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APPROACHES TO STEREOSPECIFIC PREFORMULATION OF IBUPROFEN

A.J. Romero and C.T. Rhodes
University of Rhode Island, Department of Pharmaceutics
Kingston, RI 02881

Abstract

In an effort to formulate the pharmacologically active ibuprofen isomer ((+)-S-ibuprofen) into a solid oral dosage form, preformulation studies were performed on both the racemate and this stereoisomer of ibuprofen. Results of the respective physical pharmacy profiles were compared to predict the pharmaceutical behavior of the S(+) ibuprofen compound. The enantiomer was more soluble than the racemate in aqueous media but exhibited lower intrinsic dissolution rates, as would be expected from the very small specific surface area. This characterisitic could be a limiting step in the formulation of the optical isomer although less energy was required for the solution of S(+) ibuprofen. On this crystal, there was ten times more moisture layered at the surface and comparative thermal analysis indicated that for both compounds a loss in crystallinity occured upon grinding. Properties in the solid state of S(+) ibuprofen included higher density and excellent flowability as compared to the racemate.

INTRODUCTION

Recently extensive emphasis has been given to the stereospecific nature of drug disposition in the context of drug development. Regulatory bodies in Europe already recommend the use of stereospecific assays when a racemate is formulated (1). In this case, when the chiral synthesis is possible, the formulation of pure active enantiomers also becomes a priority for research and development. Thus, for drug candidates in the development pipeline stereospecific considerations are critical. For drug products already marketed as racemates, the study of their optical isomers might present a different sets of problems (2).

The use of an enantiomer as part of a solution for common pharmaceutical problems is not new. In the early seventies, formulators at Wyeth had described the advantages of using the pure optical isomer of a cytotoxic agent to overcome a solubility problem (3). The differences in physicochemical properties between racemic and enantiomer have been known and studied for a long time; solid state properties, crystal structures and the effect of isomeric purity on phase solubilities (4-6) have been investigated. Recently the effect of chiral asymmetry on crystal properties was reviewed and it was concluded that for such compounds, biopharmaceutical characteristics must be carefully monitored (7).

Ibuprofen is administered as a racemate and is one of 50 compounds for which detailed stereospecific pharmacokinetics have been reported. Properties in solution and the solid state have been documented in the literature and conventional preformulation programs have been applied to the study of this antiinflammatory agent (8). It is now generally recognized that formulating ibuprofen is difficult and relies mainly on the expertise of the

formulator. Its low solubility in aqueous media at low pHs as well as its poor handling properties contribute to its tedious processing. S(+) ibuprofen, the biologically active isomer of ibuprofen, is now available in large scale quantities through economically viable chemical synthesis and the objectives of this study are to draw a preformulation profile for this enantiomer, investigate the feasibility of a conventional formulation and compare this stereoisomer to the racemate currently used.

EXPERIMENTAL

MATERIALS

Rac-ibuprofen (lot# LH6-72) and (+)-S-ibuprofen (lot# AC-1R) were obtained from the Ethyl Co., Baton Rouge, LA. Monobasic potassium phosphate and sodium hydroxide from the Fisher Scientific Company, were of analytical grade.

METHODS

Analytical: all quantitative determinations in solution were performed using an ultra violet spectrophotometer (Hewlett Packard 8450). The instrument was calibrated at 264 and 220 nanometer wavelengths.

Intrinsic Dissolution Rate (IDR)

The procedure desribed by Woods et al (9) was used to determine the intrinsic dissolution rates. A modified Woods apparatus, designed by Ciba-Geigy researchers (fig. 1) was used. One gram of sample powder was weighted in the die and precompressed at 500 lbs with a Carver hydraulic press. After cleaning the exposed

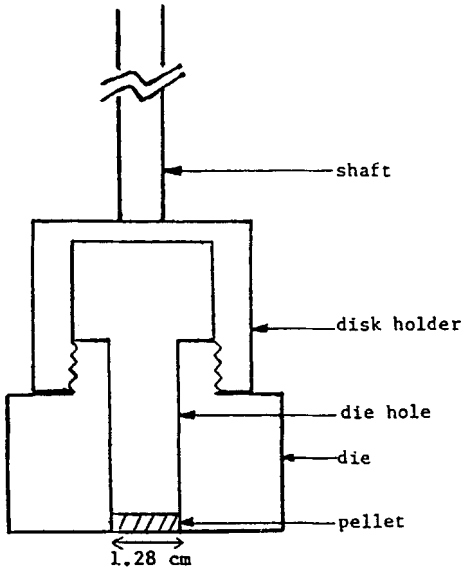

Figure 1

Cross-Section of the Modified Woods Rotating Apparatus

surface the compact was recompressed at 1000 lbs for a dwell time of 5 seconds. The rotating disk assembly was immersed in 500 ml of USP simulated intestinal fluid (SIF) at 37 +/- 0.8 ^{o}C and rotated at 100 rpm. The sampling regimen, included 2,5,10,15,20,25,30 and 35 minute time points. Sample volume was 4 cm^3, withdrawn with micro-syringes and replaced with the same volume of SIF at 37^{o}C. All samples were passed through a 0.45 um cellulose acetate filter before analysis. Amounts of drug dissolved were plotted versus time and the slope of the straight line portion was divided by the area of the pellet (A=1.281 cm^2) to yield the intrinsic dissolution rates in $mg.sec^{-1}.cm^{-2}$.

Solubility and Heat of Solution

The method used was the procedure described by Higuchi et al (10). Ibuprofen was added in large excess to buffered solutions

in screw-capped vials at various pHs. The tubes were rotated on a labquake shaker in dry ovens for 24 hours to reach saturation (11). The vials were then centrifuged at 2000g for 10 minutes, supernatants withdrawn, filtered, and further analyzed for pH and drug concentrations. Four pH's were studied at temperatures ranging from 25 to 51 ^{o}C.

Solid State Properties

Particle size was measured using a laser light scattering technique (Brinckman Particle Size Analyzer). Surface areas were determined with a Nitrogen adsorption technique and calculated using the B.E.T. equation. This experiment was performed on a Quantasorb instrument. Compressibility and density were evaluated using a procedure proposed by Rees et al (12). About 100 mg of powder were weighted in a volumetric cylinder. Up to 2000 taps were performed on an Erweka instrument. Moisture contents were estimated with a Karl-Fisher technique. Crystal analysis included differential scanning calorimetry to monitor temperatures and enthalpies of fusion on a Perkin-Elmer P7500, all thermal analysis were conducted with a heat flow of 5^{o}C/minute; samples were also analyzed through scanning electron microscopy and X-Ray powder diffraction at the R&D analytical services of Ciba-Geigy in Ardsley, NY.

RESULTS AND DISCUSSIONS

Solid State Properties

Under similar storage conditions (22^{o}C +/- 2 and 35% RH) the mass fraction of moisture for the rac-ibuprofen averaged 0.065 +/- 0.013% where (+)-S-ibuprofen exhibited 0.34 +/- 0.24% of

water corresponding to ten times more moisture for this enantiomer. After careful analysis of X-Ray diffraction patterns of dried and humidity exposed ibuprofen samples, there was no change in the crystallinity of both powders upon removal of water. It was speculated that the moisture essentially stick to the crystal surface. Both compounds had very low water content but according to Ahelc et al (13) it still requires special attention because the water distributes only in amorphous regions. X-ray powder diffraction patterns indicated different crystal structure for the racemate and its enantiomer with very different deflection peaks especially at low angles of the spectrum. Ten minutes grinding resulted in a loss of crystallinity for both powders with a decrease in deflection peaks intensity (fig. 2). For ground S(+) ibuprofen, some peaks were more intense at low angles of the spectrum (11-15). This difference might be due to the decrease in particle size but indicated a modification of the crystal nature. The thermodynamic parameters, presented in table 1 confirmed these conclusions. The endotherm temperature was 20°C lower for the S(+) enantiomer and the enthalpy of fusion averaged 48 J/g less than the racemate. Upon grinding there was a decrease in the enthalpy of fusion for the ibuprofens proportional to entropy changes. There was no modifications in the melting points in either case confirming no rearrangement of the internal lattice(s). Nevertheless, although the internal structure might not have been modified, upon grinding there was a decrease in the particle size of (+)-S-ibuprofen and the compound became difficult to handle as a result of flowability loss.

Based on the monolayer gas adsorption theory we calculated the true surface area of the two compounds using the B.E.T. equation. The B.E.T. values for racemate and the S(+) isomer were respectively $3.4\ 10^{-1}$ (0.01) and $2.8\ 10^{-3}$ ($1.9\ 10^{-4}$) m^2/gram indicating a specific surface area more than 100 times smaller

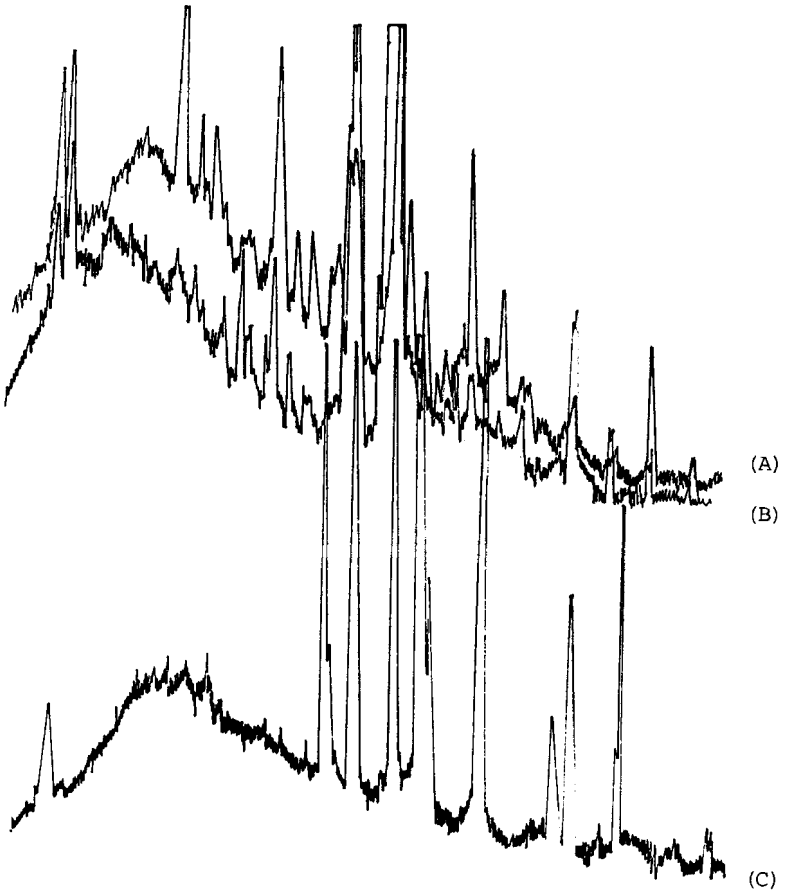

Figure 2

Powder X-Ray Diffraction Patterns: Effect of Grinding
(A): S(+) ibuprofen "ground", (B): S(+) ibuprofen "as received", (C): Rac-ibuprofen "as received"

Table I : THERMAL ANALYSIS OF IBUPROFEN			
"As Received"	Racemate	S(+)	R(-)
MELTING RANGE	75-77 oC	53-55 °C	53-55 °C
ENTHALPY OF FUSION	135.1 J/G	86.8 J/G	87.0 J/G
"Ground"			
MELTING POINT	75.3 C	55.1 C	
ENTHALPY OF FUSION	115.2 J/G	82.3 J/G	

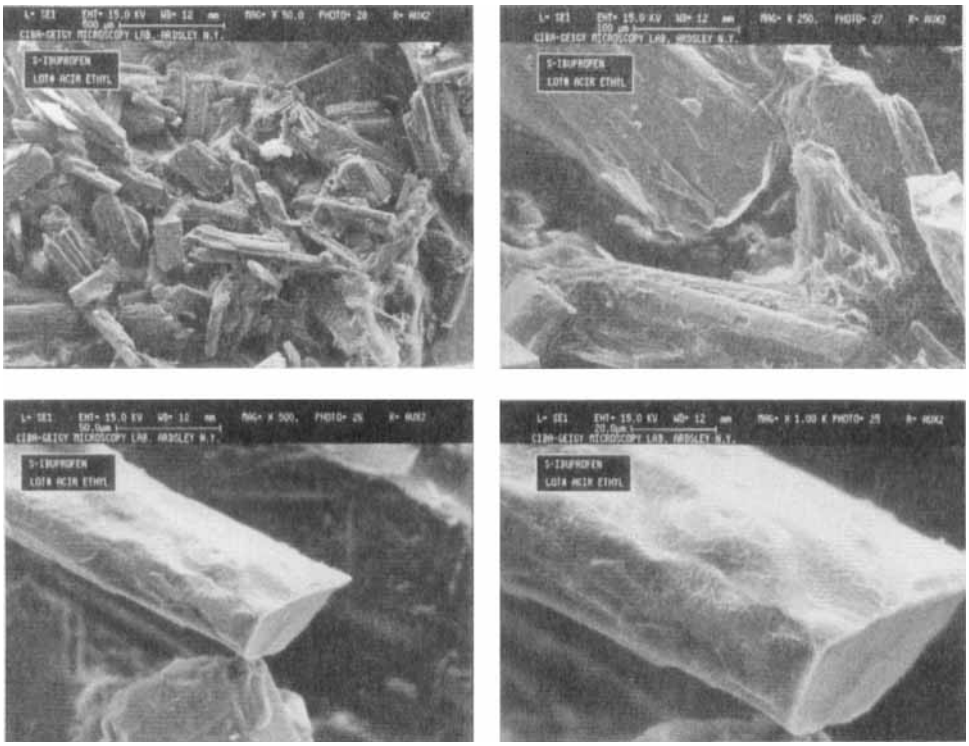

Figure 3

Scanning Electron Microscopy Photographs of S(+) Ibuprofen

50, 250, 500 and 1000X Magnification

for the enantiomer. Although it has been found that BET values vary between sources (14), the amplitude of this difference might be a potential problem of the formulation specifically in the dissolution/bioavailability behavior. The particle size with a mean ranging from 83 to 149 um was very large compared to 5-38 um for the racemate (14) and was responsible for the excellent flowability of the bulk material. The scanning electron microscopy observations in fig.3 indeed confirmed the descriptive analysis and the unusual nature of the crystal surface of (+)-S-

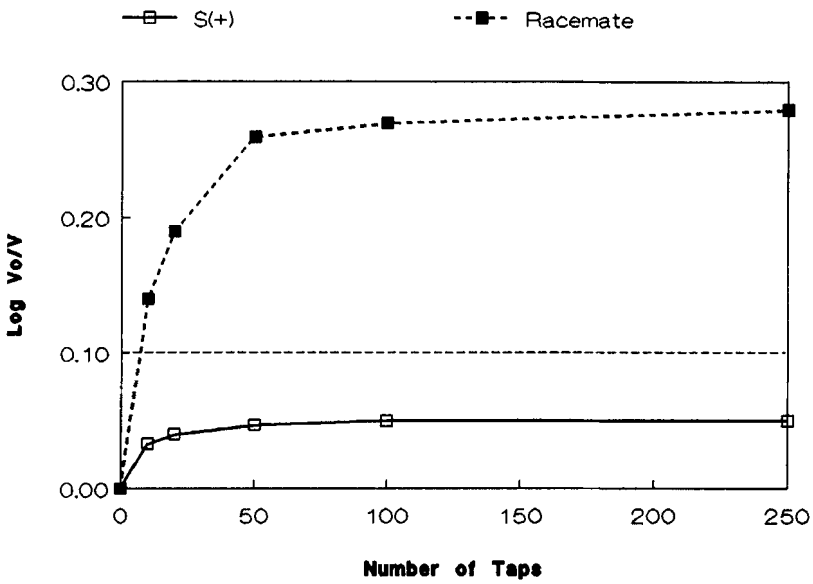

Figure 4
Log Vo/V Versus No of Taps

ibuprofen. The optical isomer existed as large boxy needles consisting of the crystal unit. All particles had a very smooth surface.

Bulk and tapped densities averaged 34 and 56 % respectively and were similar to the racemate analyzed. The compressibility/flowability as evaluated by plotting Log Vo/V against the number of taps (fig.4), where Vo is the initial volume and V the tapped volume, was consistently above the 0.1 assymptote for the racemate and considered poor (12) as compared to the S(+) enantiomer. Thus the optical isomer might be a good candidate for direct compression.

Dissolution Kinetics

Because of the unique dissolution characterisitics of each compound, the rate plots presented in fig.5 had different slopes,

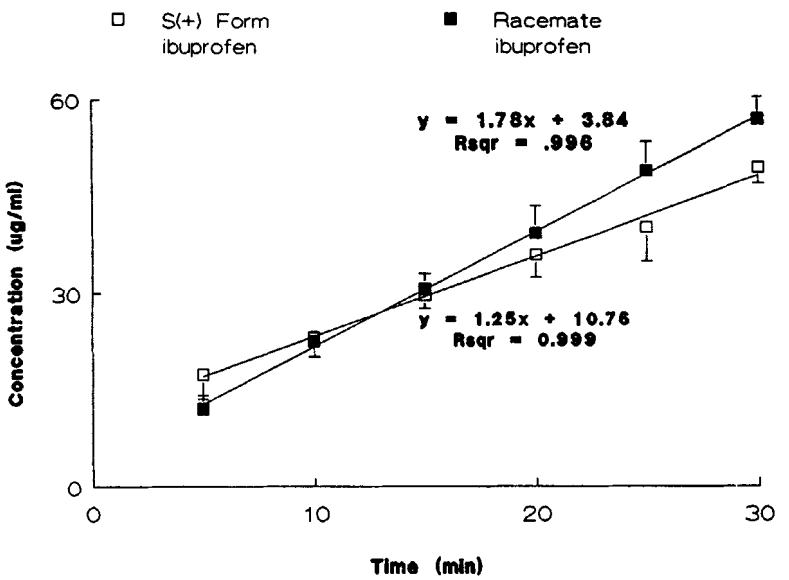

Figure 5: Intrinsic Dissolution Modified Woods Apparatus

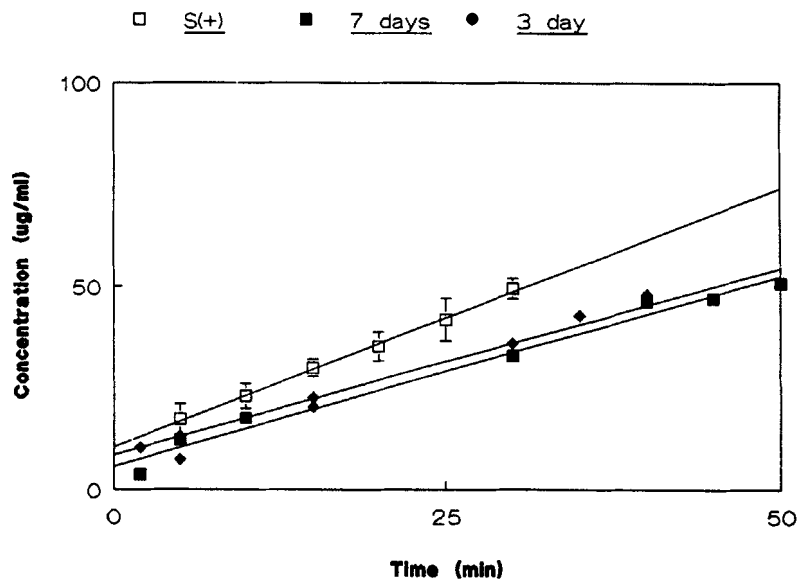

Figure 6: Dissolution of S(+) ibuprofen Effect of Aging

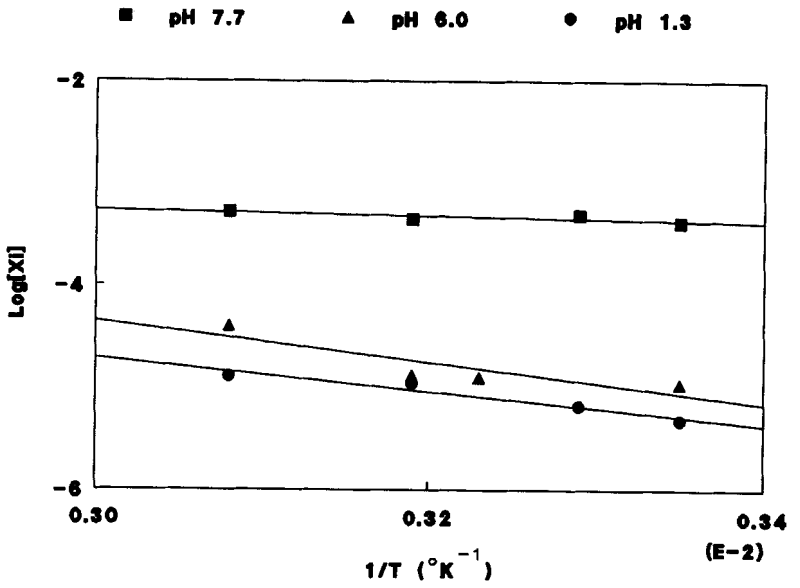

Figure 7
Vant'Hoff Plots [Rac-ibuprofen]

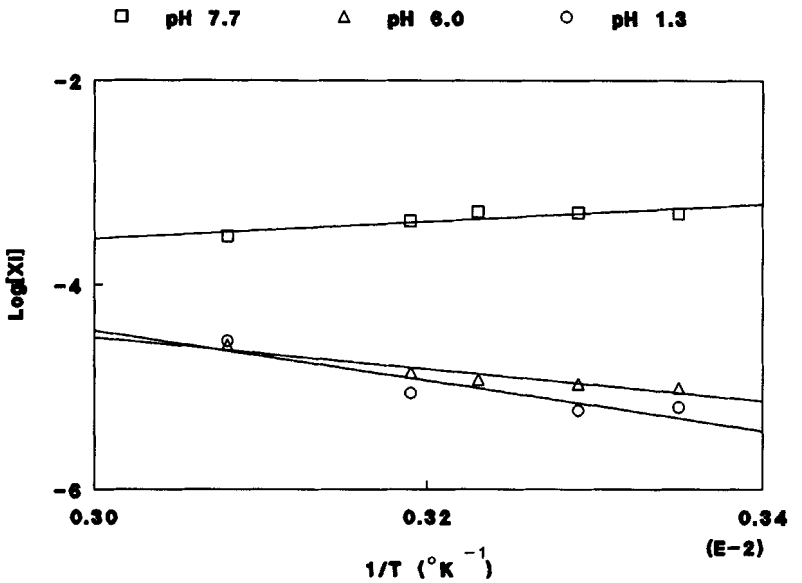

Figure 8
Vant'Hoff Plots [(+)-S-ibuprofen]

Table II : HEAT OF SOLUTION FOR IBUPROFEN		
	pH	ΔH (KJ.MOLE^{-1})
RACEMATE	1.3	31.2
	4.5	-0.3
	6.0	38.8
	7.7	-5.2
S(+)	1.3	51.6
	4.5	-0.0
	6.0	29.9
	7.7	-16.4

and consequently different intrinsic dissolution rates. Surprinsingly the IDR for S(+) ibuprofen averaging 8.1 ug.sec^{-1}.cm^{-2} was smaller than the IDR of the racemate with a mean at 11.6 ug.sec^{-1}.cm^{-2}. It appears that under our experimental conditions, the dissolution rate of the enantiomer was limited by its very small surface area (rather than enhanced by its high solubility). In addition, aged compacts at Room Temperature for 3 days and further analyzed under the same conditions had lower intrinsic dissolution rates IDR than original disks immediately analyzed after manufacture (fig.6).

Heat of Solution

The solubility of the two ibuprofens was determined at different temperatures in various buffers. The van't Hoff equation relates the solubility in mole fraction or mole percent to the inverse of the absolute temperature of an ideal solution:

$$-\text{Log } Xi = (\Delta Hf/RT) + \text{constant}$$

where Xi is the ibuprofen concentration in mole fraction, ΔHf

the heat of solution, R in J/mole, the perfect gas constant and T the absolute temperature in degree Kelvin. The Van't Hoff plots for rac-ibuprofen (fig.7) and (+)-S-ibuprofen (fig.8) yield heats of solution at different pH's presented in table 2. The slopes varied with pH indicating that the heat absorbed by the systems during dissolution varied with the extent of ionization. The energy of solubilization decreased with ionized species and at pH 7.7, the heat of solution became slightly exothermic for both ibuprofens. This result confirmed that when ionization was the principal factor in dissolution (at high pHs) this phenomena actually released energy. At this level of lower [H+] concentrations, S(+) ibuprofen consistently exhibited lower heat of solutions than its racemate form showing that the enantiomer is more soluble in aqueous media. For example the aqueous solubility of (+)-S-ibuprofen in a pH 7.7 phosphate buffer at 37 ^{o}C was 6.0 mg/ml compared to 5.0 mg/ml for the racemate. Under our experimental settings, at pH 4.5 (pKa of ibuprofen) the concentrations were most variable and yield close to zero slopes for both ibuprofens.

CONCLUSIONS

The physical pharmacy profiles of S(+) ibuprofen and its racemate form were compared. Thermal analysis indicated that the optical isomer existed as a different crystal form exhibiting different solid state properties which could be of concern for the formulator. Particle size was increased and the flowability was improved. The enantiomer existed as large boxy crystals with unusually low surface area. This might be a major limitation for an oral solid formulation. In fact the intrinsic dissolution rate of this compound was found smaller than the IDR of the rac-ibuprofen which was not predicted from the solubulity data and

not previously documented in the literature. Solubility determinations revealed that (+)-S-ibuprofen was more soluble in aqueous media at pHs higher than 4.5 but not to the extent anticipated from a review of the stereochemical literature. Also at pH 7.7 heats of solution were slightly exothermic for both ibuprofens indicating that at this pH the solubilization process released some energy. It has been argued from a pharmacokinetic/pharmacodynamic stand point that formulating S(+) ibuprofen might be a therapeutic improvement (9), however, considering these elements of physical pharmacy special attention should be given to the formulation, in order to overcome the potential problems of dissolution, low melting levels and compatibility. Thus, S(+) ibuprofen might be readily absorbed through the jegunum but its dissolution characteristics could be a rate limiting step of bioavailability for an oral solid dosage form. If lower doses are required, it is anticipated that S(+) ibuprofen could be a good candidate for direct compression.

In summary, we believe that the formulation of (+)-S-ibuprofen is certainly achievable provided the unique characteristics of this drug are kept in mind. There are significant differences between this enantiomer and the racemate and the potential advantages (therapeutic and biopharmaceutical) of the S(+) drug might be considerable.

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