Supermolecular Inclusion of Piroxicam with ß-Cyclodextrin: Pharmacokinetic Properties in Man

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Summary

Piroxicam ß-cyclodextrin is a novel inclusion complex in which the piroxicam molecule has higher wettability and faster dissolution characteristics than plain piroxicam. Pharmacokinetic studies comparing piroxicam ß-cyclodextrin with plain piroxicam have been carried out in both patients and healthy subjects. The absorption rate of piroxicam from the complex, determined using t_{max}, absorption rate constant (K_a) and plasma concentrations at 15 min and 30 min post-dose, is considerably faster than that for plain piroxicam. This difference, that can be demonstrated with both tablet and sachet formulations, is still present during repeated dose administration and when the drugs are administered after food. After absorption from piroxicam ß-cyclodextrin formulations, the kinetic disposition of piroxicam and bioavailability parameters are identical to those for plain piroxicam. The more rapid rise in piroxicam plasma concentrations and the reduced contact time of piroxicam in the upper gastrointestinal-tract may be reasons for the reduced incidence of gastrointestinal complaints and gastrointestinal bleeding and the rapid attainment of pain relief with piroxicam ß-cyclodextrin. The most rapid relief of pain will be achieved using piroxicam ß-cyclodextrin sachets administered in the fasting state, since piroxicam is immediately bioavailable in this formulation and the onset of action is similar to that for injectable piroxicam.

Introduction

Properties of ß-Cyclodextrin

Cyclodextrins are water soluble cyclic oligosaccharides formed enzymatically from partially hydrolysed starch. They are composed of different numbers of α-(1-4)-linked D(+) glucopyranose residues: α-, ß-, and γ-cyclodextrins contain 6, 7 and 8 residues respectively (Figure 1).

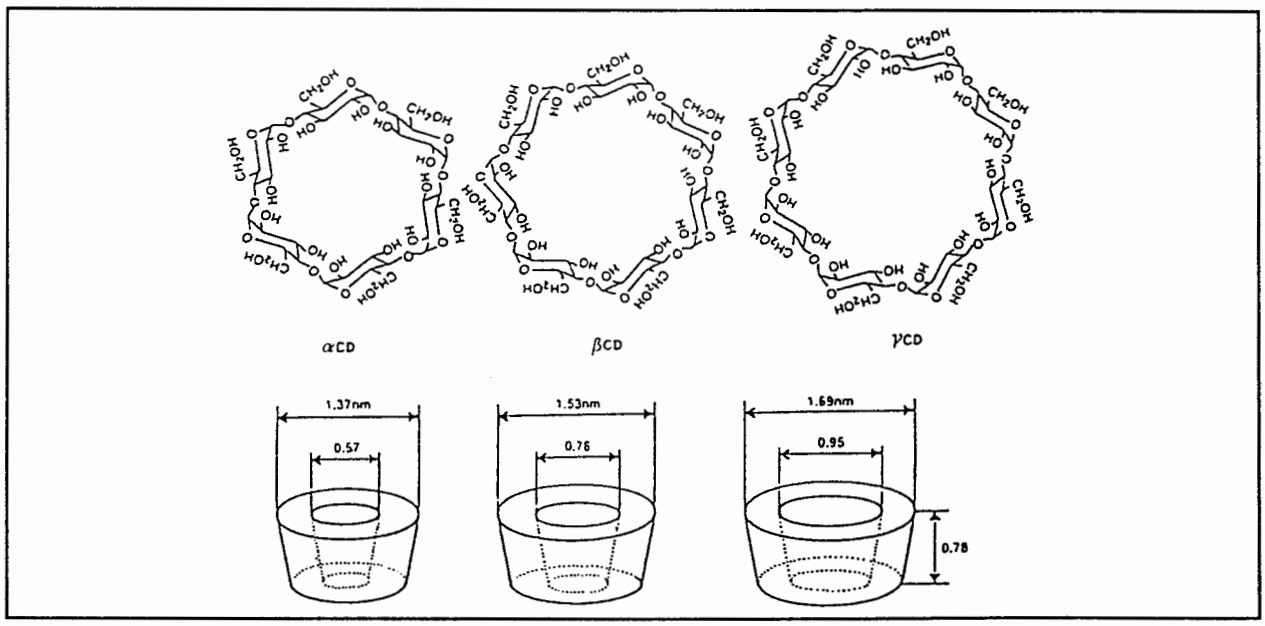

Figure 1. Structure of cyclodextrins and their approximate geometrical dimensions. (Szejtli 1990)

After oral administration, cyclodextrins (CyD) are not absorbed as such, or only to a negligible extent[1]. They are mainly metabolised by the colon's microflora to acyclic dextrins and then to simple dextrins and other compounds, which are then absorbed in the same way as starch found in many foodstuffs (bread, beer, etc.) and finally eliminated as carbon dioxide and water. The basic difference between the metabolism of starch and ß-CyD is that metabolism of the former takes place in the small intestine whereas the cyclodextrins, especially the ß-, and γ-forms, are metabolised in the colon (α-amylase).

Cyclodextrins are able to form inclusion compounds with a large variety of molecules. The interaction between the host cavity and the guest molecule causes a structural perturbation of the guest molecule and consequently a modification of its physical, chemical and biological properties.

ß-cyclodextrin (ß-CyD) is a pure homogeneous crystalline material. Its shape is that of a slightly tapered ring or torus, with a hydrophilic exterior surface and a hydrophobic interior cavity[2] (Figure 2). Small molecules having hydrophobic regions, can enter into the cavity of ß-CyD partially or completely forming an inclusion complex.

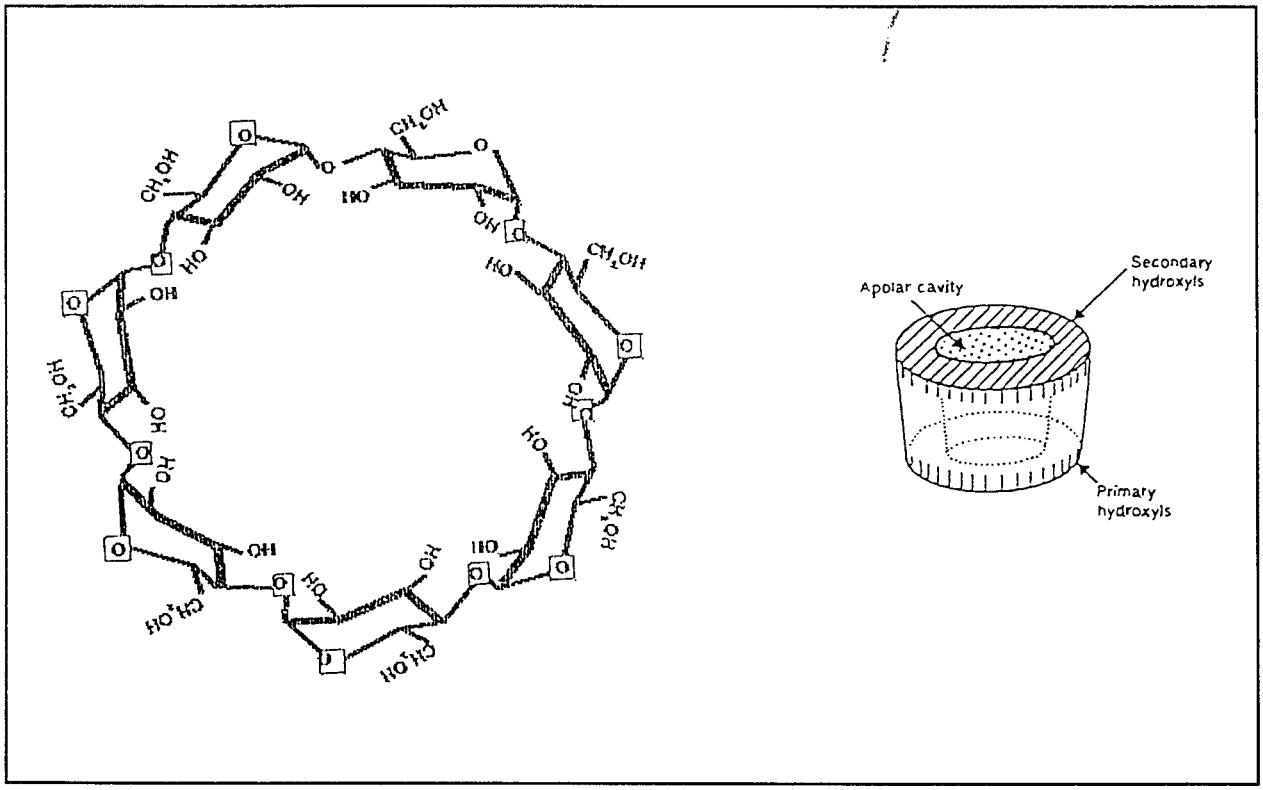

Figure 2. Macrocyclic structure of ß-cyclodextrin. (Szejtli 1990)

Properties of Piroxicam ß-Cyclodextrin

Piroxicam is a non-steroidal anti-inflammatory drug with analgesic and antipyretic activity. It is lipophilic, sparingly soluble in water (30 mg/L at pH 5, 37°C) and has a low surface wettability (water contact angle 76°). The solubility and the wettability of piroxicam are greatly increased when an inclusion complex with ß-cyclodextrin is formed (Table 1). In the solid state, the drug forming the inclusion complex is dispersed, molecule by molecule, into a carbohydrate matrix forming a microcrystalline powder. In solution, the inclusion complex is in kinetic and thermodynamic equilibrium and the equilibrium is shifted towards free components.

Table 1. Physico-chemical characteristics of piroxicam ß-cyclodextrin complex in comparison with plain piroxicam.

	Piroxicam	Complex
Molecular Weight	331.4	3168.912
Molar Ratio (P/CyD)		1 : 2.5
Water Solubility (mg/L; pH=5, 37°C)	~30	~150
Water Contact Angle	76°	~20°
Stability Constant (K_S)		~90 $M^{-1}L$

- 191.2 mg of ß-cyclodextrin-piroxicam are equivalent to 20 mg of piroxicam
- CyD + P —> CyD•P

  Free CyD guest molecule <— inclusion complex

$$Ks = \frac{[CyD \bullet P]}{[CyD][P]}$$

NMR studies show that, in the solid state, the hydrophobic portions of piroxicam are accommodated in the cavity of ß-CyD by non-covalent interactions (Figure 3) and with a stability constant of 113 M^{-1} L at room temperature and 88 M^{-1} L at 37°C. The stability constant, 90 M^{-1} L, estimated from classical solubility studies, agrees closely with that estimated using NMR[3,4].

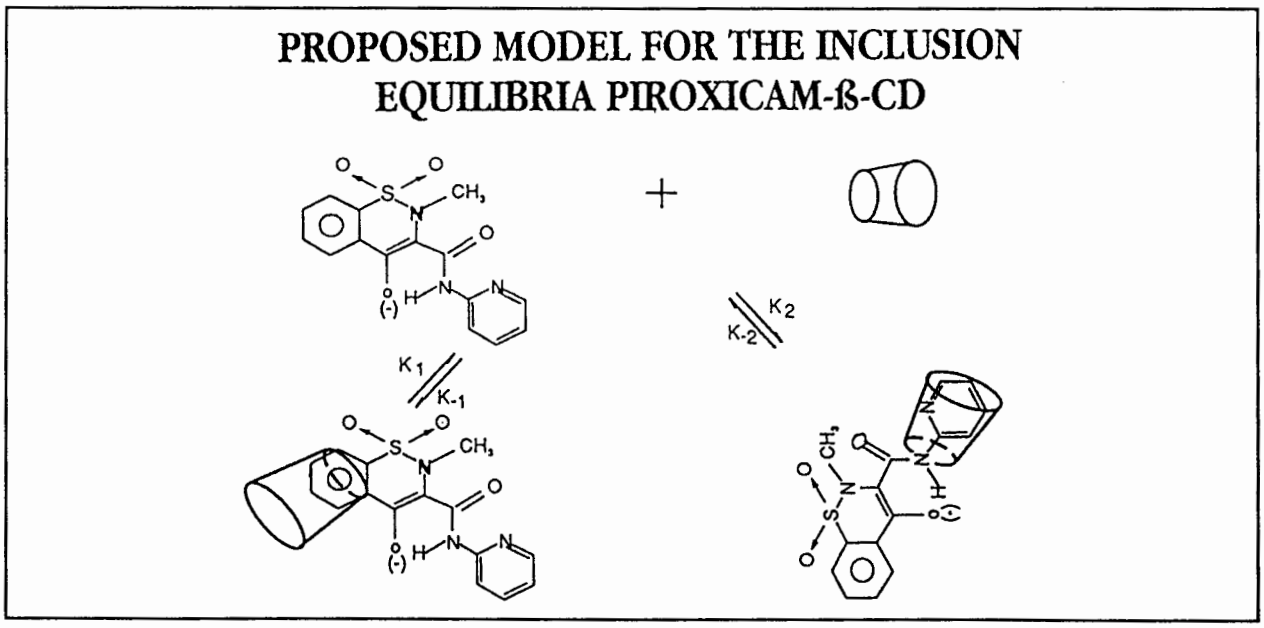

Figure 3. Complex formation between ß-cyclodextrin and hydrophobic groups of piroxicam (solid state). Redenti et al. 1992.

Dissolution of Piroxicam and Piroxicam ß-Cyclodextrin

Oral absorption of piroxicam is relatively slow and variable; maximum plasma concentrations are usually attained about 2 hours after administration, but this may vary from 1 to 6 hours between subjects[5].

Although no absolute bioavailability studies of piroxicam have been undertaken in man, such studies in rats and rabbits indicate nearly complete oral absorption of piroxicam[6]. The dissolution phase of plain piroxicam represents the rate-determining step in the absorption of the active principle.

As the rate of absorption is proportional to the concentration of piroxicam dissolved in the gastrointestinal fluids, the absorption is more rapid when the drug is administered as an inclusion complex.

Figure 4 is a scheme of events occurring following the ingestion of the piroxicam ß-CyD complex. The formation of a ß-CyD complex increases the rate of absorption of piroxicam by increasing the dissolution rate of the drug (K_d) only. ß-CyD piroxicam inclusion complex is not absorbed and ß-CyD is minimally, if at all, absorbed and only at higher than therapeutic doses. As drug in solution penetrates the intestinal epithelium, the complex dissociates further to liberate more drug leaving the ß-CyD behind in the intestinal lumen. The presence of ß-CyD in solution is a significant retarding factor of intestinal absorption only for tightly bound drugs[7], where the stability constant of the inclusion complex well exceeds 1000 M^{-1} L. Accordingly, impairment of absorption by ß-CyD will not be a factor with piroxicam which is only weakly associated with ß-CyD with a stability constant of 90 M^{-1} L.

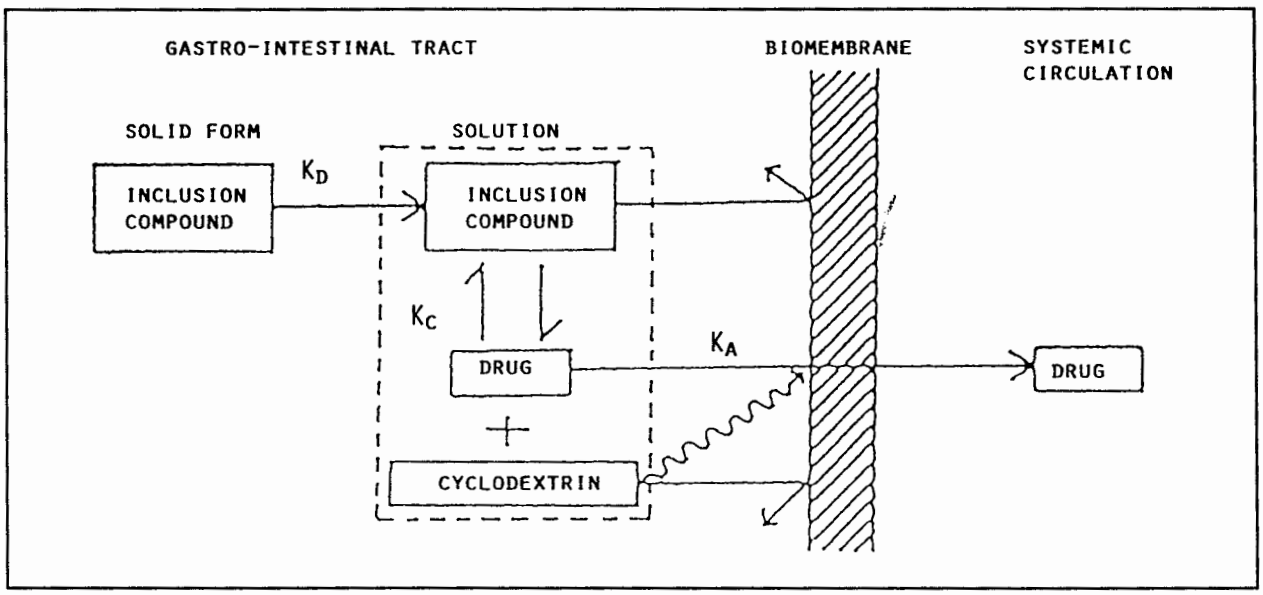

Figure 4. Scheme showing dissolution and absorption of piroxicam from piroxicam ß-cyclodextrin. (K_d = dissolution rate constant; K_c = equilibrium constant for the formation of the inclusion complex; K_a = absorption rate constant).

When piroxicam has passed through the intestinal epithelium it enters the systemic circulation and binds to plasma proteins and an equilibrium is established between free and bound forms (99% bound). From this point onwards, the pharmacokinetic behaviour of piroxicam is the same, whether it is given as such or as an inclusion complex. ß-CyD acts only as a carrier of piroxicam and influences only the absorption kinetics.

Methods and Results

Single dose studies

Plasma levels of piroxicam obtained after administration of the complex show that piroxicam is absorbed more quickly than a reference formulation of piroxicam not complexed with ß-CyD.

These results were obtained in a cross-over, randomised study in 12 healthy volunteers (6 female, 6 male) aged between 24 and 39 years, who received single doses of the two formulations (Feldene^R capsule and Brexin^R tablet, containing the equivalent of 20 mg piroxicam) with a three week washout period between applications.

Blood samples were collected over 120 hours after drug administration and piroxicam in plasma was assayed by HPLC[8,9].

Data reported in Table 2 show that AUC and MRT were similar in the two treatment groups. Other variables such as elimination half-life, clearance and distribution volume showed little variation between the two formulations. Their average values were in agreement with those reported in other studies[10,11].

Table 2. Plasma piroxicam pharmacokinetic parameters in the single dose tablet study (mean ± SEM).

Parameter	Tablet	Reference	p
C_p, 0.25 h (mg/L)	1.4 ± 0.3	0.1 ± 0.03	0.002
C_p, 0.5 h (mg/L)	2.2 ± 0.3	0.8 ± 0.1	0.0004
C_p, 1 h (mg/L)	2.2 ± 0.2	1.6 ± 0.1	0.005
C_{max} (mg/L)	2.6 ± 0.2	2.2 ± 0.1	0.001
t_{max}, median (h)	1	5	0.001
AUC_e (mg•h/L)	161 ± 23	160 ± 20	NS
MRT_e (h)	73.8 ± 8	75.1 ± 7	NS
$t1/2_{el}$ (h)	52.4 ± 5	53.0 ± 5	NS
CL/f (ml/min•kg)	0.035 ± 0.004	0.036 ± 0.004	NS
V_d/f (L/kg)	0.14 ± 0.006	0.15 ± 0.007	NS

Abbreviations: C_p = plasma concentration; C_{max} = maximum plasma concentration; t_{max} = time to maximum concentration; AUC_e = area under the plasma concentration-time curve extrapolated to infinity; MRT_e = mean body residence time extrapolated to infinity; $t1/2_{el}$ = elimination half-life; CL = body clearance; V_d = apparent distribution volume; f= bioavailability; p = statistical significance.

The mean plasma concentrations of piroxicam at 0.25 and 0.5 hours after administration of the piroxicam ß-CyD complex formulation (tablet) were approximately 15 and 3 times greater, respectively, than those after administration of the reference formulation. Peak plasma concentrations of piroxicam were only 5 to 29% higher for the tablet than for the reference formulation, but the median times to peak concentration were 1 hour for the tablet and 5 hours for the reference formulation. Comparison of the first 6 hours of the plasma concentration-time curves (Figure 5a) clearly shows that piroxicam is absorbed more rapidly after administration of piroxicam ß-CyD than the reference formulation. The mean plasma concentration-time curves for the tablet and reference formulations were similar when the absorption phase was complete (t = 6 h).

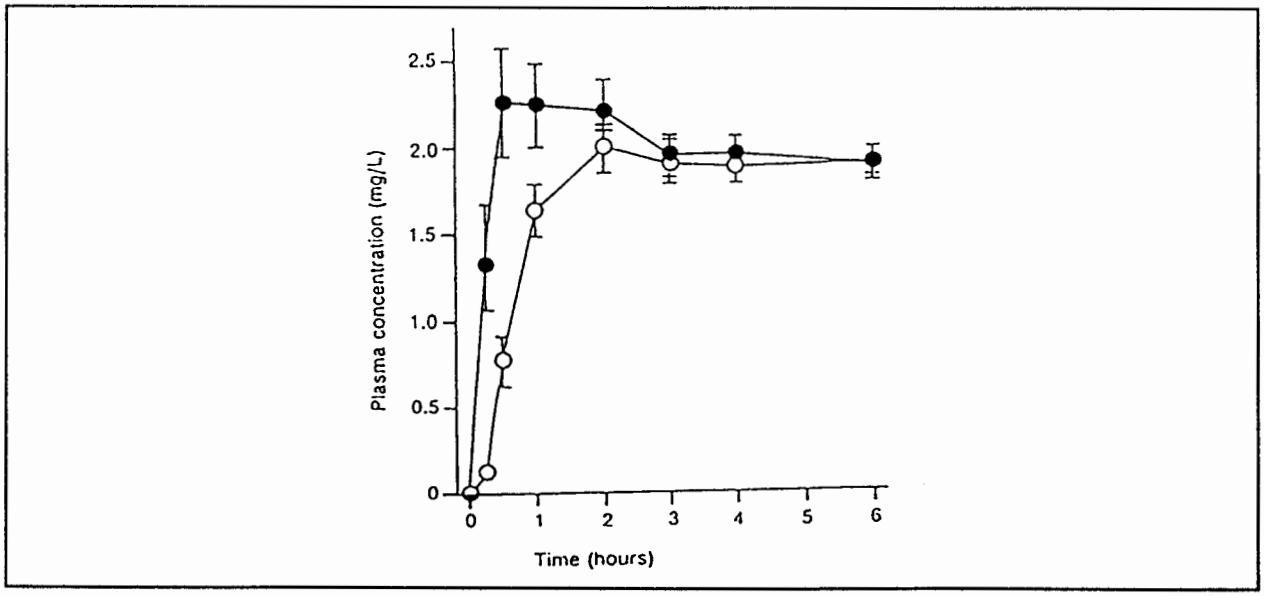

Figure 5a. Mean piroxicam plasma levels up to 6 hours after administration of the reference formulation (open circles) and the piroxicam ß-cyclodextrin tablet (solid dots)

Wagner-Nelson cumulative absorption plots confirmed the significantly higher absorption rate of the tablet formulation (Figure 5b).

Absorption of piroxicam was complete within 0.5 hour in 9 of the 12 subjects receiving the complex compared with no subjects receiving the reference formulation.

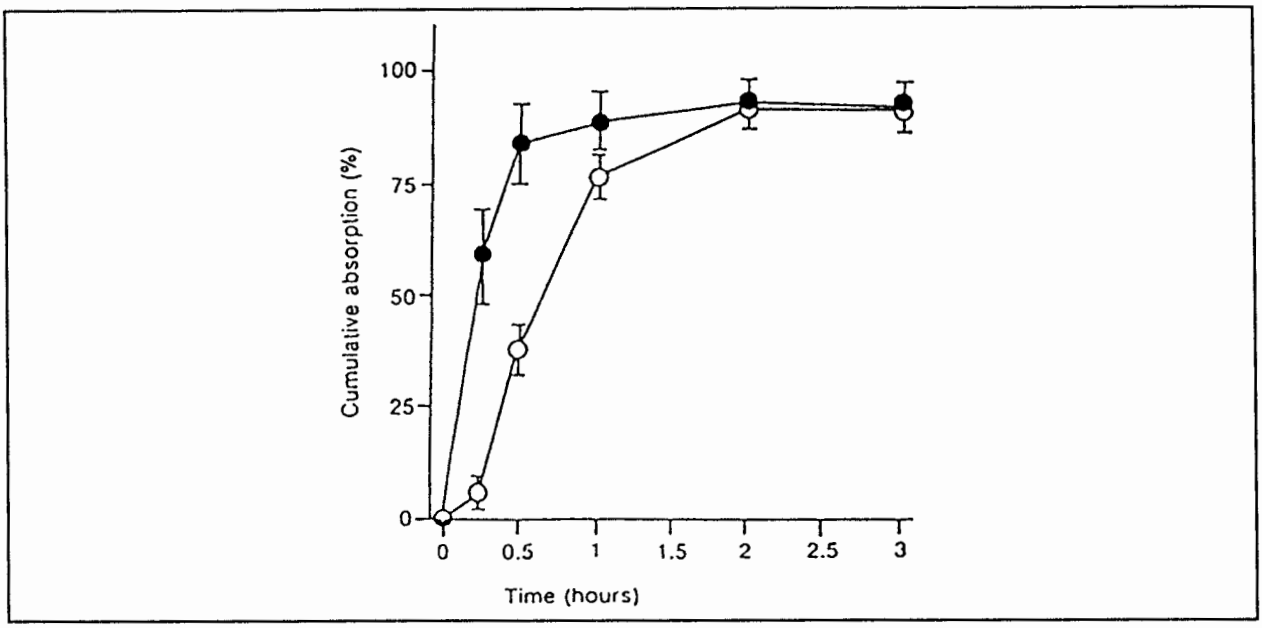

Figure 5b. In vivo cumulative absoprtion calculated in the same subjects (mean ± SEM; n = 12). (Acerbi D et al. 1990)

On average, 84 ± 9% of the dose was absorbed within 30 minutes after administration of the tablets, compared to 38 ± 6% after piroxicam capsules. According to the Westlake and Tukey tests, the tablet of piroxicam ß-CyD complex was bioequivalent to the reference formulation within less than ± 10% when the bioavailability comparison was based on the total amount of piroxicam absorbed over 120 hours.

In a further cross-over study, a sachet formulation containing piroxicam ß-CyD inclusion compound, 20 mg (as piroxicam), was compared to piroxicam capsules (Feldene^R, 20 mg) as a single dose in 12 healthy volunteers (7 female, 5 male) aged between 21 and 40 years[8].

As in the case of the tablet, piroxicam from the sachet formulation was more rapidly absorbed than piroxicam from the reference capsules (Figure 6a). Although the mean peak concentrations of piroxicam were similar (2.92 ± 0.26 mg/L vs 2.86 ± 0.20 mg/L, mean ± SEM, Table 3), these concentrations were achieved within a median time 0.5 hours after the administration of the sachet, compared with 2 hours after piroxicam capsules (p=0.003). The mean plasma concentrations of piroxicam were approximately 3 times greater at 15 minutes, (2.5 vs 0.8 mg/L) and 1.3 times greater at 30 minutes (2.8 vs 2.0 mg/L) after the administration of the sachet compared to piroxicam capsules (p<0.01).

Table 3. Plasma piroxicam pharmacokinetic parameters in the sachet study (mean ± SEM).

Parameter	Sachet	Reference	p
C_p, 0.25 h (mg/L)	2.5 ± 0.4	0.8 ± 0.2	0.002
C_p, 0.5 h (mg/L)	2.8 ± 0.3	2.0 ± 0.3	0.013
C_{max} (mg/L)	2.9 ± 0.3	2.9 ± 0.2	NS
t_{max}, median (h)	0.5	2	0.003
AUC_e (mg•h/L)	191 ± 24	201 ± 26	NS
MRT_e (h)	88 ± 14	89 ± 11	NS
$t1/2_{el}$ (h)	63.4 ± 11	63.2 ± 8	NS
CL/f (ml/min•kg)	0.032 ± 0.004	0.030 ± 0.003	NS
V_d/f (L/kg)	0.14 ± 0.006	0.14 ± 0.007	NS

Abbreviations: C_p = plasma concentration; C_{max} = maximum plasma concentration; t_{max} = time to maximum concentration; AUC_e = area under the plasma concentration-time curve extrapolated to infinity; MRT_e = mean body residence time extrapolated to infinity; $t1/2_{el}$ = elimination half-life; CL = body clearance; V_d = apparent distribution volume; f= bioavailability; p = statistical significance.

Absorption of piroxicam was complete within 15 to 30 minutes after administration of the complex (Figure 6b) compared to 1 to 2 hours after receiving piroxicam capsules. As in the previous study, the extent of absorption from the test and reference formulation was similar and bioequivalence parameters differed by less than 20%.

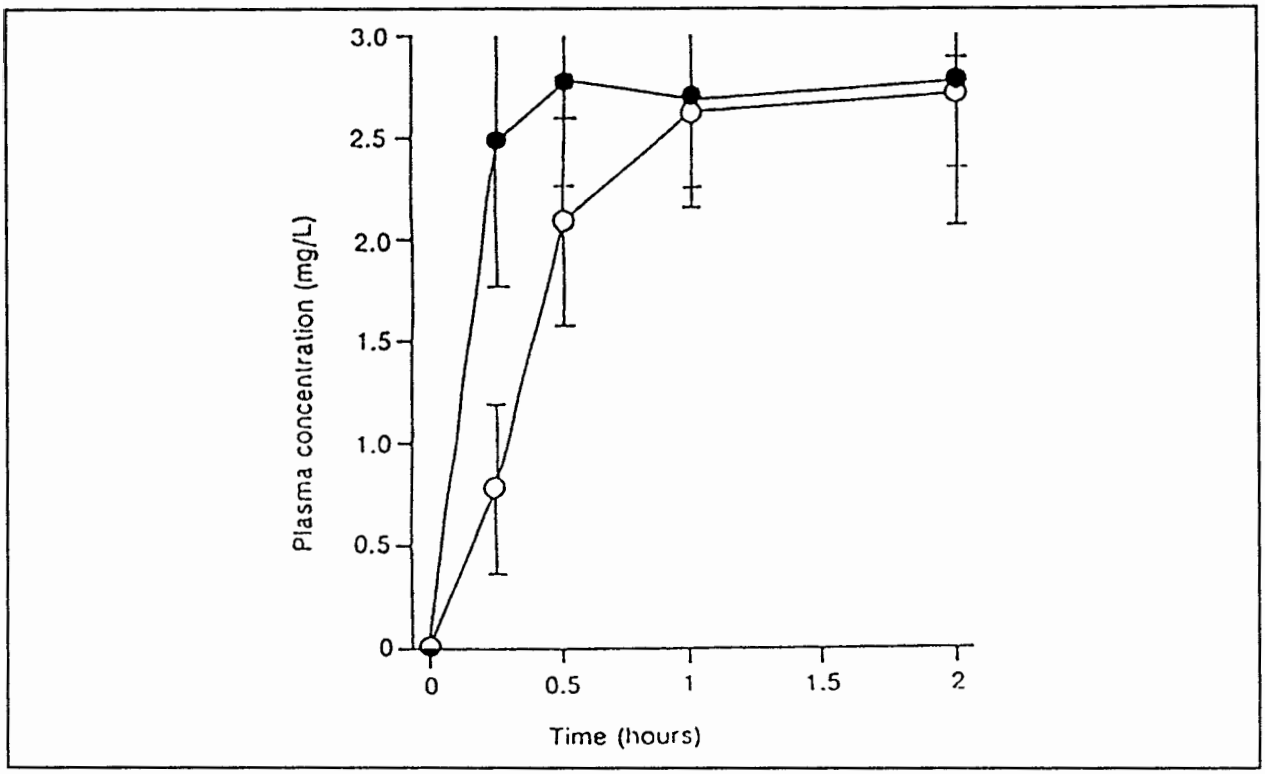

Figure 6a. Mean piroxicam plasma levels up to 2 hours after administration of the reference formulation (open circles) and the piroxicam ß-cyclodextrin sachet (solid dots).

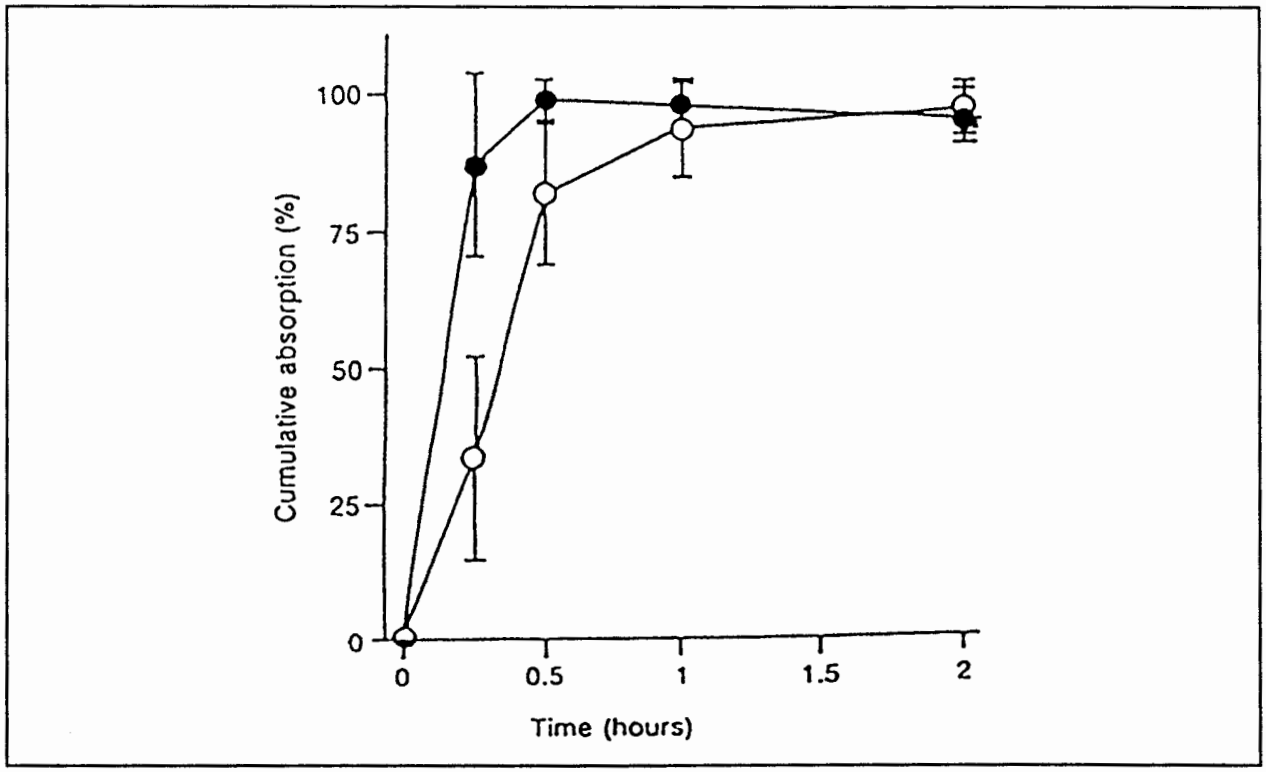

Figure 6b. In vivo cumulative absorption calculated in the same subjects (mean ± SEM; N=12). (Acerbi et al. 1990)

Single dose after food study

The more rapid absorption of piroxicam from piroxicam ß-cyclodextrin tablets and sachets also occurs when these formulations are administered after a meal. In a randomised, cross-over comparison using piroxicam capsules (Feldene^{R}) as reference, single doses of 20 mg were administered to 18 healthy subjects (9 females, 9 males aged 18 - 40 years) after an overnight fast and immediately following a breakfast containing 35 g fat, 18 g protein and 2600 KJoules.

Blood for piroxicam analysis was collected over 120 hours, piroxicam plasma concentrations determined by HPLC and concentration-time data fitted using two exponential functions and a one-compartment model. Statistical comparisons were made using the Wilcoxon matched-pair test with Bonferroni-Holm correction overall 0.05 and values reported here are means ±SD. The concentrations of piroxicam (C_p) over the first 2 hours (Table 4) show that the absorption rate of piroxicam from the piroxicam capsule is linear and slow in contrast to the sachet and the tablet, which show a rapid, almost-log linear absorption phase (Figure 7a and 8a). Although administered as a solution immediately after a meal, absorption from the sachet began almost immediately without a lag-time. A lag-time, with concentrations below or near the limit of detection (50 ng/ml), was observed with piroxicam ß-CyD tablets in about half the subjects, but the lag-time in the case of the piroxicam capsule was more frequent and generally of longer duration.

The lack of a lag-time and faster absorption seen with piroxicam ß-CyD sachet formulations resulted in a marked rise in AUC(0-2 h).

Table 4. Plasma piroxicam pharmacokinetic parameters following drug administration after food (mean ± SD)

Parameter	Tablet (T)	Sachet (S)	Reference Capsule (R)	p (T vs R)	p (S vs R)
C_p, 0.25 h (mg/L)	0.21 ± 0.24	0.59 ± 0.35	0.05 ± 0.07	0.005	<0.001
C_p, 0.5 h (mg/L)	0.44 ± 0.45	0.80 ± 0.30	0.21 ± 0.20	0.049	<0.001
C_p, 0.75 h (mg/L)	0.83 ± 0.64	0.95 ± 0.32	0.38 ± 0.26	0.022	<0.001
C_p, 1 h (mg/L)	1.06 ± 0.61	1.04 ± 0.34	0.52 ± 0.29	0.006	<0.001
C_p, 2 h (mg/L)	1.46 ± 0.42	1.29 ± 0.29	1.03 ± 0.38	0.019	0.043
C_{max} (mg/L)	2.10 ± 0.43	1.96 ± 0.29	1.96 ± 0.28	0.022	NS
t_{max} (h)	4.58 ± 2.06	4.28 ± 1.55	5.72 ± 2.54	NS	0.014
Lag-time (h)	0.36 ± 0.35	0.02 ± 0.06	0.48 ± 0.40	NS	0.001
AUC(0-2h) (mg•h/L)	1.80 ± 0.90	1.89 ± 0.55	1.02 ± 0.41	0.004	<0.001
AUC_e (mg•h/L)	125 ± 34	113 ± 22	121 ± 28	NS	NS
MRT_e (h)	69.0 ± 15.9	65.0 ± 10.0	67.0 ± 13.0	NS	NS
$t1/2_{el}$ (h)	45.2 ± 12.7	40.6 ± 8.5	42.2 ± 14.1	NS	NS

Abbreviations: C_p = plasma concentration; C_{max} = maximum plasma concentration; t_{max} = time to maximum concentration; AUC(0-2h) = area under the plasma concentration-time curve calculated in the interval 0-2h; AUC_e = area under the plasma concentration-time curve extrapolated to infinity; MRT_e = mean body residence time extrapolated to infinity; $t1/2_{el}$ = elimination half-life; p = statistical significance.

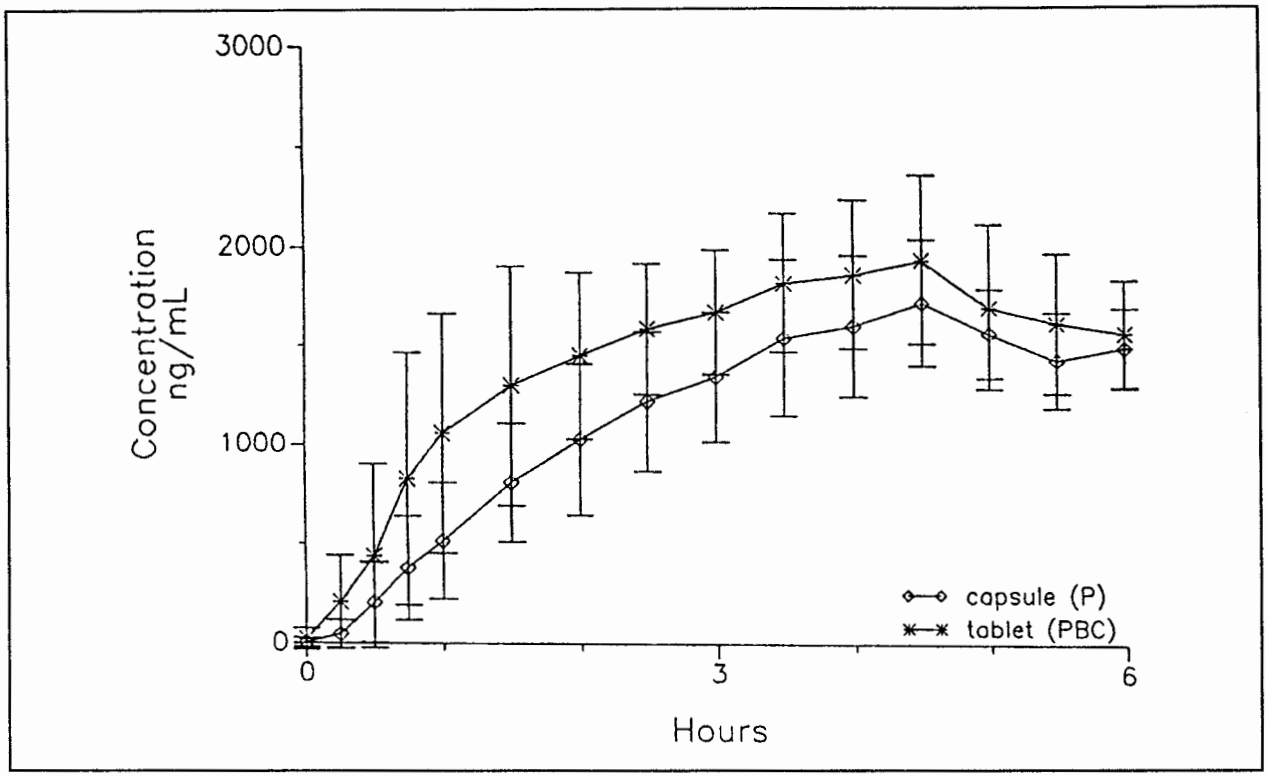

Figure 7a. Mean piroxicam plasma levels following administration of a 20mg capsule and a piroxicam ß-cyclodextrin tablet formulation after food.

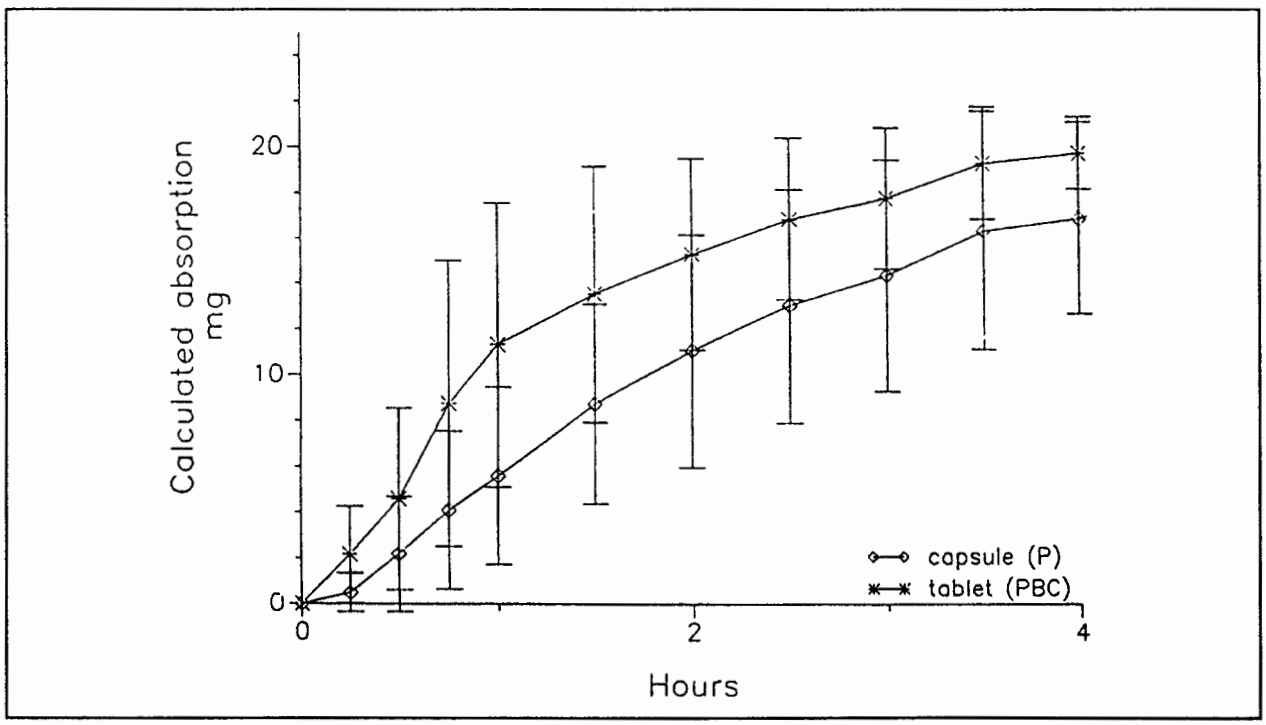

Figure 7b. Calculated piroxicam absorption in the same subjects (mean ± SD; n=18).

The time for absorption to be complete was 4 hours or longer (Figure 7b and 8b). The amount of drug absorbed 30 minutes after the dose averaged 4.6 mg (tablet), 8.3 mg (sachet) and 2.2 mg (capsule). The elimination half-life, C_{max}, t_{max}, AUC_e and MRT_e for the three formulations showed no important differences (Table 4).

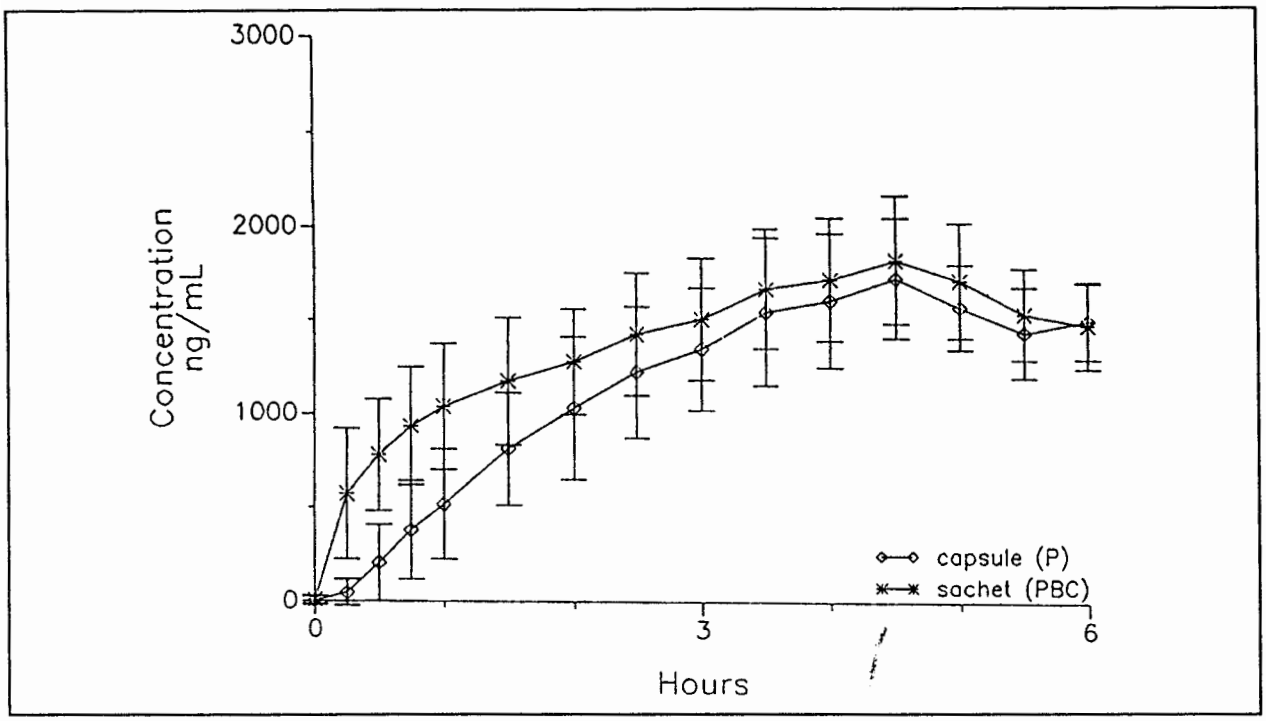

Figure 8a. Mean piroxicam plasma levels following administration of a 20mg capsule and a piroxicam ß-cyclodextrin sachet formulation after food.

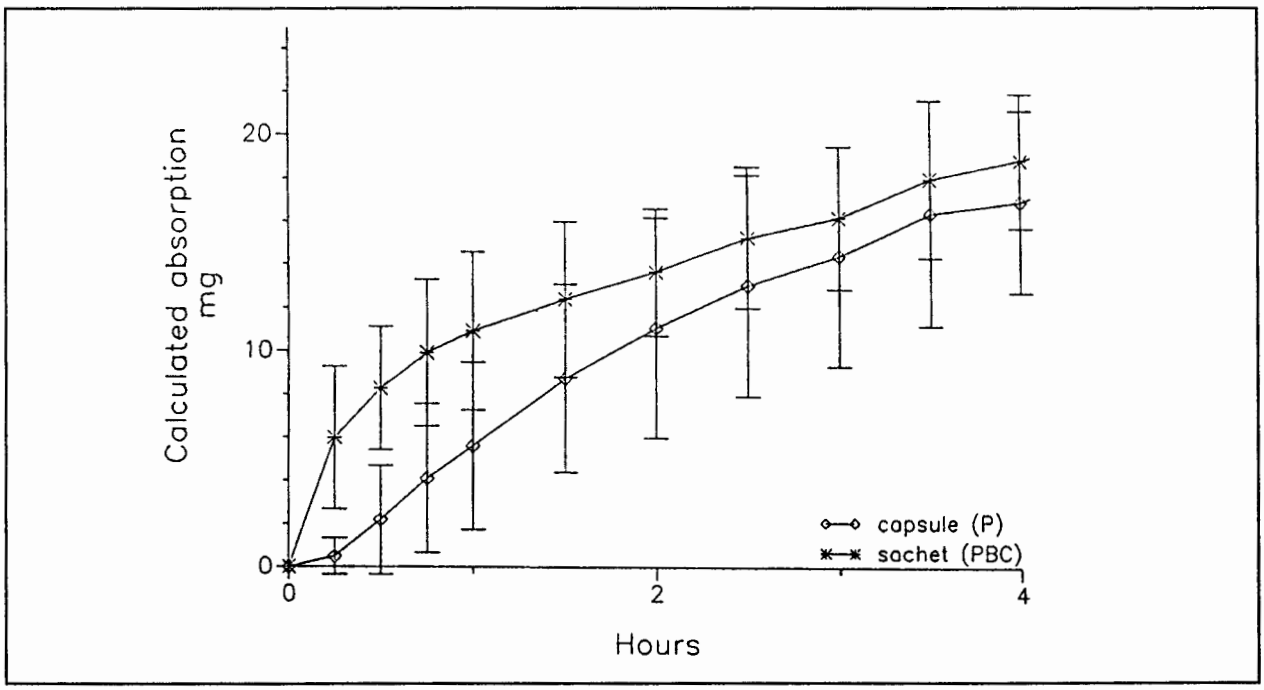

Figure 8b. Calculated piroxicam absorption in the same subjects (mean ± SD; n=18).

Repeated administration study

In a study of a single-dose followed by repeated dose administration, 12 healthy volunteers (7 female, 5 male), aged between 26 and 40 years, were given piroxicam ß-CyD complex (tablet) and reference piroxicam (Feldene^{R} capsule) at equivalent dosage (20 mg as piroxicam) in a randomised, cross-over design[12]. The subjects received the drug as a single dose, followed by a seven day wash-out period, and then the same drug was administered once daily, for 14 days. The alternative drug was administered to the subjects under the same conditions following a three week wash-out period (Figure 9).

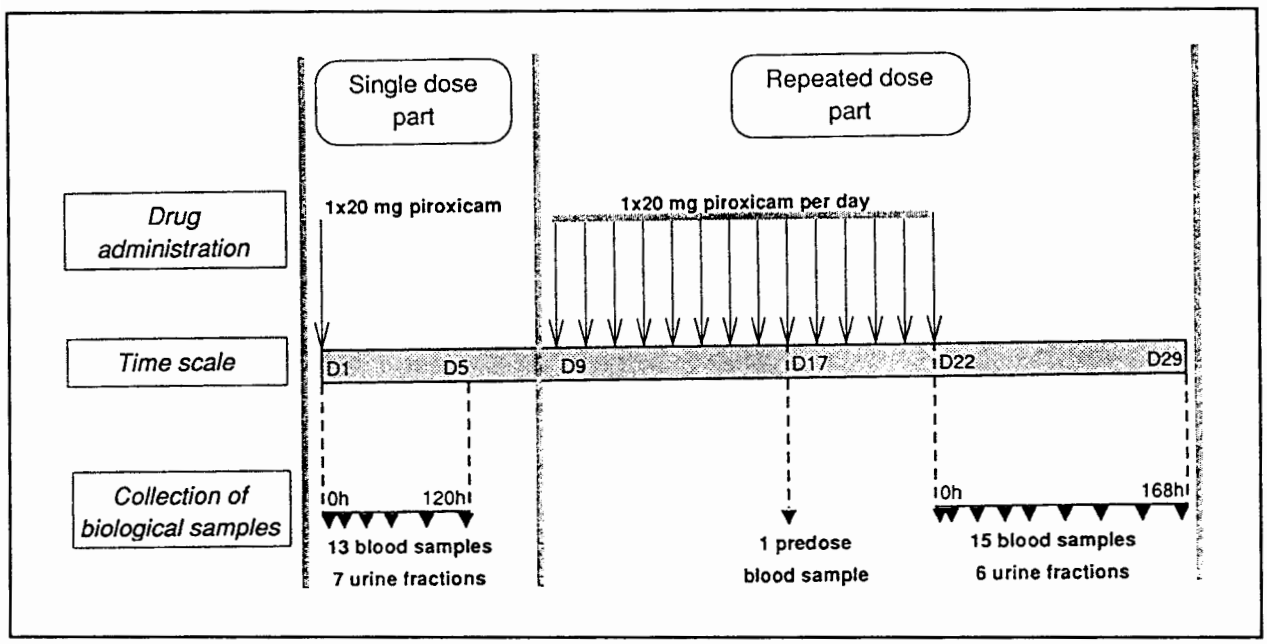

Figure 9. Schematic representation of the design of each session of the study, including single dose and multiple dose parts. Time scale is in days. Thin arrows symbolise administration of 20 mg piroxicam. Dashed line-solid head arrows indicate the collections of biological samples. (Stockis A et al. 1991)

Piroxicam and its metabolite, 5'-hydroxy-piroxicam, were measured in blood up to 120 hours after the first dose and up to 168 hours after the last dose of each formulation. 5'-hydroxy-piroxicam was measured in urine up to 120 hours after the first and the last doses.

In the single dose application, the mean plasma concentration-time curves corresponding to the two formulations were virtually superimposable after completion of the absorption phase (Figure 10). The first 0-4 hour portion of the plasma curves indicated that piroxicam was more rapidly absorbed from the complex than plain piroxicam.

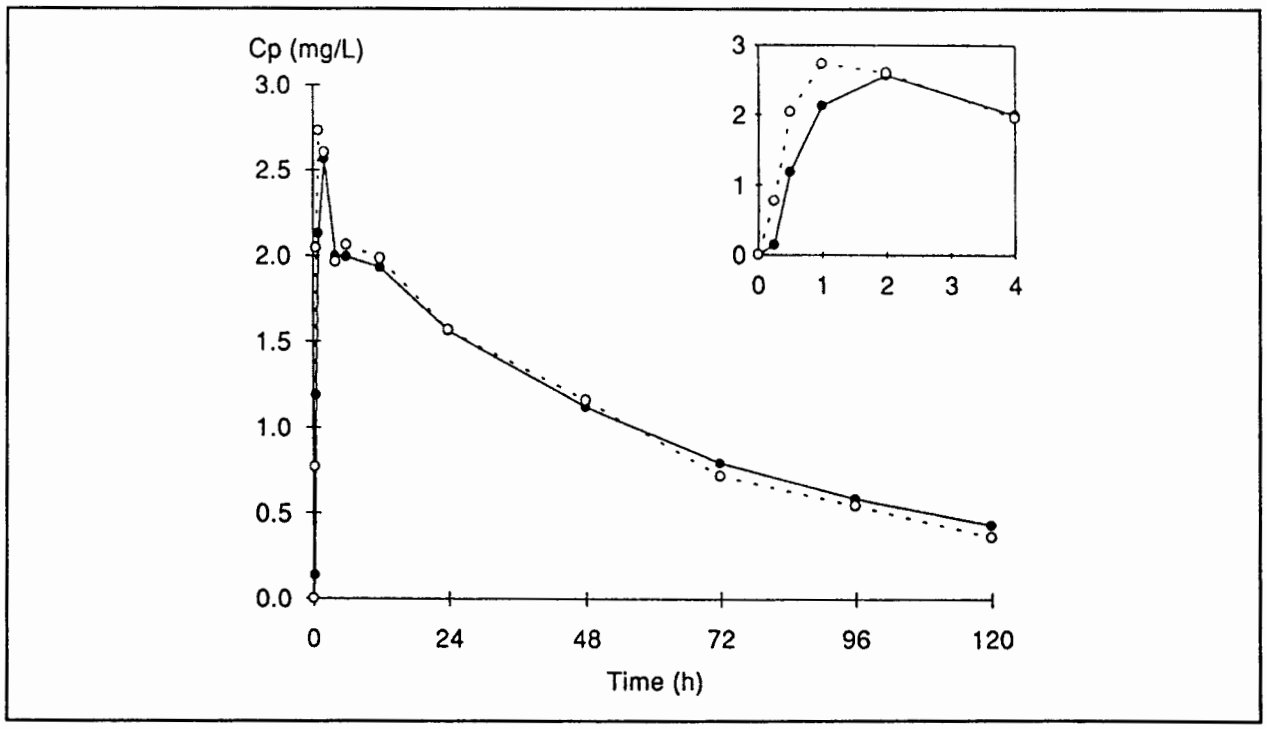

Figure 10. Piroxicam plasma concentration after single 20 mg dose administration in healthy subjects, as one PBC tablet (open circles) and as one plain piroxicam capsule (solid dots). Inset: enlargement of the 0-4 h time period. Values are means (n=12).

The peak plasma level was reached within 1 hour (median), compared to 2 hours with the reference formulation. The average plasma levels observed at 0.25 h and 0.5 h post dose were significantly higher with piroxicam ß-CyD, by a factor of 5 and 2, respectively (Table 5). The absorption rate constant for the complex was significantly higher (+83%). C_{max}, AUC_t, AUC_e, MRT_e and K_{el} did not differ by more than about 10 percent. The Westlake 95% confidence intervals for bioequivalence were ± 7% and ± 16% for piroxicam AUC_t and AUC_e, and ± 19% based on the 0-120 h urinary excretion of 5'-hydroxy-piroxicam (X_u), the main metabolite of piroxicam.

Table 5. Pharmacokinetic parameters of plasma piroxicam and urinary excretion of 5'-hydroxy-piroxicam after single 20 mg dose administration in 12 healthy subjects (mean ± SEM).

Parameter	Plain Piroxicam Capsule	PBC Tablet	p	Westlake 95% Conf. Interval
C_p, 0.25 h (mg/L)	0.14 ± 0.04	0.77 ± 0.17	<0.01	-
C_p, 0.5 h (mg/L)	1.2 ± 0.2	2.0 ± 0.3	<0.01	-
C_p, 1 h (mg/L)	2.1 ± 0.2	2.7 ± 0.3	NS	-
C_{max} (mg/L)	2.6 ± 0.2	2.9 ± 0.3	NS	±25%
t_{max} median (range) (h)	2 (1-6)	1 (0.5-6)	NS	-
AUC_t (mg•h/L)	129 ± 11	128 ± 10	NS	±7%
AUC_e (mg•h/L)	163 ± 19	153 ± 12	NS	±16%
MRT_e (h)	71 ± 6	65 ± 4	NS	±18%
K_{el} (1/h)	0.015 ± 0.003	0.016 ± 0.003	NS	±15%
K_a (1/h)	2.3 ± 0.3	4.3 ± 0.8	<0.05	-
X_u (120h) (mg)	2.8 ± 0.2	2.9 ± 0.3	NS	±19%

Abbreviations: C_p = plasma concentration; C_{max} = maximum plasma concentration; t_{max} = time to maximum concentration; AUC_t = area under the plasma concentration-time curve to last measured point; AUC_e = area under the plasma concentration-time curve extrapolated to infinity; MRT_e = mean body residence time extrapolated to infinity; K_{el} = elimination rate constant; K_a = absorption rate constant; X_u = urinary excretion; p = statistical significance.

5'-hydroxy-piroxicam was undetectable (<100 ng/ml) in all the plasma samples. Piroxicam was undetectable in all the urine samples (<100 ng/ml). The average cumulative urinary excretion of 5'-hydroxy-piroxicam (free + conjugated) was similar for both formulations (Figure 11). The total fraction of the dose eliminated over 5 days amounted to about 14% of the administered dose with both formulations.

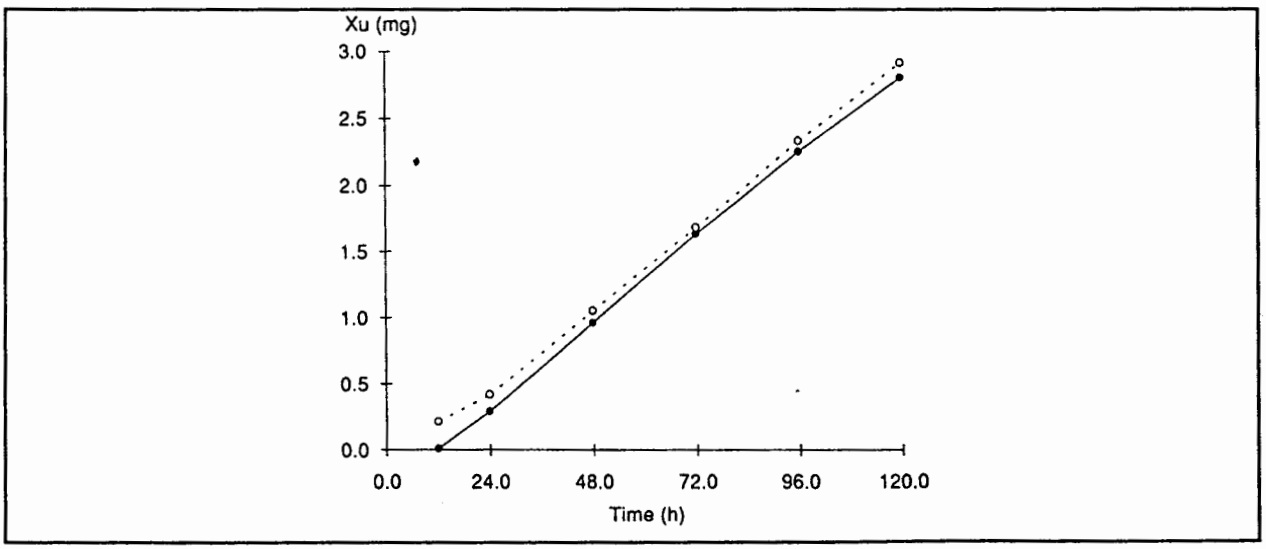

Figure 11. Cumulative excretion of 5'-hydroxy-piroxicam in urine (X_u), after single 20 mg dose administration in healthy subjects, as one PBC tablet (open circles) and as one plain piroxicam capsule (solid dots). Values are means (n=12).

Repeated dosing of the two formulations yielded similar piroxicam plasma concentration-time curves (Figure 12). Absorption was readily observable as early as 0.25 h post-dose with piroxicam ß-CyD, but not before 0.5 h with plain piroxicam capsules, and the difference between plasma concentrations at 0.25 h was statistically significant.

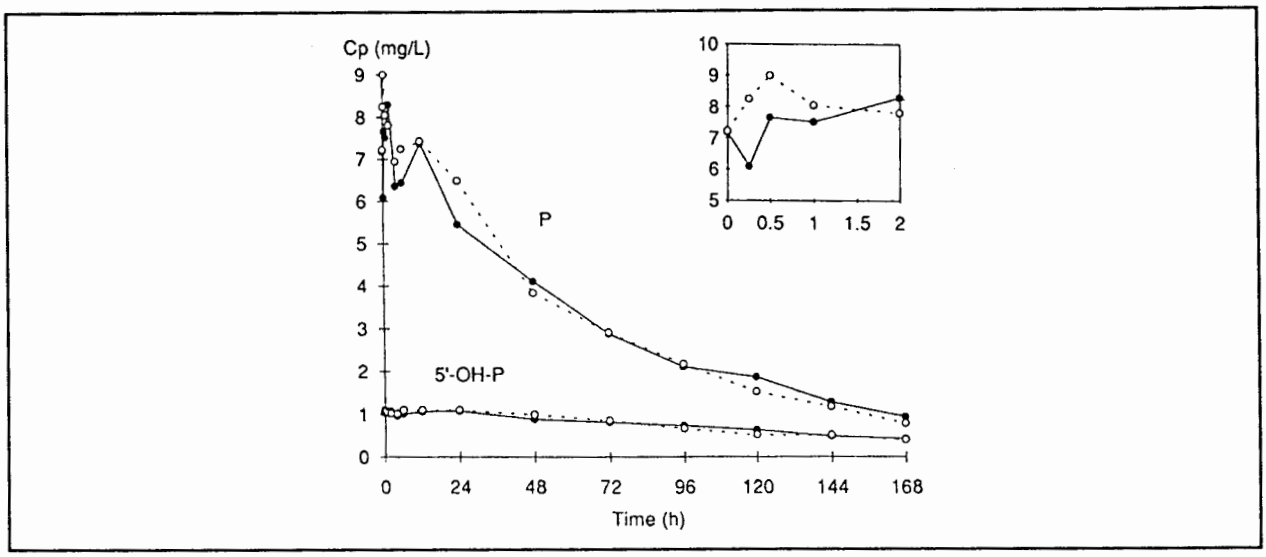

Figure 12. Piroxicam (P) and 5'-hydroxy-piroxicam (5'-OH-P) plasma concentrations after 14 days of repeated administration as PBC tablet (open circles) and as plain piroxicam capsule (solid dots), at a dose of 20 mg daily, in healthy subjects. Inset: enlargement of the 0-2 h time period for piroxicam. Values are means (n=12).

Plasma concentration of 5'-hydroxy-piroxicam reached about 1 mg/L, and showed similar patterns for the two preparations (Figure 12). The formulations differed by only 5% and 7% regarding C_{max} and AUC(0-24 h) respectively (Table 6). The Westlake 95% confidence intervals for bioequivalence were ± 25% for piroxicam AUC(0-24) and ± 17% for 5'-hydroxy-piroxicam urinary excretion. The cumulative urinary excretion of 5'-hydroxy-piroxicam was similar for both forms and the amounts of drug eliminated over 5 days were nearly identical (Table 6).

Table 6. Pharmacokinetic parameters of plasma piroxicam and urinary excretion of 5'-hydroxy-piroxicam after 14 days of repeated, 20 mg once-daily administration in 12 healthy subjects (mean ± SEM).

Parameter	Plain Piroxicam Capsule	PBC Tablet	p	Westlake 95% Conf. Interval
C_p 0 h (mg/L)	7.2 ± 1.1	7.2 ± 0.8	NS	-
C_p 0.25 h (mg/L)	6.1 ± 0.9	8.2 ± 0.8	<0.05	-
C_p 0.5 h (mg/L)	7.7 ± 1.1	9.0 ± 0.8	NS	-
C_{max} (mg/L)	9.2 ± 1.1	9.7 ± 0.8	NS	±22%
t_{max} median (range) (h)	2 (0.5-4)	0.5 (0.25-12)	NS	-
AUC (0-24h) (mg•h/L)	161 ± 20	172 ± 17	NS	±25%
AUC_t (mg•h/L)	531 ± 81	537 ± 57	NS	±25%
AUC_e (mg•h/L)	615 ± 1077	600 ± 66	NS	±29%
MRT_e (h)	76 ± 6	70 ± 4	NS	±20%
K_{el} (1/h)	0.015 ± 0.001	0.015 ± 0.001	NS	±16%
X_u (120h) (mg)	19.3 ± 1.1	20.4 ± 1.5	NS	±17%

Abbreviations: C_p = plasma concentration; C_{max} = maximum plasma concentration; t_{max1} = time to maximum concentration; AUC_t = area under the plasma concentration-time curve to last measured point; AUC_e = area under the plasma concentration-time curve extrapolated to infinity; MRT_e = mean body residence time extrapolated to infinity; K_{el} = elimination rate constant; X_u = urinary excretion; p = statistical significance.

The apparent elimination rate constants recorded after single dose and after 2-week repeated dosing were identical. Piroxicam plasma levels after repeated administration were simulated using the model parameters derived from the single dose data (one-compartment model) (Figures 13a and 13b). The experimental data for both formulations after the last dose of the repeated dosing regimen, as well as the trough concentration on Day 17, were in excellent agreement with the predicted curves.

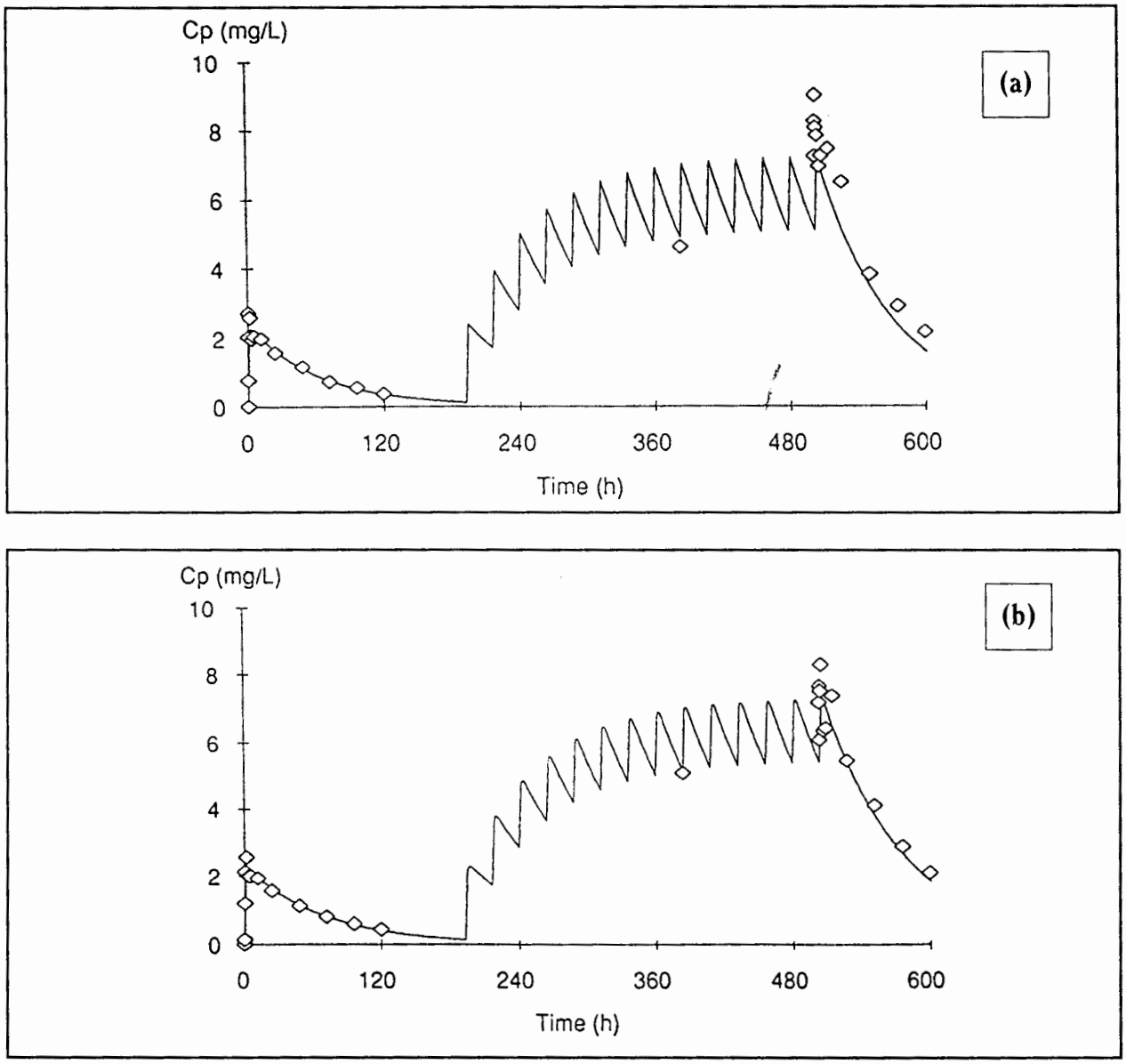

Figure 13. Simulated and observed (diamonds) piroxicam plasma levels after single and multiple, once-daily administration of 20 mg piroxicam as PBC tablet (a) and as plain piroxicam capsule (b). Simulation was performed by fitting a one-compartment model to the single dose data and then extrapolating according to a multiple dose regimen.

Discussion and Conclusions

The kinetic studies show that there are no differences in bioavailability or disposition of piroxicam administered as piroxicam ß-cyclodextrin and plain piroxicam capsules but that piroxicam enters the blood significantly more rapidly after piroxicam ß-cyclodextrin and remains in the stomach and upper gastrointestinal (GI)-tract for shorter periods than after plain piroxicam.

Detailed studies on the precise absorption site of piroxicam and piroxicam ß-cyclodextrin in the stomach and upper GI-tract, and the effects of differences in pH and gastric emptying, have not been carried out. Piroxicam, being a weak acid, will be absorbed in the upper GI-tract and the appearance

of high concentrations in blood within 15 min after oral application supports this assumption. Piroxicam absorption probably takes place mainly in the duodenum and upper small intestine and would therefore be dependent on gastric emptying. The time for complete gastric emptying after a medium-heavy breakfast is about 3 hours[13]. The Wagner-Nelson plot in the study on the effect of food on piroxicam absorption, showing more than 75% absorption after 3 hours, agrees with this finding.

The more rapid absorption of piroxicam in the case of the sachet, and the absence of a lag-time in absorption, is presumably because the drug is administered as a solution and therefore in an optimal form for passage into the duodenum. The tablet and capsule formulations must undergo wetting and dissolution in the stomach, processes which may occur with or without a lag-time.

Following administration of 20 mg piroxicam ß-cyclodextrin tablets to healthy subjects in the fasting state and after a meal, approximately 50% of the dose is absorbed within 15 min and 55 min respectively and similar values have been obtained using the sachet formulation.

In contrast, after administration of plain piroxicam, the corresponding fraction absorbed at these times is only 5% in the fasting state and 20% after food. This means that during the early post-dose period (0-1 h) the lumen of the stomach and upper GI-tract contain considerably more unabsorbed piroxicam when administered as plain piroxicam than when administered as piroxicam ß-cyclodextrin. This difference in absorption is associated with two important clinical advantages:

a. Reduced gastrointestinal adverse reactions

In three double-blind studies in healthy volunteers, the gastrointestinal tolerability of piroxicam ß-cyclodextrin was compared to that of piroxicam and placebo using the ^{51}Cr-labelled red-cell technique and endoscopic appearance of the GI mucosa. The three studies showed comparable results. Piroxicam ß-cyclodextrin caused less faecal blood loss than piroxicam, this effect being most evident towards the end of the one-month study period.

b. More rapid attainment of therapeutic plasma levels and therapeutic effect

In general there is no close relationship between the concentration of NSAIDs and therapeutic effect because analgesia is difficult to quantify, pain can vary markedly in severity and the perception of pain is influenced by the psychological state. In addition, analgesia may only occur after passage of drug into a slowly-equilibrating body compartment such as synovial fluid. Despite these variables there is evidence for a useful concentration-effect relationship under controlled conditions and a more rapid attainment of therapeutic effect after piroxicam ß-cyclodextrin can be demonstrated using the piroxicam concentration-effect relationship involving measurements of pain.

The minimal effective concentration of potent analgesic drugs such as piroxicam, indomethacin and diclofenac is about 1 µg/ml[14,15] and these findings are in agreement with Siegmeth[16], who observed a steep fall in the duration of morning stiffness and pain scores (>30%) in patients with chronic polyarthritis on the first day of treatment, when piroxicam concentrations, expressed as a mean for the group, were approximately 2 µg/ml. After discontinuation of piroxicam treatment the symptoms began to worsen when the levels fell below 2 µg/ml.

Piroxicam administered intramuscularly and oral piroxicam capsules were compared with respect to rapidity of action on pain from lumbalgia, ischialgia and scapulo-humeral periarthritis[17]. There was a significant reduction in pain intensity with intramuscular piroxicam after 15 min and 30 min whereas oral plain piroxicam did not produce significant pain relief suggesting lower plasma concentrations at these times compared to its i.m. formulation. Support for this view comes from a similar study in which plasma concentrations after oral administration of 20 mg plain piroxicam remained lower than those following the same dose given intramuscularly for up to about 2 hours post-dose. The concentration at 20 minutes post-dose for the capsule was 0.3 mg/L compared to 0.7 mg/L after intramuscular administration[18].

In a similar study from Michelacci et al[19], carried out in 24 patients with post-surgical pain, the analgesic effect of 20 mg piroxicam-ß-cyclodextrin (sachet formulation) was compared with that of 20

mg piroxicam administered by intramuscular injection. Piroxicam plasma concentrations within 1 hour from administration were between 0.5 and 1.5 mg/L for both oral piroxicam-ß-cyclodextrin and i.m. piroxicam. In accord with these findings, responses were already measurable 30 min post-dose in the case of both formulations and there was no difference in the intensity of analgesic effect measured using patients own assessment or assessment by the clinician.

In conclusion, piroxicam ß-cyclodextrin differs pharmacokinetically from plain piroxicam only in having a more rapid absorption. The resulting higher plasma concentrations in the early post-dose period and reduced contact-time in the lumen of the GI-tract are apparently associated with the lower gastrointestinal bleeding and more rapid onset of the therapeutic effect seen in patients. When piroxicam ß-cyclodextrin is used as an analgesic, the best results in terms of rapidity of action are achieved with the sachet formulation in the fasting state, with effects comparable to those of piroxicam given intramuscularly. The onset of action may be delayed when the drug is given after a heavy meal but less so than would be the case with conventional formulations of piroxicam.

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