.47 ng·h/mL, respectively. The values of $C_{\text{max}}$ and $AUC_{0-12}$ were similar between Korean and Caucasian, however, $T_{\text{max}}$ was different. The $T_{\text{max}}$ value of Korean adult male was approximate 2.6 hours but that of Caucasian was approximate 5.2 hours. And also, the $t_{1/2}$ value of Korean was approximate 48.5 hours and that of Caucasian was approximate 53.1 hours. This means that absorption and elimination time of piroxicam against Korean is faster than Caucasian. But, the difference between races must be established through more extended studies.

**Acknowledgments**

The authors are thankful to Crown Pharm. Co., Ltd. (Seoul, Republic of Korea) for supporting fund and providing piroxicam formulations and the standard reagents.

**References**

1. Amanlou K, Dehpour AR (1997) Rapid method for the determination of piroxicam in rat plasma using high-performance liquid chromatography. J Chromatogr 696: 317-319.
2. Boudinot FD, Ibrahim SS (1988) High-performance liquid chromatographic assay for piroxicam in human plasma. J Chromatogr 430: 424-428.» CrossRef » PubMed » Google Scholar
3. Brogden RN, Heel RC, Speight TM, Avery GS (1984) Piroxicam. A reappraisal of its pharmacology and therapeutic efficacy. Drugs 28: 292-323. » PubMed » Google Scholar
4. Cerretani D, Micheli L, Fiaschi AI, Giorgi G (1993) Rapid and sensitive determination of piroxicam in rat plasma, muscle and skin by high-performance liquid chromatography. J Chromatogr 614: 103-108. » CrossRef » PubMed » Google Scholar
5. Dadashzadeh S, Vali AM, Rezagholi N (2002) LC determination of piroxicam in human plasma. J Pharm Biomed Anal 28: 1201-1204. » CrossRef » PubMed » Google Scholar
6. Dixon JS, Lacey LF, Pickup ME, Langley SJ, Page MC (1990) A lack of pharmacokinetic interaction between ranitidine and piroxicam. Eur J Clin Pharmacol 39: 583-586. » CrossRef » PubMed » Google Scholar
7. Dixon JS, Lowe JR, Galloway DB (1984) Rapid method for the determination of either piroxicam or tenoxicam in plasma using high-performance liquid chromatography. J Chromatogr 310: 455-459. » PubMed » Google Scholar
8. FDA Guidance for industry (2003) Bioavailability and Bioequivalence Study for orally Administered Drug Products. Rockville, Md: Office of Generic Drugs, Division of Bioequivalence, US Food and Drug Administration.
9. Gadek-Michalska A, Bugajski AJ, Bugajski J (2008) Prostaglandins and interleukin-1beta in the hypothalamic-pituitary-adrenal response to systemic phenylephrine under basal
and stress conditions. J Physiol Pharmacol 59: 563-575.

10. Gillilan RB, Mason WD, Fu CH (1989) Rapid analysis of piroxicam in dog, rat and human plasma by high-performance liquid chromatography. J Chromatogr 487: 232-235.

11. Guidance for Industry (2001) Bioanalytical Method Validation. Center for Drug Evaluation and Research (CDER), US FDA.

12. Lee YJ, Kim YG, Lee MG, Chung SJ, Lee MH, et al. (2000) Analysis of Bioequivalence Study using a Log-transformed Model. Yakhak Hoeji 44: 308-314.

13. Macek J, Vacha J (1987) Rapid and sensitive method for determination of piroxicam in human plasma by high-performance liquid chromatography. J Chromatogr 420: 445-449.

14. Milligan PA (1992) Determination of piroxicam and its major metabolites in the plasma, urine and bile of humans by high-performance liquid chromatography. J Chromatogr 576: 121-128.

15. Rasetti-Escargueil C, Grange V (2005) Pharmacokinetic profiles of two tablet formulations of piroxicam. Int J Pharm 295: 129-134.

16. Richardson CJ, Ross SG, Blocka KL, Verbeeck RK (1986) High-performance liquid chromatographic analysis of piroxicam and its major metabolite 5′-hydroxypiroxicam in human plasma and urine. J Chromatogr 382: 389-393.

17. Riedel KD, Laufen H (1983) High-performance thin-layer chromatographic assay for the routine determination of piroxicam in plasma, urine and tissue. J Chromatogr 276: 243-248.

18. Saeed L, Becher M (1991) On-line solid-phase extraction of piroxicam prior to its determination by high-performance liquid chromatography. J Chromatogr 567: 185-195.

19. Woolf TF, Radulovic LL (1989) Oxicams: metabolic disposition in man and animals. Drug Metab Rev 21: 225-276.