International Journal of Pharmaceutics, 87 (1992) 95–104

IJP 02872

Ibuprofen racemate and enantiomers: Phase diagram, solubility and thermodynamic studies [1]

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(Received 5 November 1991)
(Modified version received 14 April 1992)
(Accepted 15 April 1992)

Key words: Ibuprofen; Enantiomer; Racemic compound; Phase diagram; Solubility

Summary

A binary phase diagram constructed from DSC curves of ibuprofen (IB) using R-IB, S-IB and ibuprofen USP (rac-IB) was typical of a eutectic system with addition compound formation. The USP material is therefore a racemic compound which melts at 71°C compared with 46°C for the enantiomers and 37°C for the eutectic compositions of 0.18 and 0.82 mole fractions of S-IB. The phase diagram was verified by calculation of the liquidus curve in the dystectic region using a rearrangement of the Prigogine-Defay equation. Powder X-ray diffraction analysis confirmed that rac-IB was a racemic compound, capable of existing as a separate phase independent of its constituent enantiomers, and not a racemic mixture. Solubilities in aqueous HCl-KCl solution, pH 1.5, were in the order eutectic-IB > R-IB or S-IB > rac-IB with eutectic-IB having twice the solubility of rac-IB. The solubility-temperature data were non-linear and could not be fitted to either van't Hoff or Hildebrand plots. A multiple regression analysis was used. The enthalpy, entropy and free energy of formation of rac-IB from R-IB and S-IB were calculated from DSC observations.

Introduction

The ibuprofen (IB) molecule has one chiral center. Hence, there are two enantiomers. When equal amounts of enantiomeric molecules are present together, the product is termed racemic, irrespective of whether it is crystalline, liquid or gaseous (Am. Chem. Soc., 1970; IUPAC, 1976, 1979). Racemic solids may be classified into three types based on a melting point phase diagram. The most common type is the racemic compound which contains an equal number of molecules of each enantiomer in the unit cell of the crystal. The solid therefore is a one-phase crystalline addition compound. In the binary phase diagram of a mixture of the two enantiomers, there are two eutectic points. The melting point of a racemic compound may be either below or above the melting point of the pure enantiomers.

The second, less common type of racemic solid is the racemic mixture or conglomerate in which

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[1] Presented in part at the American Association of Pharmaceutical Scientists Fifth Annual Meeting, Las Vegas, U.S.A., November, 1990.

the two enantiomers crystallize separately. The solid therefore is a two-phase physical mixture. In the binary phase diagram there is only one eutectic point which corresponds to the melting point of the racemic mixture.

Where the two enantiomers form a continuous series of solid solutions (mixed crystals), a sample with equimolar enantiomeric composition is designated a racemic solid solution or pseudoracemate.

We have used DSC and powder X-ray diffraction to identify the racemic modification of IB USP. The solubilities and some thermodynamic properties of IB and its enantiomers have been determined.

Materials and Methods

Materials

Samples of R-IB and S-IB were obtained from Sepracor Inc. (Marlborough, MA) and Ethyl Corp. (Baton Rouge, LA), respectively. The stereochemical purity of these samples was 97 and 96%, respectively, as determined by HPLC (Mehvar et al., 1988). Ibuprofen USP (rac-IB) was provided by the Upjohn Co. (Kalamazoo, MI). Analytical grade hydrochloric acid and potassium chloride were supplied by BDH Chemicals (Toronto, Ontario). Distilled water (Corning Mega-Pure System, Anachemia Science, Edmonton, Alberta) was used to prepare a HCl-KCl standard solution of pH 1.5 and ionic strength 0.09 for the solubility experiments. At pH 1.5, IB (pK_a 5.3; Herzfeldt and Kümmel, 1983) is 99.98% non-ionized.

Differential scanning calorimetry (DSC)

DSC was performed on a Du Pont model 910 differential scanning calorimeter controlled by a Du Pont Series 99 thermal analyzer. The signals from the DSC were fed to an Apple II + computer through a variable amplifier and an analog-to-digital converter. The DSC curves were recorded and analyzed using software developed in our laboratory.

Enthalpies of fusion were determined from the DSC curves using indium as the calibration standard. For determining heat capacities, the signal from the DSC was calibrated in terms of power output (W/V) using sapphire as the standard. The difference between the heat capacities of solid and supercooled liquid samples, ΔC_p, was determined according to the method of James and Roberts (1968).

Determination of binary phase diagram

Accurately known masses of R-IB and S-IB were weighed out directly into standard open aluminum pans to obtain enantiomeric mixtures with evenly spaced mole fractions of S-IB between 0.04 and 0.96. The total mass of each mixture was about 5 mg. The pans were heated at 10°C/min from 20 to 90°C under a stream of nitrogen flowing at 138 kPa. The samples were cooled to room temperature and reweighed. No weight loss was detected, indicating that the volatility of IB (Ertel et al., 1990) was not a problem in the interpretation of the DSC results. Standard open pans were used instead of hermetically sealed volatile sample pans for quantitative DSC because of the greater contact area between the pan bottom and the constantan sample platform in the DSC cell. No significant difference was found in the enthalpies of fusion (ΔH^f) determined in standard or volatile sample pans (e.g., for S-IB; Table 2) confirming that no solid-vapor transition occurred under the experimental conditions. All samples recrystallized within 2 h of cooling, but were annealed at room temperature for 36 h before the DSC scan was repeated. Peak temperatures from the melting endotherms were plotted vs the enantiomeric composition to give the binary phase diagram. The peak temperatures changed negligibly when the same samples were reheated after storage for 6 months at room temperature, indicating that the initial annealing of 36 h was adequate. Recrystallizing from the melt was preferred over recrystallization from solution which would require complete removal of the solvent and the possibility of solvate formation would have to be ruled out.

The phase diagram was verified by the thermal analysis of mixtures of rac-IB with R-IB and S-IB and confirmed by calculating the melting point at various enantiomeric compositions using an equa-

tion derived from that of Prigogine and Defay (1954).

Powder X-ray diffraction

Powder X-ray diffraction patterns were obtained on a Rigaku Geigerflex X-ray diffraction system. The system was operated by an IBM compatible computer via a Rigaku D/MAX-B controller. The diffraction patterns were recorded at a continuous scanning rate of 5° 2θ/min using CuK_α radiation (40 kV, 20 mA) with the intensity of diffracted X-rays being collected at intervals of 0.05° 2θ. A Ni filter was used to remove CuK_β radiation.

Determination of solubility

Excess IB was placed in tightly sealed vials containing aqueous HCl-KCl and shaken in a water bath at 25°C. Samples were withdrawn using 22 μm Millex filter tips (Millipore, Milford, MA) at daily intervals until equilibrium was reached (8 days) and for 2 days thereafter. The samples were immediately diluted with the HCl-KCl solution to minimize volatilization and analyzed spectrophotometrically (Beckman Model 25 Spectrophotometer) at 232 nm against standard solutions prepared in aqueous HCl-KCl using aqueous HCl-KCl as a blank. The equilibrium solubility was determined in triplicate at 25°C. The temperature of the water bath was progressively raised to 30, 35, 40 and 45°C and the equilibrium solubility determination was repeated at each temperature. The equilibrium solubility represents the total number of molecules of IB present in the solution regardless of their enantiomeric configuration.

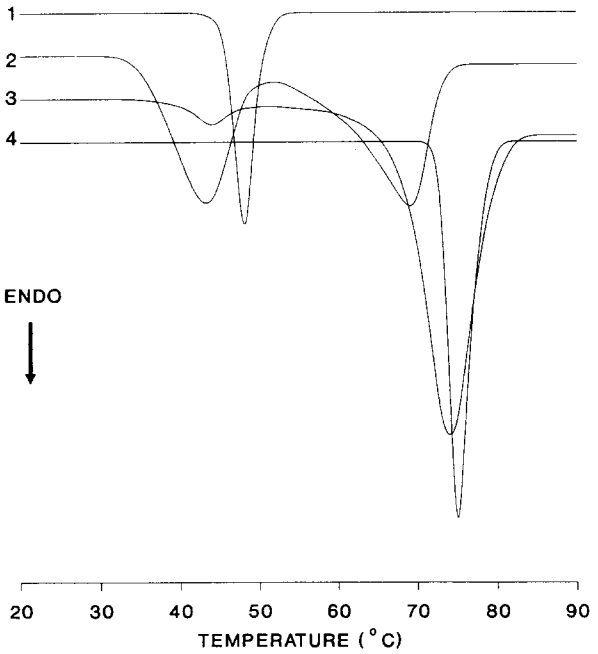

Fig. 1. Representative DSC curves of various compositions of ibuprofen: (1) 96% S-IB, (2) 27.6% S-IB, (3) 46% S-IB, (4) rac-IB.

Results and Discussion

DSC and powder X-ray diffraction

DSC scans indicate that the melting points of R-IB and S-IB are nearly identical. Some representative scans of various samples of IB are given in Fig. 1. The melting point of S-IB is much lower than that of rac-IB and samples of intermediate composition show a clearly defined eutectic melting endotherm. This suggests that rac-IB is a racemic compound.

The powder X-ray diffraction patterns (Fig. 2) of the two enantiomers were identical, but different from that of rac-IB. This confirms that rac-IB is a racemic compound capable of existing as a separate phase in the solid state independent of its constituent enantiomers. The diffraction pattern of a racemic mixture would be identical with that of its enantiomers, and that of a racemic solid solution would show slight shifts in the peak positions depending upon the nature of incorporation of the dissolved enantiomer. The term racemic mixture, often used in the literature to describe crystalline rac-IB, is therefore incorrect and misleading.

The binary phase diagram

Fundamental confirmation that rac-IB is a racemic compound, and not a racemic mixture, was provided by the binary phase diagram (Fig. 3). The phase diagram is characteristic of a eutectic system with binary addition compound formation. The melting points, determined by extrapo-

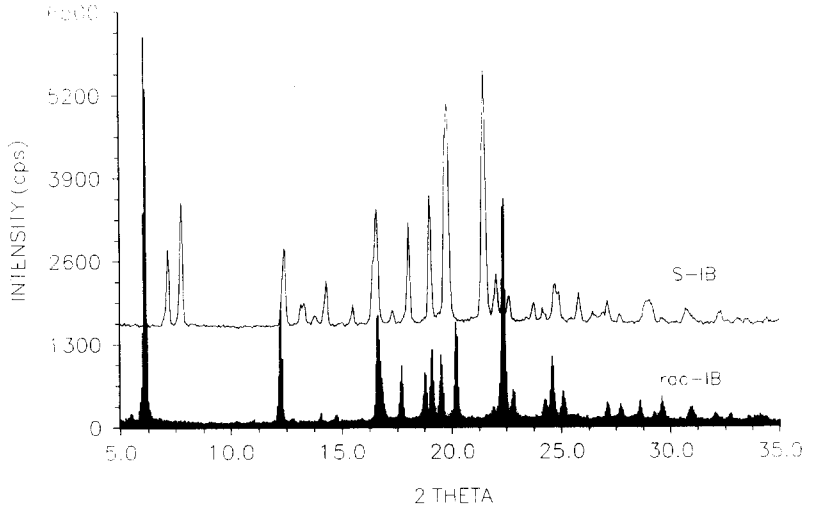

Fig. 2. Powder X-ray diffraction patterns of S-IB and rac-IB. The pattern of R-IB was identical to that of S-IB. The pattern of S-IB is shown with a baseline offset.

lating the leading edge of melting endotherm to the baseline, were 46, 46.5 and 71°C for R-IB, S-IB and rac-IB, respectively. The eutectic temperature was 37°C and the eutectic points occurred at approx. 0.18 and 0.82 mole fractions of S-IB. The extrapolation method gives accurate values of T_m for single phases such as R-IB, S-IB and rac-IB but becomes unreliable for mixtures of intermediate composition due to broadening in the eutectic and melting endotherms (Fig. 1). Hence, for constructing the phase diagram the temperatures at the peaks of the eutectic and melting endotherms (i.e., the end of fusion) were used. The peak temperatures are a function of mass of the sample, but the approximately constant sample mass (5 mg) reduces the possibility of mass-related effects when comparing results from different experiments. The eutectic melting peaks could not be observed for samples with compositions below about 0.18 mole fraction S-IB and above about 0.82 mole fraction S-IB due to their close proximity to the terminal enantiomeric melting peaks. The melting point of a 1:1 fused mixture of R-IB and S-IB coincided with the melting point of rac-IB. Additional points on the phase diagram were obtained by plotting the melting points of fused samples containing various proportions of rac-IB with either R-IB or S-IB (Fig. 3). These points were in accordance with the fact that admixture of a racemic compound with either of its component enantiomers will depress its melting point. The melting point of a racemic mixture would be the minimum temperature on a binary phase diagram, i.e., the eutectic point, and admixture with either pure

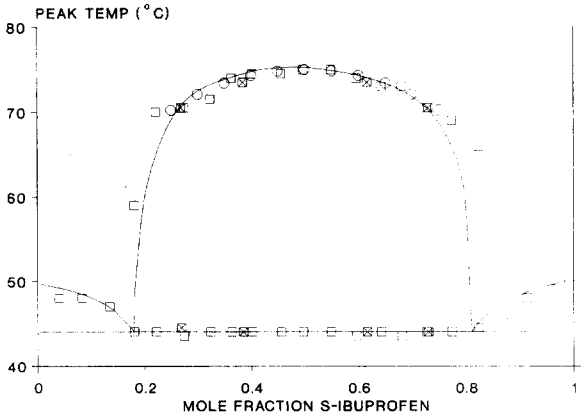

Fig. 3. Isobaric binary phase diagram of ibuprofen enantiomers showing racemic compound formation between S-IB and R-IB. (□) Fused, recrystallized, and annealed mixtures of R-IB and S-IB; (⊠) fused, recrystallized and annealed mixtures of R-IB and S-IB with rac-IB; (○) points calculated from the Prigogine-Defay equation; (◇) 99.7% S-IB from Ethyl Corp.

enantiomer would elevate it to higher temperatures.

In the phase diagram of a racemic compound, the absolute temperatures, T^f, on the liquidus curve, under which the racemic compound exists as a stable phase, can be predicted as a function of mole fraction enantiomeric composition, x, from its heat of fusion (ΔH_R^f) and absolute melting point (T_R^f, end of fusion) by using these quantities in the equation:

$$\ln 4x(1-x) = \frac{2\Delta H_R^f}{R} \cdot \left(\frac{1}{T_R^f} - \frac{1}{T^f} \right) \qquad (1)$$

where ΔH_R^f is assumed to be constant over the range of compositions for which T^f is predicted. This equation can be derived from that of Prigogine and Defay (1954). Fig. 3 demonstrates that the experimental liquidus curve determined from the DSC observations on IB was in good agreement with the liquidus curve predicted using Eqn 1. The prediction, however, is accurate only in the region of the congruent melting point (dystectic or indifferent point), but fails outside this region because the assumption of constancy of ΔH_R^f fails. The Prigogine-Defay equation was used by Bettinetti et al. (1990) and Pitre and Stradi (1990) to predict the binary phase diagrams of sobrerol and dropropizine, respectively.

A test of Eqn 1 is to plot ln $x(1-x)$ vs $1/T^f$, where T^f is determined experimentally. A linear plot should be obtained and ΔH_R^f can be calculated from the slope. For IB the plot was linear (Fig. 4) and the slope gave a ΔH_R^f value of 26.4 ± 1.89 kJ mol^{-1} which agreed with that of 26.9 ± 1.0 kJ mol^{-1} obtained directly from the area under the DSC melting endotherm of rac-IB.

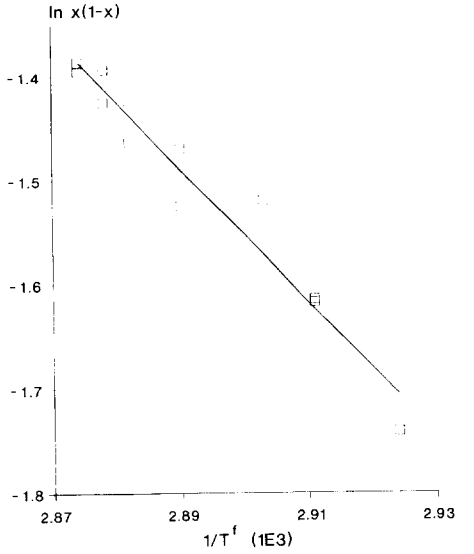

Fig. 4. Test of the Prigogine-Defay equation. The T^f values were experimentally determined from DSC. The slope affords the value of ΔH_R^f.

Dissociation of rac-IB in the liquid state

The continued existence in the liquid state of addition compounds, such as a racemic compound, in undissociated form was discussed in several early reports (Bancroft, 1899; Kremann, 1906; Findlay and Hickmans, 1907; Kendall and Booge, 1925; Ross and Somerville, 1926). An indication of the degree of dissociation can be obtained from the flatness of the liquidus curve in the dystectic region (Findlay, 1903; Rastogi, 1964). If a racemic compound remains completely undissociated upon melting, the dystectic point occurs as a sharp maximum in the phase diagram where the two liquidus curves appear to intersect. On the other hand, if the racemic compound dissociates, the products of dissociation, namely, the constituent enantiomers, depress the melting point. The two liquidus curves in the dystectic region become rounded as a result, and merge into each other forming one continuous flattened curve. The degree of rounding off will vary depending on the degree of dissociation. The liquidus curve on the IB phase diagram was rather flat and continuous over a wide range of enantiomeric compositions (from S-IB mole fractions of approx. 0.3 to 0.7, Fig. 3), indicating that rac-IB is largely dissociated in the liquid state.

The rate of dissociation of a binary addition compound is related to the degree of depression of the melting point. This can be verified by heating the compound at different rates (Bancroft, 1899). If the rate of dissociation is relatively low, then variation in the extent of dissociation at different heating rates will depress the melting point to different extents. An approx.

10-fold decrease in the heating rate from 20 to 2.5°C/min depressed the melting point of rac-IB by only about 3% (71.1 to 69.7°C), indicating that the rate of dissociation of rac-IB into its enantiomers upon melting is rapid.

Solubility

An isobaric melting-point vs composition phase diagram can be considered an inverse of the solubility vs composition phase diagram at constant pressure. Thus, the order of solubility of various compositions of IB according to Fig. 3 would be: eutetic-IB > R-IB or S-IB > rac-IB. The solubilities of these samples in pH 1.5 HCl-KCl solution at various temperatures agreed with this sequence. For example, at 25°C, the solubility of eutectic-IB (1.96×10^{-3} M) was nearly 1.1-times that of R-IB or S-IB (both 1.79×10^{-3} M) and 2.1-times that of rac-IB ($0.943-10^{-3}$ M). Despite the large number of racemic drugs currently in use, only a few examples of solubility differences at various enantiomeric compositions are available in the pharmaceutical literature (e.g., Repta et al., 1976; Liu and Hurwitz, 1978; Schmidt et al., 1988).

Solubility-temperature plots

The solubility vs temperature data of IB were treated based on two commonly used linear solubility-temperature relationships: van't Hoff plots of ln(solubility) vs the inverse of absolute temperature, $1/T$, and Hildebrand plots of ln(solubility) vs ln T.

The van't Hoff plots of IB given in Fig. 5a are based on the following integrated form of the van't Hoff isochore:

$$\ln s_2 = -\frac{\Delta H_s^*}{R} \cdot \frac{1}{T} + c \qquad (2)$$

where s_2 represents mole fraction solubility (the subscript 2 denotes a solute: IB in this case), ΔH_s^* is the apparent partial molar enthalpy of solution of the solute, R denotes the gas constant (8.3143 J K^{-1} mol^{-1}), and c is the constant of integration. The slope of a plot of ln s_2 vs $1/T$ yields ΔH_s^*, which is generally assumed to be independent of T.

The Hildebrand plots (Hildebrand, 1952; Hildebrand and Scott, 1962; Fig. 5b) are based on

$$\ln s_2 = \frac{\Delta S_2^*}{R} \cdot \ln T + c \qquad (3)$$

where ΔS_2^* is the apparent partial molar entropy of solution of the solute, and is approximately equal to ΔC_{p_2}, the change in the partial molar heat capacity of the solute (Hildebrand and Scott, 1962). Other terms have the same meaning as in Eqn 2. Since there is a proportional relationship between the mole fraction solubility and molar solubility, and since the solutions of the different

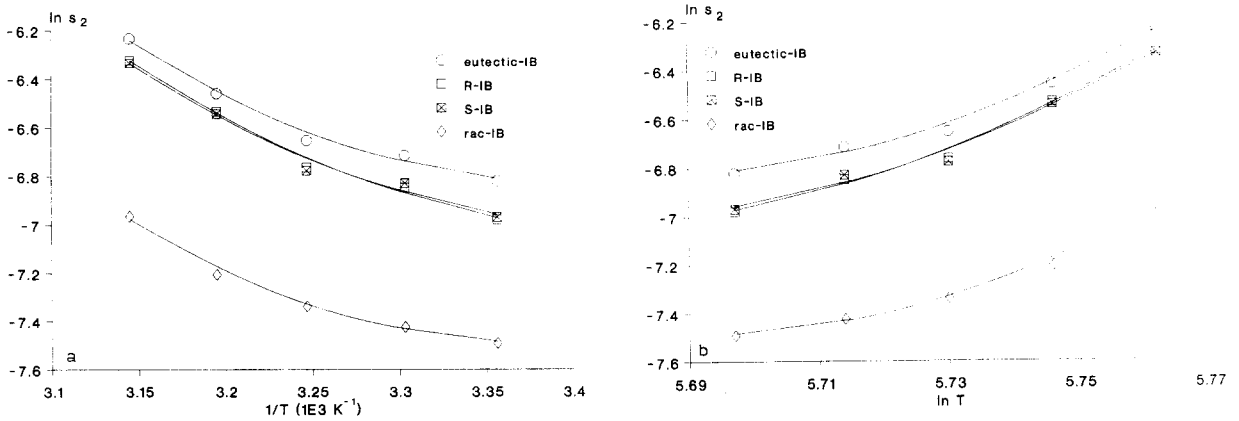

Fig. 5. (a) Van'T Hoff plots, and (b) Hildebrand plots, for various compositions of IB. The curves are calculated from multiple regression according to Eqn 4.

enantiomeric compositions of IB studied were dilute, molar solubility was used in Eqns 2 and 3.

Non-linearity of IB solubility-temperature plots

The plots corresponding to Eqns 2 and 3 were non-linear for rac-IB, R-IB, S-IB and eutectic-IB (Figs. 5a and b). Romero and Rhodes (1991) recently reported linear van't Hoff plots for S-IB and rac-IB over a similar temperature range to that used in this work. However, their samples were analyzed after 24 h agitation whereas we found up to 8 days were required for equilibration at 25°C.

Non-linearity in solubility-temperature plots is usually, and sometimes incorrectly, ascribed to a discontinuity in the slope and interpreted as a phase transition of some sort, e.g., polymorphism or solvate formation (Grant et al., 1984). DSC experiments, powder X-ray diffraction, and the phase diagram of IB enantiomers ruled out the possibility of any phase transition except eutectic melting at the highest temperatures (40 and 45°C) at which the solubilities were determined. The eutectic melting could increase the rate of dissolution, but the nearly parallel nature of the van't Hoff and Hildebrand plots of eutectic-IB (Fig. 5a and b) relative to the plots of R-IB, S-IB and rac-IB suggests that the equilibrium solubilities are not affected. The experimental techniques were designed to minimize volatilization of IB and non-linearity in the solubility-temperature plots of IB is assumed to be due to factors other than a phase transition.

Grant et al. (1984) recommended the following multiple regression model for studying non-linear solubility-temperature plots:

$$\ln s_2 = -\frac{a}{R} \cdot \frac{1}{T} + \frac{b}{R} \cdot \ln T + c \qquad (4)$$

where a, b and c are constants. The constant $b = \Delta C^*_{p_2}$, and represents ΔS^*_2 in Eqn 3. The constant c can be shown to equal $-(\Delta C^*_{p_2} + \Delta S^*_2)/R$. Eqns 2 and 3 are special cases of Eqn 4 when $b = 0$ and $a = 0$, respectively. Recently, Prankerd and McKeown (1990) used the Valentiner equation, a multiple regression equation analogous to Eqn 4, for analyzing the solubility-temperature dependence for several barbituric acid derivatives.

Table 1 gives details of the statistical treatment of the solubility-temperature data for the various IB samples using Eqns 2–4. The multiple regression model based on Eqn 4 produced the best statistical fit as indicated by the corresponding higher overall F ratios and correlation coefficients (r^2) for all enantiomeric compositions. Residual vs temperature plots for each enantiomeric composition showed that the plots for Eqns 2 and 3 were curved while the corresponding plot for Eqn 4 was parallel to the temperature axis with the residuals evenly distributed around zero, confirming that the multiple regression model best fits the solubility data.

Grant et al. (1984) applied the multiple regression model to the experimental aqueous solubilities of a number of solutes and explained that the

TABLE 1

Regression parameters for the relationship between solubility and absolute temperature for various enantiomeric compositions of ibuprofen in aqueous HCl-KCl solution, pH 1.5

Sample	(r^2) for			F ratio [a]		
	Eqn 2	Eqn 3	Eqn 4	Eqn 2	Eqn 3	Eqn 4
Eutectic-IB	−0.968	0.971	0.992	45.55	49.12	123.5
R-IB	−0.981	0.983	0.993	76.46	83.81	134.2
S-IB	−0.975	0.975	0.985	56.84	61.25	67.1
rac-IB	−0.960	0.962	0.994	34.81	37.31	169.3

[a] Overall F ratio taking into account the differences in the degrees of freedom between the three regression equations. These ratios were significant at > 99% level except for Eqn 4 for S-IB which was significant at the 98.5% level.

non-linear changes in the solubility of a hydrophobic solute with temperature in an associated solvent arise from the relatively large changes in the partial molar heat capacity of the solute with temperature, i.e., the term b in Eqn 4. Such changes can be ascribed to a large apparent partial molar heat capacity of the solute in the solvent. This will be especially true in the present work where a hydrophobic solute, IB, is dissolved in a highly associated solvent, such as aqueous HCl-KCl.

Enthalpy, entropy and free energy of formation of rac-IB

The formation of the racemic compound of IB from an equal number of moles of R-IB and S-IB is described by the following reaction:

R-IB + S-IB ⇌ rac-IB

Leclercq et al. (1976) gave expressions for obtaining the enthalpy (ΔH^R), the entropy (ΔS^R) and the free energy (ΔG^R) changes which accompany the crystallization of a racemic compound. If ΔH_A^f, ΔC_{p_R}, and T_A^f are the enthalpy of fusion of the enantiomer, the difference in heat capacity between the supercooled liquid and the solid racemic compound, and the melting point of the enantiomer, respectively, then, for IB, where $T_A^f < T_R^f$, the following expressions apply:

$$\Delta H_{T_A^f}^R = \Delta H_A^f - \Delta H_R^f + \Delta C_{pR} \cdot \left(T_R^f - T_A^f\right) \qquad (5)$$

$$\Delta S_{T_A^f}^R = \Delta S_A^f - \Delta S_R^f + R \cdot \ln 2 + \Delta C_{p_R} \cdot \ln \frac{T_R^f}{T_A^f} \qquad (6)$$

$$\Delta G_{T_A^f}^R = \Delta H_R^f \cdot \left(\frac{T_A^f}{T_R^f} - 1\right) - T_A^f \cdot R \cdot \ln 2 + \Delta C_{p_R} \cdot \left(T_R^f - T_A^f - T_A^f \cdot \ln \frac{T_R^f}{T_A^f}\right) \qquad (7)$$

The subscript T_A^f indicates that these quantities are calculated at the absolute melting temperature of the enantiomers. For rac-IB the values of $\Delta H_{T_A^f}^R$, $\Delta S_{T_A^f}^R$, and $\Delta G_{T_A^f}^R$ were −6.3 kJ mol^{-1}, −16.3 J K^{-1} mol^{-1} and −3.77 kJ mol^{-1}, respectively. A negative $\Delta H_{T_A^f}^R$ indicates a liberation of energy during the formation of rac-IB from R-IB and S-IB. Any energy change in the above reaction is additional evidence that rac-IB is a racemic compound, and not a racemic mixture.

Since the value of ΔC_{p_R} is small (30 ± 3 J K^{-1} mol^{-1} from DSC), the term including ΔC_{p_R} in Eqn 7 contributes negligibly to the value of $\Delta G_{T_A^f}^R$ and hence can be neglected. Thus, Eqn 7 can be simplified to the following linear form (Jacques et al., 1981):

$$\Delta G_{T_A^f}^R \approx \Delta S_R^f \cdot \left(T_R^f - T_A^f\right) - T_m \cdot R \ln 2 \qquad (8)$$

where $\Delta S_R^f = \Delta H_R^f / T_R^f$, the entropy of fusion of a racemic compound, and T_m is an 'average' melting point of racemic compounds (Jacques et al., 1981). Leclercq et al. (1976) showed that a plot of $\Delta G_{T_A^f}^R$ vs $T_R^f - T_A^f$ for about 40 different racemic compounds was linear with a slope of 71 J K^{-1} mol^{-1} indicating that the entropy of fusion for racemic compounds approximates a constant. The ΔS_R^f (Table 2) of rac-IB from DSC was 78.1 ± 2.9 J K^{-1} mol^{-1} which is in good agreement with this constant considering that the ΔS_R^f values of the compounds used for the plot of Eqn 8 by Leclercq et al. (1976) ranged from 59.4 to 115.9 J K^{-1} mol^{-1}. The entropy of fusion for the enantiomers was 62.4 ± 2.5 J K^{-1} mol^{-1}. The ratio of 78.1/62.4 is a rough measure of the degree of interaction between IB enantiomers in the racemic compound. This ratio would be ap-

TABLE 2

Thermodynamic parameters obtained from differential scanning calorimetry of various compositions of ibuprofen

Sample	T_m (K)	ΔH^f (kJ mol^{-1})	ΔS^f (J K^{-1} mol^{-1})
Eutectic-IB	310	–	–
R-IB	319.5	–	–
S-IB	319	19.9 ± 0.8 [a]	62.4 ± 2.5 [a]
		19.5 ± 0.3 [b]	–
rac-IB	344	26.9 ± 1.0	78.1 ± 2.9

[a] Mean ± S.D. (n = 3).

[b] Value determined using hermetically sealed volatile pans.

proximately equal to unity if rac-IB were a racemic mixture.

The phase diagram, X-ray analysis and the thermodynamic evidence all indicate that IB USP is a racemic compound and that the USP XXII (1990) monograph description of IB as a '(±) mixture' is ambiguous.

Currently, there is a great interest in the significance of drug chirality in pharmaceutical development and regulation (Hutt, 1991) and increasing emphasis is being placed on the use of single enantiomers, rather than the racemic drug, in dosage forms. In addition to pharmacokinetic differences between rac-IB and its enantiomers (e.g., Jamali et al., 1988; Ahn et al., 1991; Beck et al., 1991), the differences between the thermodynamic properties of S-IB and rac-IB should be considered if a decision is made to use S-IB rather than rac-IB in solid dosage forms.

Acknowledgements

The authors thank the various suppliers for the gift of IB samples used in this study, Dr A.H.L. Chow for helpful discussion of the solubility data, the Medical Research Council of Canada for financial support, and the Berlex Foundation of U.S.A. for a fellowship to S.K.D.

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