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Scalemic Mixtures Preparation for Optimized Composition of Ibuprofen Solid Dosage Forms

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ABSTRACT

The stable and metastable phase diagrams between the *sinister* and the *rectus* ibuprofen enantiomers were established by means of thermal analysis and X-ray powder diffraction experiments as a function of temperature. The results obtained allow proving for the first time the existence, for the stable system, of a solid solution by mixing the ibuprofen racemate with one of its enantiomers for low concentration of the enantiomer. Since the *rectus* ibuprofen is a non-active pharmaceutical agent which can be partially bio-converted into the *sinister* enantiomer, the present work offers a new approach for scalemic mixtures preparation in order to improve the benefit/risk ratio related to ibuprofen administration.

KEYWORDS

Drug-drug interaction; Enantiomeric mixtures; Thermal behavior; X-ray pattern; Phase diagram; Solid solution; Racemate

INTRODUCTION

Racemate ibuprofen is one of the most non-steroidal anti-inflammatory drugs used in the pharmaceutical field [1, 2]. RS- ibuprofen crystallizes in the monoclinic $P2_{1/c}$ lattice [3-6] while the chiral counterpart, or enantiomer, crystallizes in the monoclinic $P2_1$ [4, 7-9]. The ibuprofen *rectus* enantiomer has no therapeutic activity and is partially stocked in the adipose tissues (~ 30% of the total ibuprofen dose) – the other part being bio-converted in the *sinister* enantiomer which is the pharmaceutical active form [2, 10-16]. Such bio-conversion pathway may contribute to the *in vivo* sustained ibuprofen action. In a physicochemical point of view, previous phase diagrams between ibuprofen enantiomers were reported in the literature [4, 17, 18]. All the results agree to state that a eutectic system is formed between one enantiomer and the racemate. But contradictory results are reported especially for the location of the eutectic point and the eutectic melting point. Indications are given about an unstable phase encountered near the eutectic point but the results were unexploited [17]. Moreover, on each of the three phase diagrams [4, 17, 18], the eutectic invariant near the pure components has never been observed and no clear explanations have been given. However, a complete immiscibility domain in the solid state is proposed from $x = 0$ to 0.5 and from $x = 0.5$ to 1. On this statement, we decided to examine carefully the thermal behavior of the stable and metastable phases from samples prepared from pure enantiomers and from mixtures between one enantiomer and the racemate. On the basis of these experiments, a new stable phase diagram is thus proposed, and the contribution of a metastable system is discussed.

MATERIALS AND METHOD

Chemicals. S- and RS-ibuprofen were purchased from Acros Organics (99% purity). R-ibuprofen was purchased from Santa Cruz Technology (purity higher than 98%). The components were used as received.

Binary mixture preparations. The compounds were separately weighted, then gently mixed by grinding in a mortar during 5 minutes at room temperature.

Thermal experiments. The DSC runs were performed at $2 \text{ K}\cdot\text{min}^{-1}$ under atmosphere of dry nitrogen gas, using a differential scanning calorimeter 822e (Mettler-Toledo, Switzerland), calibrated beforehand using high purity indium (99.9 % provided by Mettler-Toledo. $T_{\text{fus}} = 156.6 \text{ }^\circ\text{C}$; $\Delta_{\text{fus}}H = 28.45 \text{ J}\cdot\text{g}^{-1}$) and zinc (99.9 % provided by Mettler-Toledo. $T_{\text{fus}} = 409.6 \text{ }^\circ\text{C}$; $\Delta_{\text{fus}}H = 107.50 \text{ J}\cdot\text{g}^{-1}$). The samples were introduced in DSC aluminum pans at room temperature, and then hermetically sealed.

X-ray powder diffraction experiments. X-ray data collection was performed on a home-made diffractometer with a Rigaku RA-HF18 rotating anode generator (50 kV, 300mA). Monochromatic Cu $K_{\alpha 1}$ ($\lambda = 1.5406 \text{ \AA}$) radiation was selected by means of a nickel filter. The sample was placed inside a cryofurnace (TBT - Air Liquide) with a temperature range between -190 and 210 °C, using liquid nitrogen. Each data scan was recorded between 4 and 30 deg. in 2θ , with a step size of 0.02 deg. and a counting time of 1 second per step.

RESULTS AND DISCUSSION

To apprehend the stable phase diagram, thermal analyses were carried out on scalemic mixtures prepared from R- or S- and RS-ibuprofen. The *sinister* and racemate compounds have previously been characterized thermodynamically in our group by using calorimetry experiments [19]. With regard to the R-ibuprofen enantiomer, the results are clearly comparable to those of the S- enantiomer.

As far as the establishment of the phase diagram is concerned, selected DSC curves are presented in Figure 1. For mixtures containing less than 85% of enantiomer (R- or S-), two endothermic signals were observed. The first one takes place at constant temperature and corresponds, undoubtedly, to the crossing of a eutectic invariant, as previously reported in the literature [4, 17, 18]. The second endothermic signal necessarily refers to the crossing of the (liquid + RS-ibuprofen) biphased region ending by the crossing of the liquidus curve.

The mean eutectic temperature value, obtained from the DSC experiments, is equal to $48.8 \pm 0.7 \text{ °C}$ and is in close agreement with the previous reported values of 48 °C for Romero and Rhodes [4] as well as Burger *et. al* [17], but disagrees with the value found by Dwivedi *et al.* (*i.e.* 37 °C) [18].

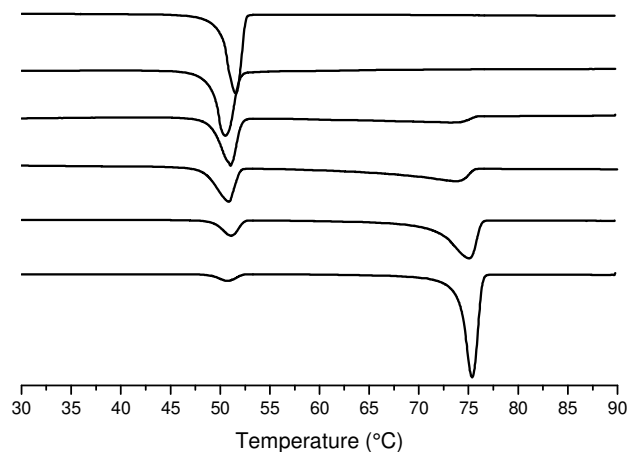


Figure 1. Selected DSC curves of mixtures containing RS- and S-ibuprofen as a function of the mol fraction in R-ibuprofen (from top to bottom): 0.02, 0.09, 0.25, 0.30, 0.42 and 0.46.

For mixtures containing more than 85% of enantiomer (R- or S-), only 1 endothermic peak is observed (*cf.* the two upper curves in Figure 1). The same statement is made when the mixtures are freshly prepared from R and S enantiomers. Even after 56 days of annealing at room temperature, no change is observed on the shape of the DSC signals. This suggests that the so-obtained samples are stable over the time. Furthermore, the related onset temperatures are slightly higher than those of the stable eutectic invariant for mixtures enriched in one enantiomer. This could indicate, the presence of a partial solid solution [20] between R- and S-ibuprofen near the pure enantiomer fractions.

Unfortunately, the region of demixing could not have been detected by DSC due, certainly, to endothermic effects too small. Consequently, the solubility curve of RS-ibuprofen, between the two eutectic points, was examined using the Prigogine-Defay equation [21]:

$$\ln(4x.(1-x)) = \frac{\Delta_{fus}H}{R} \cdot \left(\frac{1}{T_{fus}} - \frac{1}{T_x} \right)$$

where x stands for the mol fraction in enantiomer; T_x , the liquidus temperature of the corresponding mixture. $\Delta_{fus}H$ and T_{fus} are respectively the enthalpy and the temperature of fusion of the racemate. R is the gas constant. The temperatures are in Kelvin.

The plot of $\ln[4x.(1-x)]$ vs. $(1/T_{fus}-1/T_x)$ is linear (**Figure 3**). The melting enthalpy of the racemic compound is deduced from the slope of the straight line: $\Delta_{fus}H = 53.6 \pm 2.7$ kJ per mol of RS-ibuprofen, *i.e.* 26.8 ± 1.4 kJ.mol⁻¹ on the basis of ½ mole of each enantiomer. This value is in agreement with the one found from DSC experiments (25.5 ± 0.3 kJ.mol⁻¹).

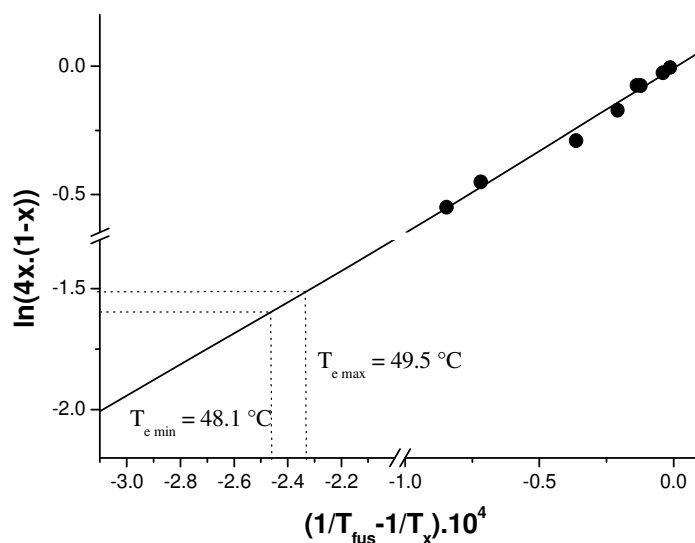


Figure 2. Dependence of mole fraction with the liquidus temperature using the Prigogine-Defay model.

The linearity of the plot of $\ln[4x \cdot (1-x)]$ against $(1/T_{fus} - 1/T_x)$ implies the complete dissociation, in the molten state, of the racemate, as suggested by Rastogi and Nigam for the stability study in the liquid state of addition compounds [22]. This complete dissociation involves, as well, an ideal state for the liquid state (*i.e.* no excess quantities in the liquid). This is the reason why the solubility curve of RS-ibuprofen follows an ideal behavior, as it will be confirmed further below.

The two extreme data points in Figure 2 correspond to the racemate melting point ($x = 0.5$) and the eutectic point. Since the eutectic temperature was determined to be comprised between 48.1 and 49.5 °C, it comes that, from that graph, the eutectic composition can be extrapolated for both limits (dotted lines) and the mean value is equal to $x_e = 0.056 \pm 0.003$ mol fraction in enantiomer.

To highlight the solid solution obtention for mixtures enriched in one enantiomer, scalemic mixtures of R- and S-ibuprofen were freshly prepared in the solid state before thermal analysis investigations, since ibuprofen does not spontaneously recrystallize from its molten state. The corresponding DSC thermograms are presented in Figure 3.

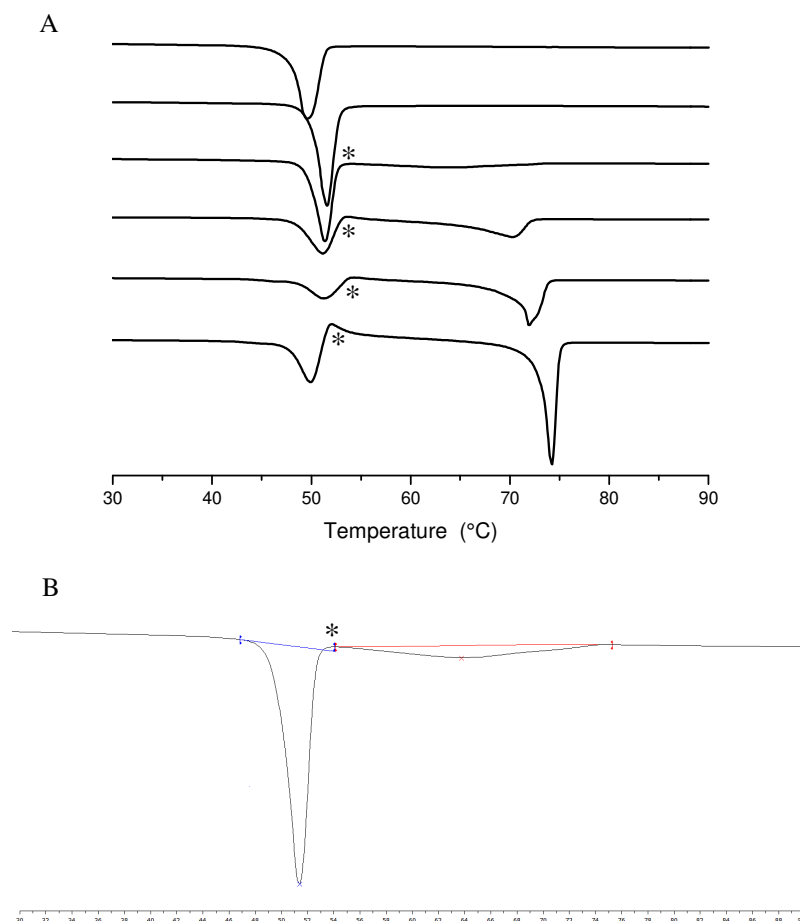


Figure 3. (A) Selected DSC curves of mixtures containing R- and S-ibuprofen as a function of the mol fraction in R-ibuprofen (from top to bottom): 0.05, 0.10, 0.15, 0.28, 0.38 and 0.50. (B) The DSC curve obtained for 0.15 mol fraction in R-ibuprofen sample after integration by using the STARe software (version 15.00) from Mettler-Toledo. The recrystallization events are marked with an asterisk (*).

For composition comprised between the 2 eutectic points (*i.e.* for mol fractions comprised between 0.06 and 0.94 in R-ibuprofen), one can observe an exothermic signal appearing just after the first endothermic signal. The first signal can be attributed to the melting of the metastable solid solution – due to partial miscibility in the solid state [20] – formed between both enantiomers. The formation of such a solid phase has been also confirmed by X-ray experiments performed with S- and R-ibuprofen mixture samples ($x_{R\text{-ibuprofen}} = 0.01$ and 0.37) annealed at temperature higher than room temperature (Figure 4). Interestingly, when the scalemic mixture is composed of an enriched fraction of one of the enantiomers (*e.g.* $x_{R\text{-ibuprofen}} = 0.01$), the annealing protocol at 47 °C does not change the phase contrary to $x_{R\text{-ibuprofen}} = 0.37$ samples which transform into RS/S physical mixtures.

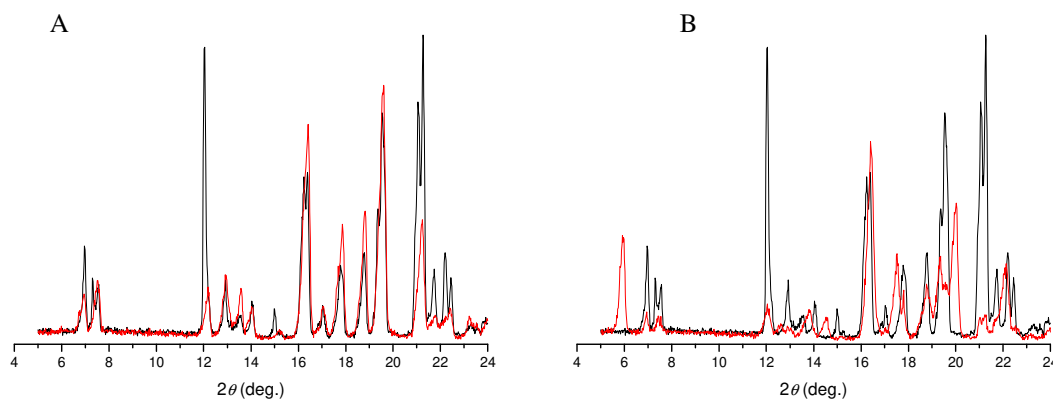


Figure 4. X-ray powder diffraction patterns obtained at room temperature for s-ibuprofen (—), and R- and s-ibuprofen mixtures after 6 days annealing (—). (A) $x_{R\text{-ibuprofen}} = 0.01$ and $T_{\text{annealing}} = 47\text{ }^{\circ}\text{C}$, (B) $x_{R\text{-ibuprofen}} = 0.37$ and $T_{\text{annealing}} = 40\text{ }^{\circ}\text{C}$.

The two different **thermal** behaviors confirm that the metastable domain is formed by a solid solution with lower melting temperatures than that of the stable eutectic invariant between 0.06 and 0.94 in the chiral counterpart. As far as the second endothermic signal **from the DSC results** is concerned, it corresponds to the recrystallization in the stable state of the liquid obtained after the melting process of the solid solution (Figure 3). Upon heating, after the recrystallization, another **endothermic** signal takes place. This signal is identical to the one obtained, at the same mol fraction, from mixtures prepared from one enantiomer and the racemate. As a result, this signal corresponds to the crossing of the liquidus curve. **Interestingly, the recrystallization phenomenon highlighted upon heating is followed by a liquidus event (Figure 3) at the same temperature as that of the liquidus event of the stable system (Figure 1), while no recrystallization and no second endothermic signals were noticed for the mixtures enriched in one enantiomer.**

When the samples are annealed, at room temperature, for 56 days (Figure 5), the first endotherm is shifted to higher temperature corresponding to the eutectic one, and the exothermic event disappears. Concerning the liquidus point, it remains unchanged. This clearly indicates that the solid solution melts at lower temperature than the (S+RS) or (R+RS) mixtures. This entails that the solid solution is a metastable phase compared to the mixtures between one enantiomer and the racemate in the mol fraction range 0.06 – 0.94 in R-enantiomer.

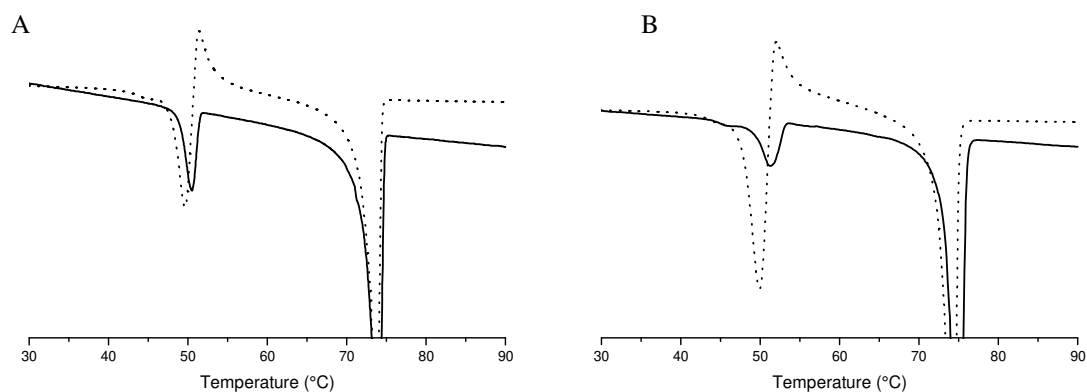


Figure 5. Effect of the time on the stability of the R/S-ibuprofen mixtures. DSC curves obtained for the freshly prepared samples (dotted line), and for the same composition sample after 56 days annealing at room temperature (solid line). Mol fraction in R-ibuprofen: (A): 0.42; (B): 0.50.

All these findings allow us to propose the stable and metastable temperature-composition (T-x) phase diagrams presented in Figure 6 as a function of the mol fraction in R-enantiomer. The stable phase diagram has the same shape as the menthol dextrorotatory/levorotatory stable diagram established by our group in 2012 [23]. However, in the case of the ibuprofen study, the solution solid melting points (metastable phase) and the invariant points (stable phase) are close from one to another, regardless of the mixture composition. This can be explained by the fact that both racemate and enantiomer crystallize in the monoclinic $P2_1$ lattice, the former being centrosymmetric. Furthermore, variation of the molecular volume between S- and RS- ibuprofen, $\Delta(\%)$, has been determined from crystal structure of the related racemate [3, 5] and chiral counterpart [8, 9] in order to check if the Wallach's rule [24, 25] can be applied in the case of ibuprofen. Interestingly, ibuprofen verify the Wallach's rule between room and cold temperatures since $\Delta(\%)$ is 1.9%, and 2.4% at 25 and -173 °C, respectively. For that range of temperature, one can confirm that racemic crystal of ibuprofen is denser than its chiral counterparts. Noteworthy, according to Wallach or Brock, RS-ibuprofen belongs to group II, *i.e.* the group of chemical compounds presenting enantiomers that can be resolved. The relative stability of the racemic ibuprofen over its enantiomers can be also confirmed by determining the Petterson value i [26, 27], or the Gibbs free energy of the $R + S = RS$ transformation at the melting temperature of the chiral counterpart since $T_{\text{fus, S- or R-ibuprofène}} < T_{\text{fus, RS-ibuprofen}}$ [27, 28]. Indeed, stable racemic compounds should present $i > 1.5$ and $\Delta G^\circ \ll 0$. From the data of the present study, the i and $\Delta G^\circ(T_{\text{fus, S- or R-ibuprofen}})$ values have been calculated as follows: 9.6 (non-dimensional data) and -3.6 kJ.mol^{-1} respectively.

Notably, Li *et al.* have obtained the same $\Delta G^\circ(T_{\text{fus, S- or R-ibuprofen}})$ value for racemic ibuprofen [28]. Finally, to complete the stable phase diagram survey, a 48.8 °C temperature invariant is also proposed via data analysis (Figure 6). The composition range of this invariant is comprised between 0.03 and 0.97.

Simulation of the metastable phase diagram was performed using the LIQFIT thermodynamic method [29], taking into consideration the thermal properties of the enantiomers. Thus, a Roozeboom's type III diagram has been obtained [21, 29-31], confirming the existence of a solid solution between the two ibuprofen enantiomers. The related solidus and liquidus temperatures decrease when approaching the equimolar composition from the pure chiral counterpart composition (Figure 6, red curves). At a given composition on the rich-enantiomer part of the diagram, the small difference of temperature between the solidus and the liquidus justifies that the two beginnings of melting loops are merged when the composition approaches the center of the diagram. This results in the existence of a continuous solid solution that is metastable between the two eutectic points, *i.e.* in the 0.06 – 0.94 composition range. Over this range, the solid solution is the stable phase of the scalemic mixtures. Interestingly, by comparing this range to the 0.03 – 0.97 range of the eutectic invariant, one can deduce a symmetrical $\Delta x = 0.03$ for the crossing regions between the stable enantiomer/racemic physical mixture and the stable scalemic solid solution. In addition, the Roozeboom's type III diagram presents a single point at $x = 0.5$, suggesting the existence of a pseudo-racemate which melts at 47.2 °C. This racemic solid solution might correspond to a new polymorph different from the one discovered by Dudognon *et al.* which melts at 17 °C, namely RS-ibuprofen phase II [32]. Also, the modelling gives rise to two minima ($x = 0.20$ and 0.80) for the metastable phase diagram. These points do not necessarily have a physical meaning but were the only solution of the modelling from the experimental points.

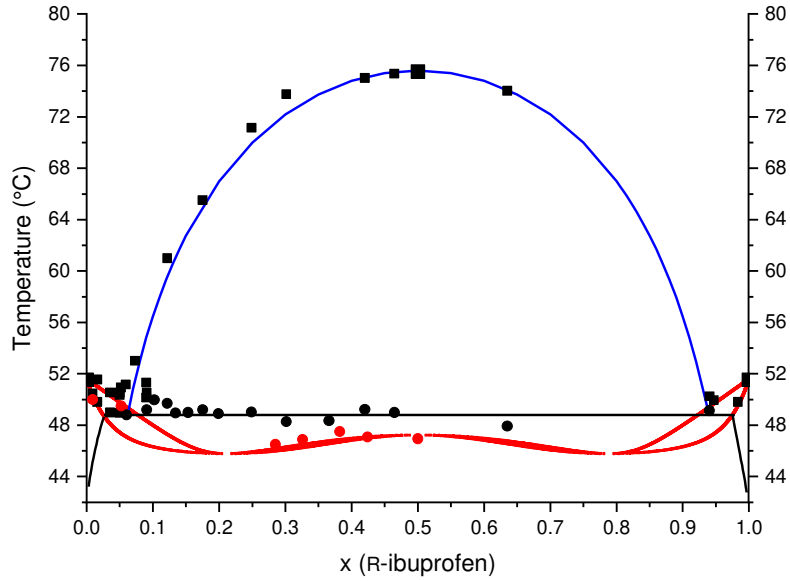


Figure 6. Stable and metastable T-x phase diagrams established between the chiral counterparts of ibuprofen. The experimental data obtained from the DSC results interpretations (full circles and squares) were modeled for the eutaxia (horizontal —), the liquidus (—), and the solid solution (—).

The proposed phase diagram was comforted by X-ray diffraction powder experiments performed as a function of temperature. Indeed, mixtures of *sinister* and racemate ibuprofen ($X_{R-ibuprofen} \sim 0.01$) were studied between 22 and 52 °C. The diffraction patterns are presented in Figure 7.

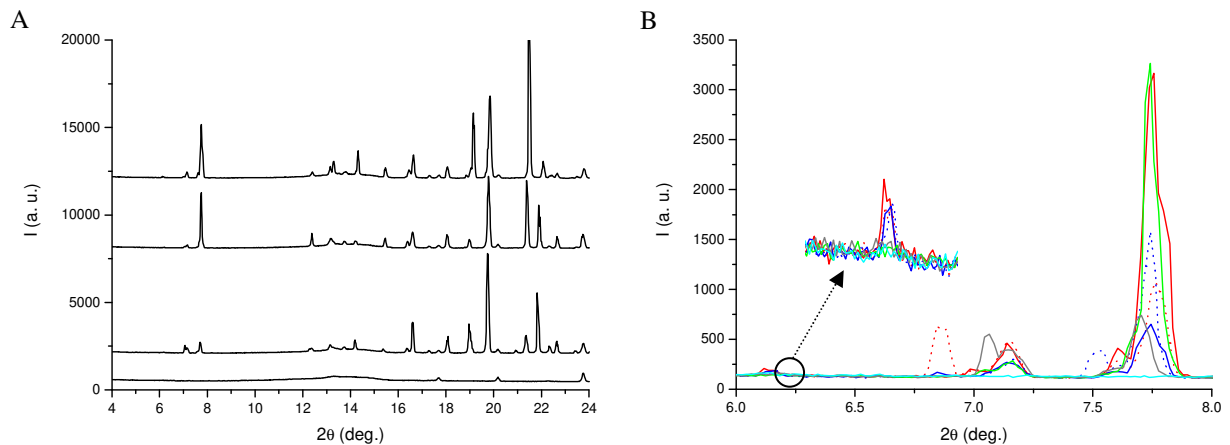


Figure 7. X-ray powder diffraction patterns obtained for a given RS- and S-ibuprofen mixture, $X_{R-ibuprofen} = 1\%$, as a function of temperature. (A) Temperature: 22, 42, 47, and 52 °C, from the top curve to the bottom curve, respectively. (B) Patterns for 2θ scale comprises between 6 and 8 deg. Temperature: (—) 22, (····) 27, (—) 32, (····) 37, (—) 42, (—) 47, and (—) 52 °C.

The $x_{R\text{-ibuprofen}} = 1\%$ sample formulated between S- and RS-ibuprofen is a physical mixture at room temperature since one can observe on the corresponding XPRD pattern a superposition of racemate and enantiomer signal (Figure 7A) [19]. However, before melting, the physical mixture transits to a solid solution as expected from the thermal analysis experiments (Figures 1, 3 and 6). The latter transition takes place between 37 and 42 °C. Indeed, the peak at 6.1 deg. which belongs to the racemate ibuprofen XPRD pattern disappears in the patterns recorded from 42 °C, presenting the solid solution XPRD signals (Figure 7B). The X-ray diffraction experiments hence confirm the assumption if the solid solution between $x_{R\text{-ibuprofen}} = 0$ and 0.06, as well as for the symmetric composition. Consequently, the pseudo-racemate that has been highlighted in the present work ($T_{\text{fus}} = 47$ °C) is a solid solution formed from the stable chiral counterparts in equimolar proportions. This solid solution may correspond to the "unstable phase near the eutectic point" proposed by Burger and co-workers [17] although it is stable for mol fraction of enantiomer comprise between 0 to 0.06, but metastable for mol fraction of enantiomer higher than 0.06 since the stable state is, in such a case, the physical mixture between the racemate and one of the enantiomer.

CONCLUSIONS

The *rectus/sinister* ibuprofen stable phase diagram proposed here is an overlapping of a Roozeboom's type III solid solution curve with the racemate solubility curve, crossing at low concentration of one of the enantiomers. The existence of the solid solution has been demonstrated in this work for the first time and corresponds to the scalemic S+R-ibuprofen mixtures that are stable for mol fractions in enantiomer lower than 6% and metastable for higher values until 94%. As far as the latter range of concentrations is concerned, the stable state is the S+RS-ibuprofène or R+ RS-ibuprofen eutectic mixtures. The kinetics of metastability vs stability conversion has also been apprehended by annealing of the materials at room temperature. Such data can be of interest for preparation of non-steroidal anti-inflammatory drugs with new ratio of ibuprofen chiral counterparts with optimized bioavailability, pharmacokinetics, metabolism, and toxicity parameters. As an example, amphetamine can be marketed either in its racemic form (Eveko[®], approved by the FDA in 2012) or as a 75:25 S:R scalemic mixture (Adderall[®], approved by the FDA in 1996). Therefore, Adderall[®] can be considered as a formulation with improved therapeutic effect

since differences in onset and duration of action between the S- and R-amphetamine have been described in rats [33, 34] and a stereospecific metabolism of amphetamine has been evidenced in human [35, 36] and rat [37-39] *in vivo* studies.

References

- [1] S. Srisanga, J.H. ter Horst, Racemic compound, conglomerate, or solid solution: Phase diagram screening of chiral compounds, *Cryst. Growth Des.*, 10 (2010) 1808-1812. <https://doi.org/10.1021/cg901483v>
- [2] T. Lee, Y.H. Chen, Y.W. Wang, Effects of homochiral molecules of (s)-(+)-ibuprofen and (s)-(-)-sodium ibuprofen dihydrate on the crystallization kinetics of racemic (r,s)-(\pm)-sodium ibuprofen dihydrate, *Cryst. Growth Des.*, 8 (2008) 415-426. <https://doi.org/10.1021/cg070045c>
- [3] J.F. McConnell, The 2-(4-isobutylphenyl) propionic acid. Ibuprofen or profen, *Cryst. Struct. Commun.*, 3 (1974) 73-75.
- [4] A.J. Romero, C.T. Rhodes, Stereochemical aspects of the molecular pharmaceuticals of ibuprofen, *J. Pharm. Pharmacol.*, 45 (1993) 258-262. <https://doi.org/10.1111/j.2042-7158.1993.tb05549.x>
- [5] N. Shankland, C.C. Wilson, A.J. Florence, P.J. Cox, Refinement of ibuprofen at 100 k by single-crystal pulsed neutron diffraction, *Acta Crystallogr., Sect. C*, C53 (1997) 951-954. <https://doi.org/10.1107/S0108270197003193>
- [6] P. Derollez, E. Dudognon, F. Affouard, F. Danede, N.T. Correia, M. Descamps, Ab initio structure determination of phase ii of racemic ibuprofen by x-ray powder diffraction, *Acta Crystallogr., Sect. B*, 66 (2010) 76-80. <https://doi.org/10.1107/S0108768109047363>
- [7] A.A. Freer, J.M. Bunyan, N. Shankland, D.B. Sheen, Structure of (s)-(+)-ibuprofen, *Acta Crystallogr., Sect. C*, C49 (1993) 1378-1380. <https://doi.org/10.1107/S0108270193000629>
- [8] L.K. Hansen, G.L. Perlovich, A. Bauer-Brandl, Redetermination and h-atom refinement of (s)-(+)-ibuprofen, *Acta Crystallogr., E*, 59 (2003) o1357-o1358. <https://doi.org/10.1107/S160053680301451X>
- [9] M.D. King, W.D. Buchanan, T.M. Korter, Understanding the terahertz spectra of crystalline pharmaceuticals: Terahertz spectroscopy and solid-state density functional theory study of (s)-(+)-ibuprofen and (rs)-ibuprofen, *J. Pharm. Sci.*, 100 (2011) 1116-1129. <https://doi.org/10.1002/jps.22339>
- [10] E.J.D. Lee, K. Williams, R. Day, G. Graham, D. Champion, Stereoselective disposition of ibuprofen enantiomers in man, *Br. J. Clin. Pharmacol.*, 19 (1985) 669-674. <https://doi.org/10.1111/j.1365-2125.1985.tb02694.x>
- [11] R.F.N. Mills, S.S. Adams, E.E. Cliffe, W. Dickinson, J.S. Nicholson, Metabolism of ibuprofen, *Xenobiotica*, 3 (1973) 589-598. <https://doi.org/10.3109/00498257309151547>
- [12] W.J. Wechter, D.G. Loughhead, R.J. Reischer, G.J. Van Giessen, D.G. Kaiser, Enzymic inversion at saturated carbon. Nature and mechanism of the inversion of r(-) p-isobutyl hydratropic acid, *Biochem. Biophys. Res. Commun.*, 61 (1974) 833-837. [https://doi.org/10.1016/0006-291X\(74\)90231-9](https://doi.org/10.1016/0006-291X(74)90231-9)
- [13] S. Kirkiacharian, Guide de chimie médicinale et médicaments, in, Éditions Tec & Doc, Paris, 2010.
- [14] S.S. Adams, P. Bresloff, C.G. Mason, Pharmacological differences between the optical isomers of ibuprofen: Evidence for metabolic inversion of the (-)-isomer, *J. Pharm. Pharmacol.*, 28 (1976) 256-257. <https://doi.org/10.1111/j.2042-7158.1976.tb04144.x>

- [15] G. Geisslinger, O. Schuster, K.P. Stock, D. Loew, G.L. Bach, K. Brune, Pharmacokinetics of s(+)- and r(-)-ibuprofen in volunteers and first clinical experience of s(+)-ibuprofen in rheumatoid arthritis, *Eur. J. Clin. Pharmacol.*, 38 (1990) 493-497. <https://doi.org/10.1007/BF02336690>
- [16] A.M. Evans, Comparative pharmacology of s(+)-ibuprofen and (rs)-ibuprofen, *Clin. Rheumatol.*, 20 (2001) 9-14. <https://doi.org/10.1007/BF03342662>
- [17] A. Burger, K.T. Koller, W.M. Schiermeier, Rs-ibuprofen and s-ibuprofen (dexibuprofen). Binary system and unusual solubility behavior, *Eur. J. Pharm. Biopharm.*, 42 (1996) 142-147.
- [18] S.K. Dwivedi, S. Sattari, F. Jamali, A.G. Mitchell, Ibuprofen racemate and enantiomers: Phase diagram, solubility and thermodynamic studies, *Int. J. Pharm.*, 87 (1992) 95-104. [https://doi.org/10.1016/0378-5173\(92\)90232-Q](https://doi.org/10.1016/0378-5173(92)90232-Q)
- [19] Y. Corvis, P. Negrier, P. Espeau, Physicochemical stability of solid dispersions of enantiomeric or racemic ibuprofen in stearic acid, *J. Pharm. Sci.*, 100 (2011) 5235-5243. <https://doi.org/10.1002/jps.22727>
- [20] A. Mbodji, G. Gbabode, M. Sanselme, Y. Cartigny, N. Couvrat, M. Leeman, V. Dupray, R.M. Kellogg, G. Coquerel, Evidence of conglomerate with partial solid solutions in ethylammonium chloxyphos, *Cryst. Growth Des.*, 20 (2020) 2562-2569. <https://doi.org/10.1021/acs.cgd.9b01699>
- [21] I. Prigogine, R. Defay, *Thermodynamique chimique*, tome ii, Dunod, Paris, 1946.
- [22] R.P. Rastogi, R.K. Nigam, Thermodynamic properties of associated mixtures, *J. Phys. Chem.*, 64 (1960) 722-726. <https://doi.org/10.1021/j100835a004>
- [23] Y. Corvis, P. Negrier, S. Massip, J.-M. Leger, P. Espeau, Insights into the crystal structure, polymorphism and thermal behavior of menthol optical isomers and racemates, *CrystEngComm*, 14 (2012) 7055-7064. <https://doi.org/10.1039/C2CE26025E>
- [24] C.P. Brock, W.B. Schweizer, J.D. Dunitz, On the validity of wallach's rule: On the density and stability of racemic crystals compared with their chiral counterparts, *J. Am. Chem. Soc.*, 113 (1991) 9811-9820. <https://doi.org/10.1021/ja00026a015>
- [25] O. Wallach, Terpenes and ethereal oils, *Justus Liebigs Ann. Chem.*, 286 (1895) 90-118.
- [26] K. Pettersson, Stereochemical studies in the α -aryl carboxylic acid series, *Ark. Kemi*, 10 (1956) 297-323.
- [27] A.A. Bredikhin, Z.A. Bredikhina, D.V. Zakharychev, L.V. Konoshenko, Spontaneous resolution among chiral glycerol derivatives: Crystallization features of ortho-alkoxysubstituted phenyl glycerol ethers, *Tetrahedron: Asymmetry*, 18 (2007) 1964-1970. <https://doi.org/10.1007/s11095-008-9655-7>
- [28] Z.J. Li, M.T. Zell, E.J. Munson, D.J.W. Grant, Characterization of racemic species of chiral drugs using thermal analysis, thermodynamic calculation, and structural studies, *J. Pharm. Sci.*, 88 (1999) 337-346. <https://doi.org/10.1021/js980205u>
- [29] J.A. Bouwstra, N. Brouwer, A.C.G. Van Genderen, H.A.J. Oonk, A thermodynamic method for the derivation of the solidus and liquidus curves from a set of experimental liquidus points, *Thermochim. Acta*, 38 (1980) 97-107. [https://doi.org/10.1016/0040-6031\(80\)87152-8](https://doi.org/10.1016/0040-6031(80)87152-8)
- [30] H.W.B. Roozeboom, Solubility and melting point as criteria for racemic compounds, pseudoracemic mixed crystals and inactive conglomerates, *Z. Physik. Ch.*, 28 (1899) 494-517.
- [31] S. Chen, H. Xi, R.F. Henry, I. Marsden, G.G.Z. Zhang, Chiral co-crystal solid solution: Structures, melting point phase diagram, and chiral enrichment of (ibuprofen)₂(4,4-dipyridyl), *CrystEngComm*, 12 (2010) 1485-1493. <https://doi.org/10.1039/B910662F>
- [32] E. Dudognon, F. Danede, M. Descamps, N.T. Correia, Evidence for a new crystalline phase of racemic ibuprofen, *Pharm. Res.*, 25 (2008) 2853-2858. <https://doi.org/10.1007/s11095-008-9655-7>

- [33] D.S. Segal, Behavioral characterization of d- and l-amphetamine. Neurochemical implications, *Science*, 190 (1975) 475-477. <https://doi.org/10.1126/science.1166317>
- [34] K.M. Taylor, S.H. Snyder, Differential effects of d- and l-amphetamine on behavior and on catecholamine disposition in dopamine and norepinephrine containing neurons of rat brain, *Brain Res.*, 28 (1971) 295-309. [https://doi.org/10.1016/0006-8993\(71\)90661-5](https://doi.org/10.1016/0006-8993(71)90661-5)
- [35] L.M. Gunne, The urinary output of d- and l-amphetamine in man, *Biochem. Pharmacol.*, 16 (1967) 863-869. [https://doi.org/10.1016/0006-2952\(67\)90059-7](https://doi.org/10.1016/0006-2952(67)90059-7)
- [36] J.T. Cody, S. Valtier, S.L. Nelson, Amphetamine excretion profile following multidose administration of mixed salt amphetamine preparation, *J. Anal. Toxicol.*, 28 (2004) 563-574. <https://doi.org/10.1093/jat/28.7.563>
- [37] J. Gal, Mass spectra of n-[(s)- $\alpha\pm$ -methoxy- $\alpha\pm$ -(trifluoromethyl)phenylacetyl] derivatives of chiral amines. Stereochemistry of amphetamine metabolism in the rat, *Biomed. Mass Spectrom.*, 5 (1978) 32-37. <https://doi.org/10.1002/bms.1200050107>
- [38] L.M. Gunne, L. Galland, Stereoselective metabolism of amphetamine, *Biochem. Pharmacol.*, 16 (1967) 1374-1377. [https://doi.org/10.1016/0006-2952\(67\)90170-0](https://doi.org/10.1016/0006-2952(67)90170-0)
- [39] C. Gunaratna, P.T. Kissinger, Investigation of stereoselective metabolism of amphetamine in rat liver microsomes by microdialysis and liquid chromatography with precolumn chiral derivatization, *J. Chromatogr.*, 828 (1998) 95-103. [https://doi.org/10.1016/S0021-9673\(98\)00822-X](https://doi.org/10.1016/S0021-9673(98)00822-X)

