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Research Article

EVALUATION OF PHARMACOKINETIC PARAMETERS OF SOLID DISPERSIONS OF PIROXICAM

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ABSTRACT

Dissolution rate and dissolution efficiency of poorly soluble non-steroidal anti-inflammatory drugs (NSAIDs) could be markedly enhanced by solid dispersion technologies. Solid dispersions of piroxicam (PRX) are subjected to *in vivo* pharmacokinetic evaluation to evaluate whether these systems improve oral bioavailability of the piroxicam. All the pharmacokinetic parameters of absorption, namely K_a, C_{max}, T_{max}, percent absorbed to various times and AUC indicated rapid absorption and higher bioavailability of piroxicam when administered as solid dispersion. The absorption rate constant (K_a) was found to be 1.56 hr^{-1} in the case of piroxicam-CC-PVP solid dispersion. Where as in the case of piroxicam K_a was only 0.87 hr^{-1}. An increase of 2.16 fold in K_a was observed with piroxicam-Croscarmellose-Polyvenyl pyrollidine (PRX-CC-PVP) solid dispersion. AUC (extent of absorption) was also much higher in the case of piroxicam solid dispersion when compared to piroxicam. $[AUC]_{0\text{-}12h}$ was increased from 55.58 µg-hr/ml for piroxicam to 56.21 µg-hr/ml for piroxicam solid dispersion . Both K_a and AUC were markedly increased by solid dispersion. Thus, the results of pharmacokinetic studies indicated rapid and higher oral absorption of piroxicam when administered as CC-PVP solid dispersion.

Key Words: Dissolution Rate, Absorption Rate, Solid dispersion.

INTRODUCTION

Non steroidal anti inflammatory drugs, are drugs with analgesic, antipyretic and anti-inflammatory effects. They reduce pain, fever and inflammation. Most of the NSAIDs belong to class II category under Biopharmaceutical Classification System (BCS) i.e., they are inherently highly permeable through biological membranes, but exhibit low aqueous solubility. They need enhancement in solubility and dissolution rate for improving their oral bio availability. Among the various methods for improving the dissolution rate and bioavailability, solid dispersion technology is more efficient and industrially accepted method for improving the dissolution rate and bioavailability of the selected NSAIDs. As a consequence of the solid dispersion of piroxicam many physico chemical properties, such as solubility, dissolution rate stability and bioavailability can be favorably affected[1]. Piroxicam (PRX) (official in IP, USP and Europpean Pharmacopoeia) is the first member of enolic acid class and was introduced in US in the year 1982 as feldene (Pfizer) and gained immediate acceptance in US where it was among the top 50 prescription drugs for several years. Oxicams represent a potential growing class of NSAIDS. Piroxicam is indicated for long-term use in rheumatoid arthritis and osteoarthritis. The initial recommended maintenance dose is a single 20 mg dose that may be divided[2]. It is available in 10 mg and 20 mg capsules and tablets. It is rapidly and completely absorbed 99% protein bound; largely metabolized in liver by hydroxylation and glucuronide conjugation; excreted in urine and bile, enterohepatic cycling occurs. Plasma half-life is long nearly 2 days. Single daily administration is sufficient.

MATERIALS AND METHODS

Healthy rabbits of either sex (weighing 1.5-2.5 kg) were fasted overnight. piroxicam and its solid dispersions μ were administered at dose equivalent to 5 mg/kg of piroxicam. Each product was repeated 6 times (n=6). The in vivo experiments were conducted as per the following crossover

RBD. A washout period of one month was given between the treatments. After collecting the zero hour blood sample (blank), the product in the study was administered orally in a capsule shell with 10 ml of water. Blood samples (3 ml) were collected from marginal ear vein at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0 and 12 h after administration. The blood samples were allowed to clot and centrifuged at 5000 rpm and the serum separated was collected into dry tubes. All the samples were stored under refrigerated conditions prior to assay. Serum concentration of piroxicam was determined by the HPLC method.

Estimation of Piroxicam Serum Samples

Piroxicam in blood samples was determined by the HPLC method[3]. Piroxicam from blood samples was extracted with acetonitrile and acidified with 1.47 M $HClO_4$ and determined spectrophotometrically at 330 nm. The method was reported to be specific for the parent compound, piroxicam.

Materials

1. Piroxicam I.P. (gift sample from M/s.Ranbaxy Laboratories, Gurgaon).
2. Acetonitrile (Qualigens)
3. Perchloric acid (Qualigens)

Stock Solution

10 mg of piroxicam was dissolved in acetonitrile and the volume was made up to 10ml to give a solution of strength 1000 µg /ml.

Procedure

The stock solution of piroxicam was subsequently diluted with acetonitrile to obtain a series of dilutions containing 2, 4, 6, 8 and 10 µg of piroxicam in 1ml of solution. One ml of each dilution was again diluted to 5 ml with acetonitrile. To this solution added 1 ml of blood from un dosed

subjects. The tubes were then centrifuged at 2500 rpm for 15 minutes. 4 ml of supernatant was removed and 0.2 ml of 1.47 M aqueous $HClO_4$ was added to it. The absorbances of these solutions were measured in ELICO-SL 150 UV spectrophotometer at 330 nm against blank prepared in the same manner without piroxicam. The corresponding absorbances are given in Table 1 . The absorbances were plotted against concentration of piroxicam as shown in Fig. 1.

Table 1. Calibration Curve for the Estimation of Piroxicam in Blood samples

Piroxicam Concentration (µg/ml)	Absorbance		
	$\bar{x}$	SD	RSD (%)
2	0.025	0.0002	0.80
4	0.050	0.0004	0.77
6	0.075	0.0005	0.66
8	0.100	0.0009	0.89
10	0.125	0.0008	0.64

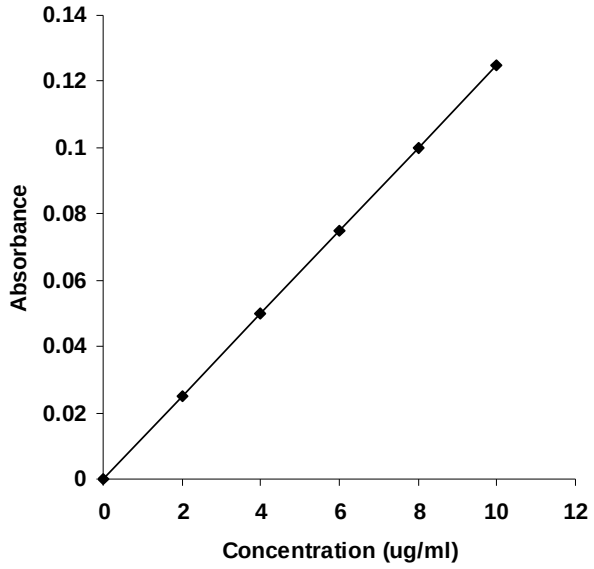

Fig 1. Calibration Curve for the Estimation of Piroxicam in Blood

Estimation in Blood

Blood (1.0 ml) was taken in a dry centrifuge tube. Acetonitrile (5ml) was added and mixed. The tubes were then centrifuged at 2500 rpm for 15 minutes. 4 ml of supernatant was collected into a dry test tube and 0.2 ml of 1.47M aqueous $HClO_4$ solution was added and mixed. The absorbance of the resulting solution was measured at 330 nm against a blank prepared in the same manner with blood collected before drug administration.

Discussion

The method obeyed Beer's Law in the concentration range of 0-10 µg/ml. The minimum detectable concentration is 0.02 µg/ml. When a standard solution assayed repeatedly (n=6), the relative standard deviation (RSD) in the estimated values was found to be 1.2%.

One ml blood was pipetted into glass stoppered centrifuge tube. Acetonitrile (5ml) was added and mixed for 10 min. The contents of the tube were then centrifuged at 2500 rpm for 15 min. The supernatant fluid (4ml) was transferred into a test tube containing 0.2 ml of 1.47 M aqueous $HClO_4$ solution and mixed. The absorbance of the solution was measured at 330 nm against blank prepared in the same manner using zero hour drug free blood sample. Time versus plasma concentrations observed following the oral administration of piroxicam and its products are given in Table 2 and shown in Fig 2.

Table 2. Plasma Concentrations of Piroxicam Following the Oral Administration of Piroxicam and Its Products

Time (hrs)	Plasma Concentration (µg/ml)	
	Piroxicam	**Piroxicam-CC-PVP**
0	0	0
0.5	1.16±0.28	2.09±0.86
1	2.15±0.19	4.90±1.2
1.5	3.08±0.32	7.20±1.65
2	4.84±0.40	10.56±2.4
2.5	6.41±0.15	14.80±2.12
3	7.99±0.06	10.50±1.8
3.5	9.25±0.14	7.80±1.52
4	10.58±0.19	6.5±0.85
6	5.66±0.24	5.15±0.75
8	3.24±0.40	3.25±0.56
12	2.24±0.27	1.65±0.68

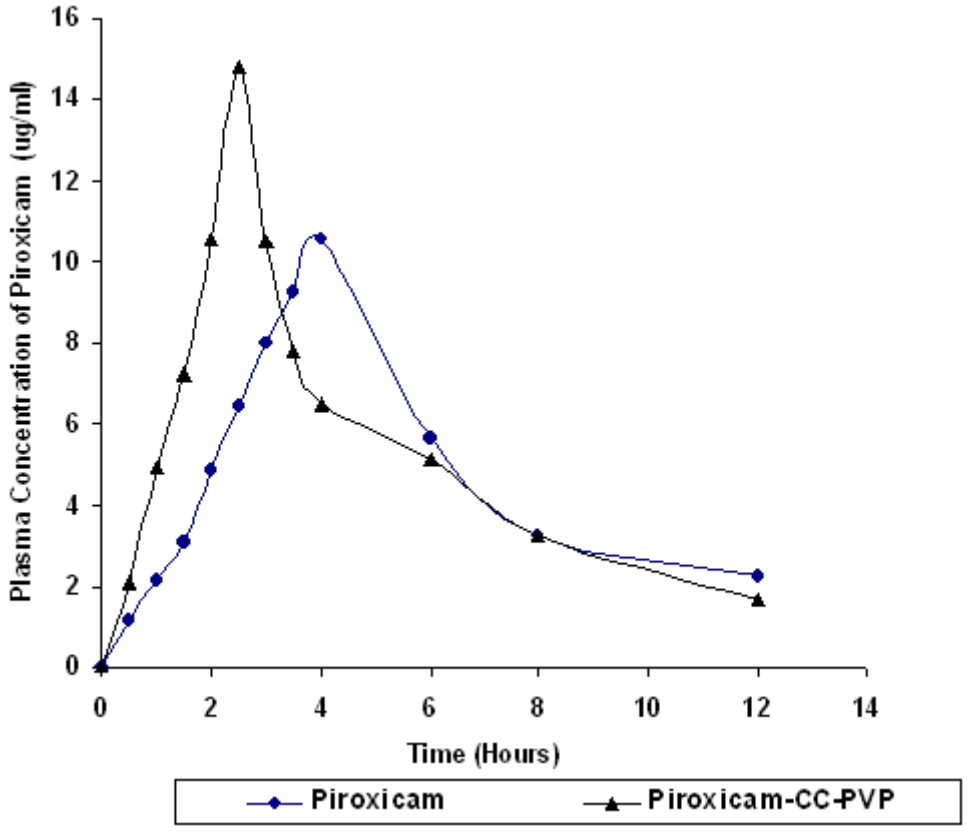

Fig 2. Blood Level Curves Following the Oral Administration of Piroxicam and its Products

RESULTS AND DISCUSSION

Pharmacokinetics of Piroxicam and its Solid Dispersion

Pharmacokinetic parameters estimated following the oral administration of piroxicam and its products are given in Table 3. The elimination rate constant (K_{el}) for piroxicam was found to be 0.17±0.3 hr^{-1} and the corresponding biological half life ($t_{1/2}$) value of piroxicam obtained in the present study is 4.03 and is in good agreement with earlier reported value of 4.33 hr. The absorption rate constant (K_a) was found to be 0.87±0.12 hr^{-1} following the oral administration of piroxicam. Piroxicam was found to be absorbed slowly when given orally and a peak serum concentration

(C_{max}) of 10.6±0.19 ng/ml was observed at 4.0 hr following administration. All the pharmacokinetic parameters of absorption (Table 3) namely K_a, C_{max}, T_{max}, percent absorbed to various times and AUC indicated rapid absorption and higher bioavailability of piroxicam when administered as its solid dispersion. Higher C_{max} and shorter T_{max} values were observed with these products when compared to those of piroxicam as such. The absorption rate constant (K_a) was found to be 1.881±0.24 hr^{-1} in the case of piroxicam-CC-PVP solid dispersion. Where as in the case of piroxicam, Ka was only 0.87 hr^{-1}. An increase of 2.16 fold in K_a was observed with piroxicam-CC-PVP solid dispersion. AUC (extent of absorption) was also much higher in the case of piroxicam solid dispersion when compared to piroxicam. $[AUC]_{0\text{-}12h}$ was increased from 55.58 ng-hr/ml for piroxicam to 56.21 ng-hr/ml for piroxicam -CC-PVP solid dispersion. Thus, the results of pharmacokinetic studies indicated rapid and higher oral absorption of piroxicam when administered as solid dispersion. Both Ka and AUC were markedly increased by solid dispersion with CC-PVP.

Table 3. Summary of Pharmacokinetic Parameters Estimated Following the Oral Administration of Piroxicam and its Products

Product	C_{max} (µg/ml)	T_{max} (hrs)	$[AUC]_o^{2.5h}$ (µg-h/ml)	$[AUC]_o^{12h}$ (µg-h/ml)	K_a (hr^{-1})	K_{el} (hr^{-1})	$T_{1/2}$ (h)
Piroxicam	10.6 ±0.19	4.0	7.22 ±6.58	55.58 ±10.3	0.87 ±0.12	0.17 ±0.3	4.03
Piroxicam CC-PVP	14.80 ±2.12	2.5	18.91 ±3.4	56.21 ±10.5	1.881 ± 0.24	0.18 ±0.6	3.8

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