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Disposition of ibuprofen enantiomers following the oral administration of a novel controlled release formulation to healthy volunteers

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Summary

The enantiomeric composition of ibuprofen in plasma has been investigated following the oral administration of the racemic drug in a novel controlled release (CR) formulation to healthy subjects. The plasma concentration-time profiles suggest that drug release from the CR preparation was suitably modified and that the fluctuation between the peaks and troughs observed following a conventional tablet formulation were reduced. The plasma concentrations of (*S*)-ibuprofen were greater than those of the (*R*)-enantiomer following either formulation, and the enantiomeric plasma ratio (*S*/*R*) was reduced, both in magnitude and variability, following the CR preparation. The proportion of the total area under the plasma concentration-time curves, due to (*S*)-ibuprofen were slightly reduced following the CR formulation compared to the tablet formulation. The importance of a consideration of stereochemistry in bioequivalence studies of chiral drugs is discussed.

Introduction

There is presently considerable interest in the pharmacodynamic and pharmacokinetic properties of the enantiomers of chiral drug molecules (Ariens, 1984; Williams and Lee, 1985; Drayer, 1986; Evans et al., 1988; Ariens et al., 1988; Caldwell et al., 1988b). Of particular importance are the stereochemical properties of the 2-arylpropionic acid non-steroidal anti-inflammatory drugs (NSAIDs), the 'profens'. These agents possess a chiral centre α to the carboxyl group and their pharmacological activity resides mainly in the enantiomers of the (*S*)-absolute configuration, the (*R*)-enantiomers being either inactive or weakly active in vitro (Adams et al., 1976; Hutt and Caldwell, 1984). These differences in activity are often obscured in vivo due to the metabolic chiral inversion of the inactive (*R*)-enantiomers to their active (*S*)-antipodes in both animals and man (for review see Hutt and Caldwell, 1983). The

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effect of chiral inversion, together with other stereoselective metabolic transformations, generally results in the more rapid plasma elimination of the (*R*)-enantiomer than that of its (*S*)-antipode following administration of the racemic drug (Caldwell et al, 1988a). As the majority of these agents are used as racemic mixtures the determination of the enantiomeric composition of the drugs in biological fluids is of considerable importance, particularly in studies which attempt to relate therapeutic response to drug plasma concentrations.

Ibuprofen ((*R*,*S*)-2-(4-isobutylphenyl)propionic acid) is an important NSAID used for the treatment of a variety of inflammatory conditions and was the first of the profens to be shown to undergo metabolic chiral inversion (Wechter et al., 1974). As a result of this initial observation ibuprofen is, in terms of the stereochemical aspects of its disposition, the most extensively studied compound of this group (Wechter et al., 1974; Van Giessen and Kaiser, 1975; Kaiser et al., 1976; Cox et al., 1985, 1988; Lee et al., 1985; Williams et al., 1986; Jamali et al., 1988; Baillie et al., 1989). As a result of stereoselective processes involved in the metabolism and excretion of ibuprofen, the inactive (*R*)-enantiomer has been found to be eliminated from plasma more rapidly than the active (*S*)-isomer following administration of the racemic drug (Van Giessen and Kaiser, 1975; Lee et al., 1985). However, recently Jamali et al. (1988) have reported similar plasma elimination half-lives for both enantiomers following the administration of commercially available film and sugar coated tablets of the racemic drug.

In common with many related carboxylic acid NSAIDs, racemic ibuprofen has a short biological half-life (Collier et al., 1978; Stead et al., 1983) necessitating the frequent administration of conventional dosage forms to maintain therapeutic effectiveness. An additional problem associated with NSAIDs of short biological half-life is that they do not protect patients against morning joint stiffness which is common in rheumatoid disease states. Thus the development of a controlled release formulation of ibuprofen may offer a number of advantages in the therapeutic situation. In view of the stereochemical complexities of ibuprofen disposition it was of interest to examine the enantiomeric composition of the drug in plasma following the administration of a novel controlled release formulation of the racemic drug to healthy volunteers.

Materials and Methods

Dosage forms

The controlled release formulation (CR) consisted of a multidose pellet formulation, comprising an inert core surrounded by racemic ibuprofen, with an outer release rate controlling permeable membrane designed to release the drug over a 12 h period. 20% of the stated drug content was coated onto the outer layer of the membrane and was therefore available for rapid dissolution and hence absorption. The mean weight of each pellet was about 1 mg, the drug comprising approx. 75% w/w of the pellets, which were administered in hard gelatin capsules equivalent to 300 mg of racemic ibuprofen.

The tablet formulation consisted of conventional 200 mg ibuprofen tablets which conformed to the BP requirements for such tablets.

Volunteer study

Four informed volunteers (2 male, 2 female; aged 24–37 years) designated healthy by a pre-study medical examination, including biochemical and haematological tests, participated in the investigation, which had received ethical approval. The subjects refrained from other medication for 1 week prior to the study and from alcohol and caffeine containing beverages for 24 h preceding, and for the duration of the study. On the morning of the study each subject consumed a light breakfast consisting of fruit juice and toast. The subjects were assigned in a randomised manner to one of two treatment groups and received either the tablet formulation (ibuprofen 200 mg) at experimental time zero, 6 and 12 h or the controlled release pellet formulation (as a capsule equivalent to 300 mg ibuprofen) at time zero and 12 h. After a one week washout period the treatments were repeated with the alternative formulations being administered. Blood samples (10 ml), obtained by venepuncture, were collected into heparinised

tubes and the plasma separated by centrifugation and stored at −20 °C until analysed. Samples were obtained immediately prior to drug administration and at 1, 2, 3, 4, 6, 7, 8, 9, 10, 12, 13, 14, 16, 24, 28 and 32 h post initial drug administration.

Analytical methods

High-performance liquid chromatography (HPLC) was carried out using a Perkin-Elmer Series 10 liquid chromatograph equipped with an LC-75 detector, set at 254 nm, and an R-100 chart recorder (Perkin-Elmer). The column was Hypersil (250 × 4.5 mm, 10 μm); mobile phase hexane-ethyl acetate (4 : 1 v/v) flow rate 3.2 ml min^{-1}. Samples were introduced into the system via a Rheodyne injector fitted with a 20 μl loop. In this system the (*S*)-1-(naphthen-1-yl)ethylamides of (*R*)- and (*S*)-ibuprofen and *p*-chlorophenoxyacetic acid (internal standard) had retention times of 1.6, 2.5 and 4.9 min, respectively.

Sample preparation

To heparinised plasma (0.5 ml) was added 100 μl of *p*-chlorophenoxyacetic acid (60 μg ml^{-1}), internal standard, and hydrochloric acid (0.2 ml, 1.2 M) and the whole extracted with benzene (5 ml). The samples were mixed using a vortex mixer (5 min) and the phases separated by centrifugation, the organic phase was removed and evaporated to dryness and the residue taken up in dichloromethane (1.0 ml) and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, (*S*)-1-(naphthen-1-yl)ethylamine and 1-hydroxybenzotriazole (100 μg of each as 100 μl of 1 mg ml^{-1} solutions in dichloromethane) as previously described (Hutt et al., 1986). After 2 h at room temperature the solvent was evaporated and the residue taken up in the HPLC mobile phase (0.5 ml) and 20 μl aliquots were injected on column. The enantiomers of ibuprofen were quantified as their diastereoisomeric (*S*)-1-(naphthen-1-yl)ethylamides, by comparison of the amide peak heights to that of the amide of the internal standard. Calibration curves were prepared over the range 0.5-25 μg ml^{-1} of each enantiomer, as non-racemic isomeric mixtures, and were routinely established each time the assay was performed. The coefficient of variation over the calibration range was less than 5% (Avgerinos and Hutt, 1987).

Treatment of data

The maximum observed drug enantiomer plasma concentrations ($C_{P\,max}$) and the time to attain them (t_{max}) were obtained from an examination of the individual data following the initial drug dose; area under the plasma concentration time curves (AUC) were estimated by the trapezoidal rule up to the last assayed plasma sample, 24 and 32 h for the tablet and controlled release formulation, respectively. The plasma sampling scheme (see above) precluded an estimation of the drug enantiomer terminal elimination rate constants and hence AUC values to infinite time. However, an estimate of the apparent drug elimination half-lives following administration of the controlled release formulation was determined using the method of least squares. Statistical analysis of these data was carried out using Student's paired *t*-test.

Results

The mean ibuprofen enantiomer plasma concentration time profiles following the repeated oral administration of a conventional tablet formulation and the novel controlled release pellet formulation, both containing the racemic drug, to four healthy volunteers, are shown in Fig. 1. The pharmacokinetic parameters derived from an examination of the individual data are presented in Table 1.

There were no statistically significant differences in the highest observed plasma concentrations of total ibuprofen, following the initial drug doses, nor in the time to attain them, between the two formulations as was expected from the design of the controlled release pellets. Examination of the enantiomeric composition of ibuprofen at $C_{P\,max}$ however, indicated significantly lower ($2P < 0.025$) concentrations of the (*S*)-isomer following administration of the controlled release preparation than the tablet formulation. Following repeated administration of both formulations the plasma concentrations of (*S*)-ibuprofen were con-

sistently greater than those of its (*R*)-antipode (Fig. 1); an observation in agreement with previously reported data following single dose studies (Van Giessen and Kaiser, 1975; Lee et al., 1985). The more rapid elimination of (*R*)-ibuprofen following the tablet formulation resulted in an enrichment of plasma ibuprofen with respect to the (*S*)-enantiomer over each dosage interval (Fig. 1), the plasma concentration ratio of ibuprofen enantiomers, *S/R*, being 2.5 ± 0.86 (mean ± S.D.) with a range of 1.3–4.2 over the study period. In contrast, following administration of the controlled release formulation the plasma enantiomer concentration ratio was reduced, both in magnitude and variation (mean ± S.D.: *S/R* 1.8 ± 0.4, range 1.2–2.6). The apparent enantiomer plasma elimination half-lives were longer and similar following the controlled release formulation (Fig. 1; apparent $t_{1/2}$, (*S*)-enantiomer 8.4 ± 2.2 h, (*R*)-enantiomer 8.8 ± 4.1 h).

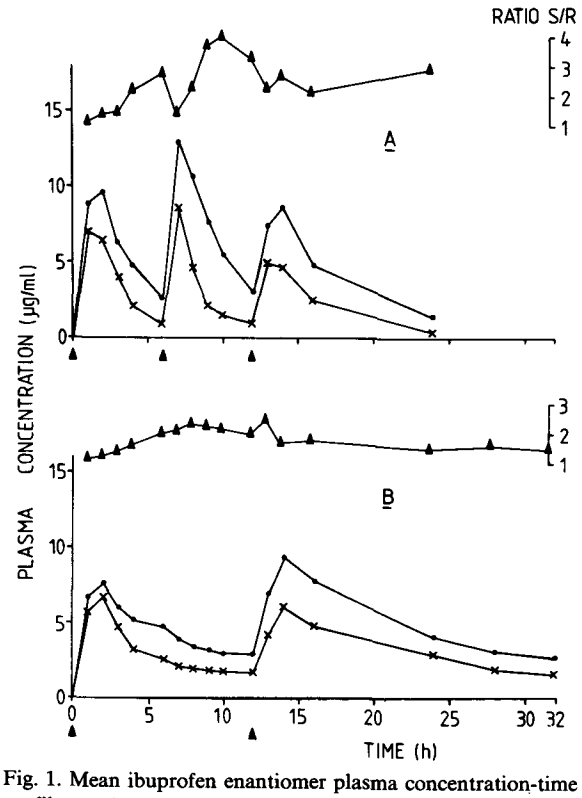

Fig. 1. Mean ibuprofen enantiomer plasma concentration-time profiles, and enantiomeric ratios following the oral administration of the racemic drug as tablet (A) and novel controlled release pellet formulations (B) to four healthy volunteers. (*R*)-ibuprofen (×), (*S*)-ibuprofen (●), enantiomeric ratio *S/R* (▲); arrowheads on the time axis indicate the time of drug administration.

TABLE 1

Ibuprofen enantiomer pharmacokinetic parameters following the administration of the racemic drug in a conventional tablet and a novel controlled release formulation to healthy volunteers

	Enantiomer						AUC (% *S*)
	S-(+)			*R*-(−)			
	C_{Pmax} (µg ml^{-1})	t_{max} (h)	AUC [a] (µg ml^{-1} h)	C_{Pmax} (µg ml^{-1})	t_{max} (h)	AUC [a] (µg ml^{-1} h)	
Tablet formulation							
Subject							
A	10.9	2	145	8.2	2	64	69.3
B	9.2	1	133	6.4	1	46	74.3
C	11.3	2	139	7.3	2	77	64.4
D	11.8	1	124	9.8	1	77	61.7
Mean	10.8	1.5	135	7.9	1.5	66	67.4
Controlled release formulation							
Subject							
A	9.2	2	188	9.2	2	118	61.4
B	6.3	2	140	3.4	2	65	68.5
C	8.8	2	170	8.6	2	136	55.6
D	6.9	2	141	6.2	2	98	59.0
Mean	7.8	2	160	6.9	2	104	61.1

[a] AUC values 0–24 h and 0–32 h following administration of the tablet and controlled release formulations, respectively.

The areas under the plasma enantiomer concentration-time curves (AUCs) of (*S*)-ibuprofen were significantly greater than those of the (*R*)-isomer following the administration of either formulation (tablet $2P < 0.01$; controlled release $2P < 0.02$). The proportion of the total AUC due to the active (*S*)-isomer, i.e. the measure of exposure of the volunteers to the active agent, was slightly reduced from 67% following the tablet to 61% ($2P < 0.02$) following the controlled release formulation.

Discussion

The purpose of the present study was to investigate the enantiomeric disposition of ibupro-

fen following the administration of the racemic drug in a controlled release formulation rather than to compare the relative bioavailabilities of the two products. The study design was intended to simulate the normal, in the case of the tablet formulation, and the intended, in the case of the controlled release formulation, daily dosage regimens of ibuprofen.

The plasma concentration-time profiles (Fig. 1) suggest that drug release from the controlled release formulation was suitably modified and that the fluctuation between the peaks and troughs, observed following the conventional formulation, were reduced. In addition, and importantly for an NSAID, the drug plasma concentrations were maintained overnight as determined by measurement of the enantiomer concentrations at $t = 24$ h. The plasma profiles, and apparent enantiomer elimination half-lives, of ibuprofen following the controlled release formulation are consistent with dissolution rate limited drug absorption, i.e. a 'flip-flop' pharmacokinetic model (Gibaldi and Perrier, 1982). Similar observations have also been reported for the elimination of ibuprofen enantiomers following the administration of a generic tablet formulation (Cox et al., 1988) and also with a controlled release formulation of the related NSAID ketoprofen (Houghton et al., 1984).

As stated previously the stereochemical aspects of ibuprofen disposition are complex (for references see Introduction), which is probably a result of both the metabolic chiral inversion and enantiomer-enantiomer interactions in plasma protein binding (Lee et al., 1985). It has been suggested recently that the chiral inversion of (*R*)-ibuprofen may be a presystemic event probably taking place in the gastrointestinal tract (Jamali et al., 1988). Ibuprofen is thought to be absorbed throughout the entire gastrointestinal tract (Parr et al., 1987) and as multidose pellet formulations are known to be widely distributed, and release their contents, throughout the gastrointestinal tract (Beckett, 1985) differences in tissue (*R*)-ibuprofen racemase activity could account for the reduction in the proportion of the total area under the plasma concentration time curves due to the active (*S*)-isomer following administration of the controlled release formulation.

The plasma enantiomeric concentration ratio (S/R) of ibuprofen was reduced and showed much less variation following the administration of the controlled release formulation than the conventional tablet formulation. A progressive increase in the plasma (S/R) ratio was observed following the administration of the tablet formulation, which decreased on the administration of the second drug dose. Jamali et al. (1988) also observed a progressive increase in the plasma enantiomeric ratio for up to 4–6 h post drug administration, after this time the ratio decreased and eventually levelled off. This observation was used to support the idea that the chiral inversion reaction is a presystemic transformation (Jamali et al., 1988). We also observed a similar decrease in plasma enantiomeric ratio, at a similar time interval, following the administration of the second tablet dose (Fig. 1). However, in a more recent study (Avgerinos and Hutt, 1990) of the plasma ibuprofen enantiomeric composition following a single dose of the racemic drug to 24 volunteers we found a progressive increase in a (S/R) ratio which would indicate a systemic contribution to the inversion reaction.

It is of interest to compare the results obtained in the present study with ibuprofen, a compound known to undergo stereoselective plasma disposition, with ketoprofen a compound which undergoes minimal enantioselective plasma disposition (Foster et al., 1988a,b). Sallustio et al. (1988) have recently examined the enantiomeric disposition of ketoprofen following the administration of a controlled release formulation to elderly patients. The results obtained were similar to those of Foster et al. (1988a,b) in that only small differences in enantiomeric plasma concentrations were observed, the ratio of the time averaged enantiomer plasma concentrations being 1.04 ± 0.21, and it was concluded that non-stereospecific analysis could be used to yield a fairly good estimate of enantiomeric composition of the drug in plasma (Sallustio et al., 1988).

The results of the present study, together with that of Cox et al. (1988), have some significance for the evaluation of product bioequivalence. Cox et al. (1988) carried out a comparative bioequivalence study on two commercially available

ibuprofen formulations utilizing both enantiospecific and achiral analytical techniques. The same conclusions concerning differences between the two formulations, in terms of rate of drug absorption were reached regardless of analytical methodology, whereas differences in drug elimination were significant only when enantiospecific methodology was employed (Cox et al., 1988). Similarly non-enantiospecific analysis in the present study would have yielded information concerning the modifications to the drug plasma profile but not the reduction in fluctuation in plasma ibuprofen enantiomeric composition following the controlled release formulation. Both these effects being potentially advantageous in terms of producing a more predictable response to the drug.

In conclusion, we would suggest that bioavailability data obtained by measurement of total drug content, following the administration of various formulations of racemic drugs, for which pharmacokinetic and pharmacodynamic differences between enantiomers are known to exist, should be examined with some caution in assessing product equivalence.

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References

Adams, S.S., Bresloff, P. and Mason, C.G., Pharmacological differences between the optical isomers of ibuprofen: evidence for the metabolic inversion of the (-)-isomer. *J. Pharm. Pharmacol.*, 28 (1976) 256–257.

Ariens, E.J., Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology. *Eur. J. Clin. Pharmacol.*, 26 (1984) 663–668.

Ariens, E.J., Wuis, E.W. and Veringa, E.J., Stereoselectivity of bioactive xenobiotics. A pre-Pasteur attitude in medicinal chemistry, pharmacokinetics and clinical pharmacology. *Biochem. Pharmacol.*, 37 (1988) 9–18.

Avgerinos, A. and Hutt, A.J., Determination of the enantiomeric composition of ibuprofen in human plasma by high-performance liquid chromatography. *J. Chromatogr. Biomed. Appl.*, 415 (1987) 75–83.

Avgerinos, A. and Hutt, A.J., Interindividual variability in the enantiomeric disposition of ibuprofen following the oral administration of the racemic drug to healthy volunteers. *Chirality*, (1990) in press.

Baillie, T.A., Adams, W.J., Kaiser, D.G., Olanoff, L.S., Halstead, G.W., Harpootian, H. and Van Giessen, G.J., Mechanistic studies of the metabolic chiral inversion of (R)-ibuprofen in humans. *J. Pharmacol. Exp. Ther.*, 249 (1989) 517–523.

Beckett, A.H., Once-daily rate controlled drug therapy. In Prescott, L.F. and Nimmo, W.S. (Eds), *Rate Control in drug therapy*, Proceedings of the 2nd Edinburgh Conference on Drug Absorption, Churchill Livingstone, Edinburgh, (1985) pp. 166–179.

Caldwell, J., Hutt, A.J. and Fournel-Gigleux, S., The metabolic chiral inversion and dispositional enantioselectivity of the 2-arylpropionic acids and their biological consequences. *Biochem. Pharmacol.*, 37 (1988a) 105–114.

Caldwell, J., Winter, S.M. and Hutt, A.J., The pharmacological and toxicological significance of the stereochemistry of drug disposition. *Xenobiotica*, 18 (suppl. 1) (1988b) 59–70.

Collier, P.S., D'Arcy, P.F., Harron, D.W.G. and Morrow, N., Pharmacokinetic modelling of ibuprofen. *Br. J. Clin. Pharmacol.*, 5 (1978) 528–529.

Cox, J.W., Cox, S.R., Van Giessen, G. and Ruwart, M.J., Ibuprofen stereoisomer hepatic clearance and distribution in normal and fatty in situ perfused rat liver. *J. Pharmacol. Exp. Ther.*, 232 (1985) 636–643.

Cox, S.R., Brown, M.A., Squires, D.J., Murrill, E.A., Lednicer, D. and Knuth, D.W., Comparative human study of ibuprofen enantiomer plasma concentrations produced by two commercially available ibuprofen tablets. *Biopharm. Drug Dispos.*, 9 (1988) 539–549.

Drayer, D.E., Pharmacodynamic and pharmacokinetic differences between drug enantiomers in humans: an overview. *Clin. Pharmacol. Ther.*, 40 (1986) 125–133.

Evans, A.M., Nation, R.L., Sansom, L.N., Bochner, F. and Somogyi, A.A., Stereoselective drug disposition: potential for misinterpretation of drug disposition data. *Br. J. Clin. Pharmacol.*, 26 (1988) 771–780.

Foster, R.T., Jamali, F., Russell, A.S. and Alballa, S.R., Pharmacokinetics of ketoprofen enantiomers in healthy subjects following single and multiple doses. *J. Pharm. Sci.*, 77 (1988a) 70–73.

Foster, R.T., Jamali, F., Russell, A.S. and Alballa, S.R., Pharmacokinetics of ketoprofen enantiomers in young and elderly arthritic patients following single and multiple doses. *J. Pharm. Sci.*, 77 (1988b) 191–195.

Gibaldi, M. and Perrier, D., *Pharmacokinetics*, 2nd Edn, Dekker, New York, 1982, pp. 34–35.

Houghton, G.W., Dennis, M.J., Rigler, E.D. and Parsons, R.L., Comparative pharmacokinetics of ketoprofen derived from single oral doses of ketoprofen capsules or a novel sustained-release pellet formulation. *Biopharm. Drug. Dispos.*, 5 (1984) 203–209.

Hutt, A.J. and Caldwell, J., The metabolic chiral inversion of 2-arylpropionic acids, a novel route with pharmacological consequences. *J. Pharm. Pharmacol.*, 35 (1983) 693–704.

Hutt, A.J. and Caldwell, J., The importance of stereochemistry in the clinical pharmacokinetics of the 2-arylpropionic acid non-steroidal anti-inflammatory drugs. *Clin. Pharmacokinet.*, 9 (1984) 371–373.

Hutt, A.J., Fournel, S. and Caldwell, J., Application of a radial compression column to the high-performance liquid chromatographic separation of the enantiomers of some 2-arylpropionic acids as their diastereoisomeric *S*-1-(naphthen-1-yl)ethylamides. *J. Chromatogr. Biomed. Appl.*, 378 (1986) 409–418.

Jamali, F., Singh, N.N., Pasutto, F.M., Russell, A.S. and Coutts, R.T., Pharmacokinetics of ibuprofen enantiomers in humans following oral administration of tablets with different absorption rates. *Pharm. Res.*, 5 (1988), 40–43.

Kaiser, D.G., Van Giessen, G.J., Reischer, R.J. and Wechter, W.J., Isomeric inversion of ibuprofen (*R*)-enantiomer in humans. *J. Pharm. Sci.*, 65 (1976) 269–273.

Lee, E.J.D., Williams, K.M., Day, R., Graham, G. and Champion, G.D., Stereoselective disposition of ibuprofen enantiomers in man. *Br. J. Clin. Pharmacol.*, 19 (1985) 669–674.

Parr, A.F., Beihn, R.M., Franz, R.M., Szpunar, G.J. and Jay, M., Correlation of ibuprofen bioavailability with gastrointestinal transit by scintigraphic monitoring of ^{171}Er-labelled sustained-release tablets. *Pharm. Res.*, 4 (1987) 486–489.

Sallustio, B.C., Purdie, Y.J., Whitehead, A.G., Ahern, M.J. and Meffin, P.J., The disposition of ketoprofen enantiomers in man. *Br. J. Clin. Pharmacol.*, 26 (1988) 765–770.

Stead, J.A., Freeman, M., John, E.G., Ward, G.T. and Whiting, B. Ibuprofen tablets: dissolution and bioavailability studies. *Int. J. Pharm.*, 14 (1983) 59–72.

Van Giessen, G.J. and Kaiser, D.G., GLC determination of ibuprofen d,l-2-(p-isobutylphenyl)propionic acid enantiomers in biological specimens. *J. Pharm. Sci.*, 64 (1975) 798–801.

Wechter, W.J., Loughhead, D.G., Reischer, R.J., Van Giessen, G.J. and Kaiser, D.G., Enzymatic inversion at saturated carbon: nature and mechanism of the inversion of *R*(–)*p*-iso-butylhydratropic acid. *Biochem. Biophys. Res. Commun.*, 61 (1974) 833–837.

Williams, K., Day, R., Knihinicki, R. and Duffield, A., The stereoselective uptake of ibuprofen enantiomers into adipose tissue. *Biochem. Pharmacol.*, 35 (1986) 3403–3405.

Williams, K. and Lee, E., Importance of drug enantiomers in clinical pharmacology. *Drugs*, 30 (1985) 333–354.