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Physicochemical Stability of Solid Dispersions of Enantiomeric or Racemic Ibuprofen in Stearic Acid

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ABSTRACT: The aim of this study was to investigate the solid dispersion phase behavior of S- o r RS-ibuprofen in stearic acid. By means of thermal analysis, we have demonstrated the total immiscibility, in solid state, of the corresponding binary mixtures. This indicates that no specific interactions exist between the chosen excipient and active pharmaceutical ingredient (API) that lead to eutectic systems. Furthermore, based on calorimetric and X-ray diffraction experiments, we have showed that upon cooling of the molten state, only stearic acid recrystallizes in the presence of S-ibuprofen, whereas a quaternary phase mixture is obtained for the racemic ibuprofen/stearic acid preparation. The solubility of stearic acid in S-ibuprofen liquid in all proportions was also determined. Overall, the results presented here offer an approach for the study of API/excipient interactions.

Keywords: drug–excipient interactions; phase diagram; solid-state stability; miscibility; melt-recrystallization process; solubility; polymorphism; thermal analysis; X-ray powder diffraction

INTRODUCTION

Because 80% of active pharmaceutical ingredients (APIs) are provided in the solid state, there are as many conditioning steps in the industrial process as there are solid APIs and excipients that vary regarding their composition, density, granulometry, and/or specific interaction. Lubricants are used in order to prevent APIs from clumping together and from sticking to tablet punches or capsule-filling machine, and to ensure that tablet manufacturing and ejection can occur with low friction between the solid and the die wall. Common minerals like talc or silica, magnesium stearate, or stearic acid are the most frequently used lubricants. During this process, a carrier is added to an active ingredient to confer a given consistency, or other physical characteristics, to the final product, that is, the drug. However, any interaction with the active ingredient, particularly if it is a chemical one, must be avoided. The lack of specific interactions in the solid state between the active substance and the excipient may be observed by studying the complete phase diagram involving the two entities. This paper presents results concerning the interaction between stearic acid and ibuprofen, which is a nonsteroidal, anti-inflammatory API. The generic name of this drug comes from a shortening of its chemical name, **I**so-**bu**tyl-**pro**panoic-**phen**olic acid. From a chemical point of view, with one asymmetric carbon, ibuprofen has two enantiomers, namely the S- and the R-ibuprofen (Figure 1a and 1b).

As is often the case with therapeutic compounds, only one of the enantiomer is an active ingredient. For ibuprofen, it has been proved that the S-enantiomer is the active form.[3–5] However, for economic reasons, ibuprofen is commercialized in its racemic form. This is due to the fact that the inactive R-(–)enantiomer can easily be converted *in vivo* to the active form.[6–8] Nevertheless, a certain quantity of R-enantiomer may be retained in adipose tissues and cause unwanted effects. Therefore, a reduction in the dosage of ibuprofen

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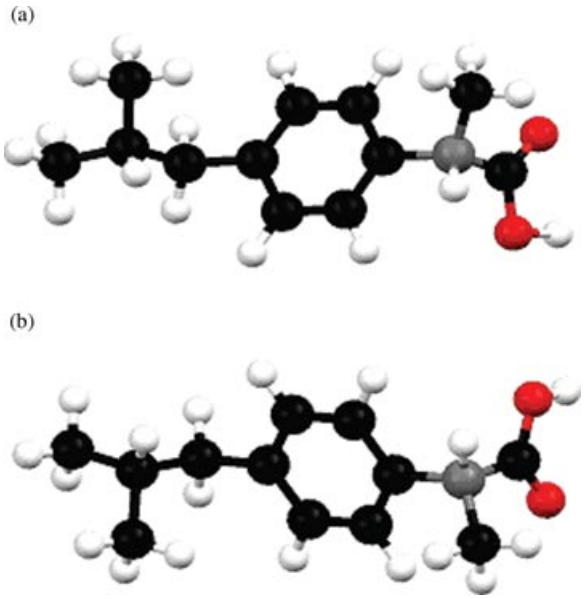


Figure 1. Chemical structure of (a) S-ibuprofen and (b) R-ibuprofen drawn from the corresponding X-ray crystallographic information files.[1,2] The asymmetric carbon atom is represented by a gray motif.

could be obtained using pure S-ibuprofen as compared with the racemic form.[9]

Association of ibuprofen and stearic acid is currently encountered in pharmaceutical manufacture of tablets and topical gel. As far as tablets are concerned, the API/excipient solid dispersion can be homogenized not only by mechanical powder mixing, but also by cooling of a comelt of the two components. In the latter case, when the components exhibit polymorphism, one cannot be sure that they crystallize into the most stable crystalline phase. Because stearic acid presents various polymorphic forms,[10–17] the thermodynamic stability of the ibuprofen/stearic acid solid dispersion prepared from the melting–cooling process must be ensured. However, a survey of the literature points to a lack of information regarding the study of the interactions between these components, in the solid state, over the whole range of compositions.

This paper presents, on one hand, the study of two binary phase diagrams between stearic acid and S-ibuprofen or RS-ibuprofen, obtained from the solid state. As a matter of fact, the phase behavior study between S-ibuprofen and stearic acid has never been reported up to now. On the other hand, stability of the solid dispersions obtained from the molten state will be investigated and discussed.

MATERIALS AND METHODS

S- and RS-ibuprofen (CAS number: 51146-56-6 and 15687-27-1, respectively; 99% purity) were purchased from Acros Organics, part of Thermo Fisher Scientific, Illkirch, France. Stearic acid (CAS number: 57-11-4; 98% purity) was obtained from Alfa Aesar, Schiltigheim, France. The components were used as received. For the binary mixture preparations, the compounds were weighed separately and mechanically mixed in a mortar in their solid state. Around 30 different compositions were prepared for each binary system.

Thermal Analysis

Differential scanning calorimetry (DSC) runs were performed at 2 K min^{-1} from 25°C to 90°C under an atmosphere of dry nitrogen gas (flow rate: 60 mL min^{-1}), using a 822e calorimeter (Mettler-Toledo, Viroflay, France), calibrated beforehand using high-purity indium (99.99%, provided by Mettler-Toledo; temperature and enthalpy of fusion: T_{fus} = 156.6°C and $\Delta_{fus} H = 28.45$ J g^{-1}, respectively). The DSC samples were weighed in aluminum pans using a microbalance sensitive to 1 µg and were hermetically sealed at room temperature. The thermograms are represented in this paper as the evolution of heat flow—arbitrary unit—versus the scanned temperature in Celsius degrees. The temperature data were determined at the onset of the thermograms single signal for the pure compounds (Fig. 2a). For the binary mixtures, the eutectic temperature was taken at the onset of the first signal, that is, the beginning of the thermal transformation (Fig. 2b). The end of the thermal transformation (liquidus or solubility curve) was found out at the extremum of the second signal (Fig. 2b).

X-ray Powder Diffraction

X-ray powder diffraction (XRPD) data were recorded by means of a horizontally mounted Inel cylindrical, position-sensitive detector (CPS-120; Inel, Artenay, France) using Debye–Scherrer geometry (2θ from 1° to 106° with a 0.029 angular step) and equipped with a liquid nitrogen 600 series Cryostream Cooler from Oxford Cryosystems Ltd, Oxford, United Kingdom. Monochromatic Cu $K\alpha_1$ (λ = 1.5406 Å) radiation powered with 1.0 kW (40 kV; 25 mA) was selected. External calibration using $Na_2Ca_3Al_2F_{14}$ cubic phase mixed with silver behenate was performed beforehand by means of cubic spline fittings. Liquid samples were placed at room temperature into 0.5-mm diameter Lindemann capillaries obtained from Bruker AXS, Champs-sur-Marne, France. During data collection, the capillaries were rotated perpendicularly to the X-ray beam direction to minimize possible effects of preferred orientations.

Macroscopic Visualization of S-Ibuprofen/Stearic Acid Mixtures

The components were weighted in a glass vial (total amount of ~180 mg). Each vial was first heated at 88°C for 2 min in order to obtain a liquid phase. The

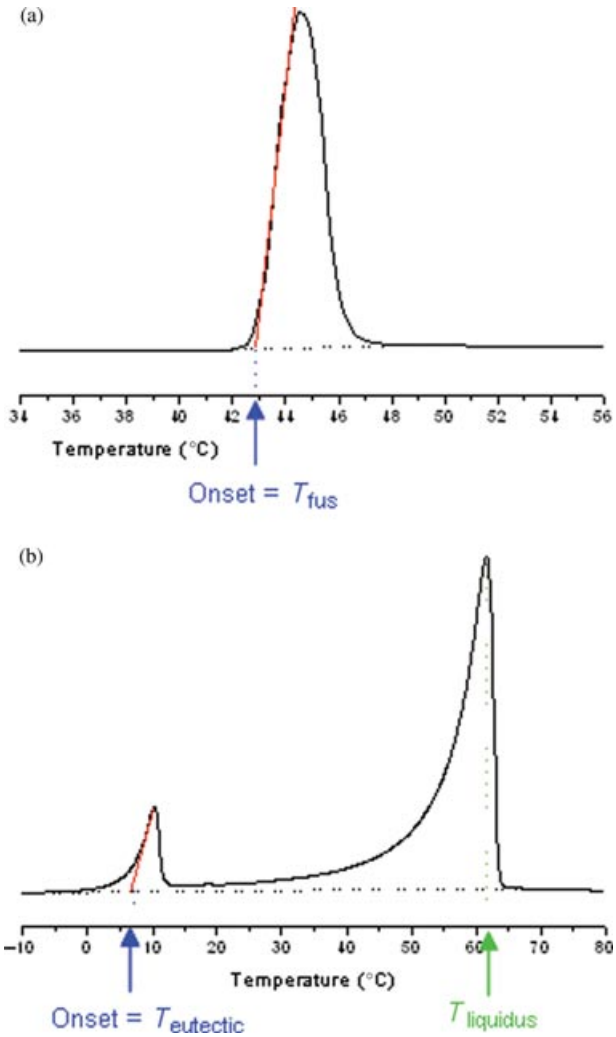


Figure 2. DSC thermogram examples obtained for (a) a pure compound and (b) a binary eutectic mixture. The corresponding temperature assignments are indicated. Endothermic transformations give signals pointing up.

samples were then homogenized without opening the vials and finally annealed at room temperature. Pictures were taken 3 days after the melting process using a two-megapixel CCD camera (Motic, Wetzlar, Germany).

RESULTS AND DISCUSSION

The pure compounds were, first of all, analyzed by thermal analysis and XRPD experiments. The XRPD patterns are presented in Figure 3. The experimental thermodynamic data obtained from the thermal analysis are in good agreement with the values reported in the literature (Table 1). However, it is commonly admitted that mixtures of stearic and palmitic acids can be labeled as "stearic acid" in a certain range of molar ratios between both components (USP32/NF27 and Ph. Eur. 07/2010:1474). This implies that

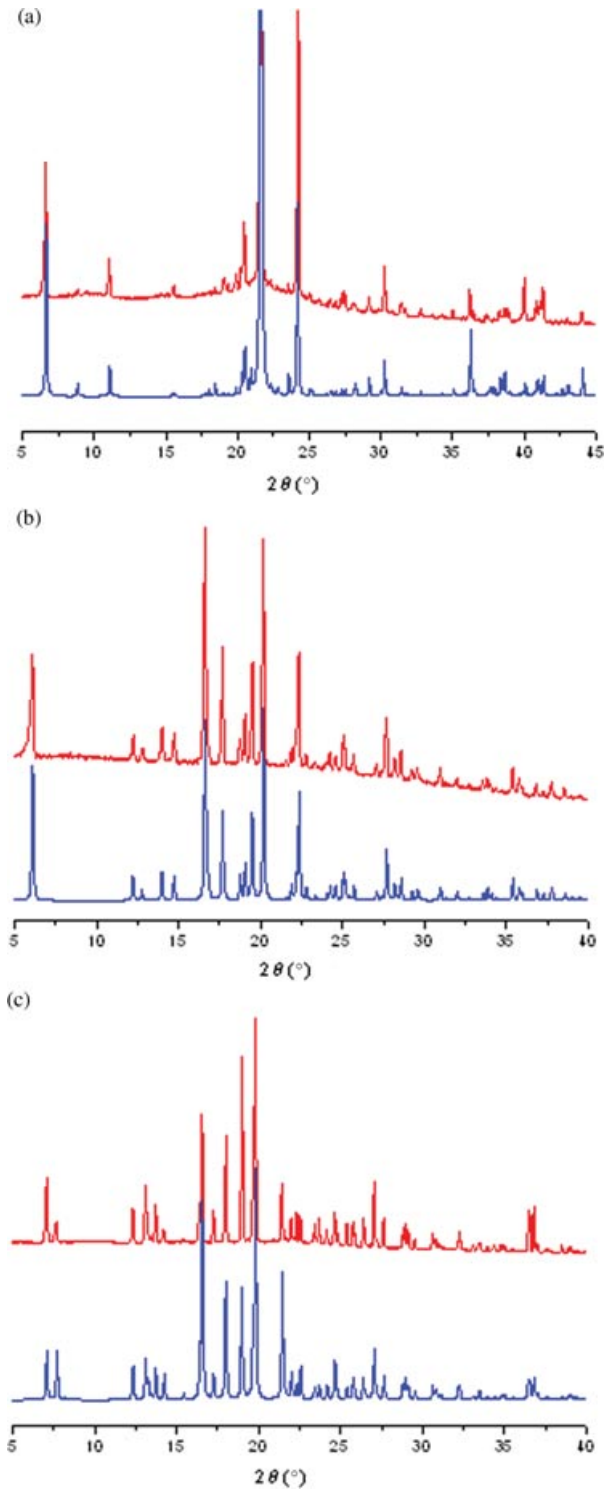


Figure 3. XRPD patterns of (a) stearic acid, (b) RS-ibuprofen, and (c) S-ibuprofen. For a same panel, the upper and lower curves correspond to the experimental and calculated[1,13,21] patterns, respectively.

depending on the batch, the stearic acid/palmitic acid ratio may vary, leading to nonreproducible temperature and melting heat data.[18,19] Furthermore, stearic acid presents at least six polymorphic forms whose

Table 1. Temperatures and Enthalpies of Fusion of Ibuprofen and the C-form of Stearic Acid

Stearic Acid	References	S-Ibuprofen	References	RS-Ibuprofen	References
T_{fus} (°C)					
69.2 ± 0.7	This work	51.6 ± 0.2	This work	75.6 ± 0.3	This work
69.4 ± 0.1	22	45.8	23	70.8	23
69.6	24	52.2	25	75.2 ± 1.1	26
69.2 ± 0.3	20	53.6	27	75.4	25
				75.6	27
				75.8	28
$\Delta_{fus}H$ (kJ mol^{-1})					
61.3 ± 1.3	This work	18.6 ± 0.3	This work	25.5 ± 0.3	This work
61.2 ± 0.2	22	19.9 ± 0.8	23	26.9 ± 1.0	23
61.3	24	18.7 ± 0.1	25	25.04 ± 0.10	26
63.2 ± 1.4	20	17.9	27	25.7 ± 0.2	25
				25.5	27
				25.8 ± 0.5	28

C-form is the high-temperature stable phase before melting.[20] As a matter of fact, no solid–solid phase transition was observed for our batch of stearic acid. This result indicates that the as-received product crystallized in the C-form (monoclinic structure). It is noteworthy that once the stearic acid is crystallized from its molten phase into the C-form, no more solid—solid transition is obtained on heating or cooling.[20] The study of the thermal behavior of ibuprofen (Table 1) was also carried out. It is interesting to emphasize that neither the S- nor the RS-compound spontaneously recrystallizes upon cooling.

The RS-ibuprofen/stearic acid phase diagram presents a eutectic equilibrium at 57.0 ± 0.3°C (Fig. 4). Besides, a complete demixing region in the solid state is confirmed by the Tammann plot shown in Figure 4 (dotted line). The enthalpy change at the eutectic composition (x^e) is estimated, from the Tammann plot, to be 42.2 kJ mol^{-1} at $x^e = 0.553$ mole fraction in RS-ibuprofen.

The liquidus curves for the stearic acid follow a quasi-ideal behavior. Taking into account an excess Gibbs energy in the liquid state, approximately equal to 0.2 kJ mol^{-1} at the eutectic point, and a complete immiscibility in the solid state, the experimental liquidus points were fitted (Fig. 4; solid blue lines) using an EXcess function coefficients from *T*-*X* phase Diagram (EXTXD) analysis.[29] Besides, no discontinuity is observed in the Tammann plot, which intercepts the eutectic enthalpy $\Delta H^e = 0$ at $x = 0$ and $x = 1$ (Fig. 4b; dotted line), as well as in the liquidus curves. Therefore, one can conclude that no stoichiometric compound is formed between stearic acid and RS-ibuprofen contrary to Lerdkanchanaporn et al.'s suggestion.[19] Indeed, for mixtures between 0.42 and 0.65 molar ratios in ibuprofen, that is, around the eutectic composition, they did not observe any DSC signal corresponding to the liquidus curve. To explain this point, they suggested the existence of a (stearic acid)·(RS-ibuprofen)$_2$ compound. In fact, as seen in Figure 4, the DSC signals that correspond to the invariant and the liquidus overlap each other for composition near the eutectic point. The latter is due to experimental limitation such as the scanning rate, the sample weight, and so on. Thus, the liquidus becomes difficult to be apprehended. Moreover, the hypothesis of the compound proposed by Lerdkanchanaporn et al.[19] is not supported by their own Tammann plots.

As discussed above, mixtures containing stearic and palmitic acids may be used as "stearic acid" label. In this case, a pseudo-binary phase diagram from the stearic acid/palmitic acid/RS-ibuprofen ternary phase diagram should be considered, assuming that the stearic acid/palmitic acid system presents miscibility domains in the solid state near pure acid compositions (formation of molecular A_xB_{1-x} alloys). This behavior was previously encountered, for instance, for binary systems between odd *n*-alkanes.[30] The so-considered alloys start to melt at lower temperatures than the pure components ones, whatever the composition. We noticed the same phenomenon regarding stearic acid used by Gordon et al.[18] to establish the phase diagram with RS-ibuprofen. The depression of the melting point observed for stearic acid (59.0°C instead of 69.2°C) is certainly due to the impurity of the compound, which results from an alloy between stearic acid and, probably, palmitic acid. Consequently, the pseudo-binary system formed between RS-ibuprofen and this alloy necessarily leads to a eutectic equilibrium at a lower temperature than our proposed diagram one.

The assumption of miscibility domains between C_{16} and C_{18} acids is easily acceptable because they present a structural similarity that may be quantified by using the degree of molecular isomorphism, ε.[31] $\varepsilon = 1 - \frac{\Delta}{\Gamma}$, where Δ is the non-overlapping volume and Γ the overlapping volume of the molecules. For long-chain molecules, the latter expression can be simplified, taking Δ equal to the difference in chain

length and Γ equal to the number of carbon in the shortest chain. In our case, the values of Δ and Γ are 2 and 16, respectively, leading to a degree of molecular isomorphism of 0.875.

For the S-ibuprofen/stearic acid phase diagram, the complete immiscibility in the solid state is also revealed by the Tammann plot (Fig. 5). The eutectic equilibrium was determined at 44.0 ± 0.3°C with a eutectic point at $x^e = 0.866$; x corresponding to the S-ibuprofen molar ratio. The enthalpy change at the eutectic point was found to be equal to 26.14 kJ mol^{-1}. Besides, compared with the ideal behavior, a slight deviation in the experimental liquidus curves can be noticed. As for the first system, the best fit for the liquidus points was obtained considering the liquid state as nonideal. For that reason, an excess Gibbs energy value of 200 J mol^{-1} was introduced in the assessment at the eutectic point.

Owing to the higher melting point of the racemate, the shift of the eutectic point from pure ibuprofen is more important for the racemate than for the enantiomer. This shift is increased by the lower melting entropy of S-ibuprofen (57 J mol^{-1} K^{-1}) than that of RS-ibuprofen (73 J mol^{-1} K^{-1}).

Considering that solid dispersions can be prepared from the molten state, the behavior of each system namely S-ibuprofen/stearic acid and RS-ibuprofen/stearic acid—was studied upon heating–cooling steps. After cooling, for compositions between $x = 0$ (pure stearic acid) and $x = x^e$, molten mixtures of S-ibuprofen and stearic acid did not undergo any eutectic reaction upon heating (Fig. 6). The same tendency has been previously reported with other systems.[32] Our result indicates that below the eutectic temperature, the equilibrium between solid stearic acid and solid S-ibuprofen was not established. Indeed the thermograms obtained presented a unique endothermic signal corresponding to the crossing of the liquidus curve for pure stearic acid. From these results we can conclude that only pure stearic acid recrystallizes upon cooling of the S-ibuprofen/stearic acid mixtures. As a consequence, a two-phase equilibrium between pure solid stearic acid and a liquid composed of stearic acid and S-ibuprofen was established. The exact composition of the liquid is then obtained by the solubility curve of stearic acid in S-ibuprofen liquid. As a matter of fact, the observed thermal event corresponds to the solubility point of a more stable form of stearic acid, the C-form.

For compositions comprised between $x = x^e$ and $x = 1$, the same behavior on cooling was observed (Fig. 6). Following the same statement upon heating, one could expect to cross the liquidus curve for solid S-ibuprofen in this range of molar ratios. Surprisingly, the endothermic one-signal observed from each DSC thermogram still corresponded to the

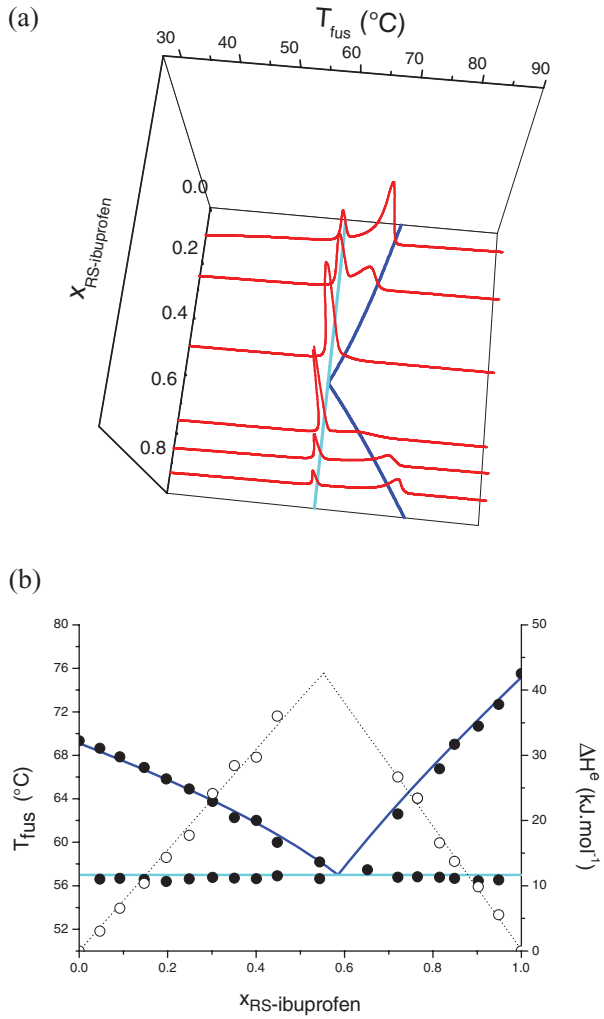


Figure 4. (a) Three-dimensional representation of selected DSC thermograms obtained for the RS-ibuprofen/stearic acid mixtures (red curves). Endothermic transformations give signals pointing up. (b) The corresponding T–x phase diagram (left axis). The Tammann plot is represented by the open circles and dotted lines (right axis). The eutectic and liquidus curves are represented in cyan and blue, respectively.

solubility curve of pure stearic acid in S-ibuprofen liquid.

In other words, for the whole range of compositions, when cooling molten mixtures of stearic acid and S-ibuprofen, only stearic acid recrystallizes. The corollary of this result is that upon heating the solubility curve of stearic acid in S-ibuprofen is followed, whatever the molar ratio. Pictures of vials containing mixtures of S-ibuprofen and stearic acid at different molar ratios, prepared in the same way as the corresponding DSC samples, confirm these statements (Fig. 7). This result is in accordance with the fact that pure S-ibuprofen does not spontaneously recrystallize upon cooling.[25] Besides, we proved that S-ibuprofen

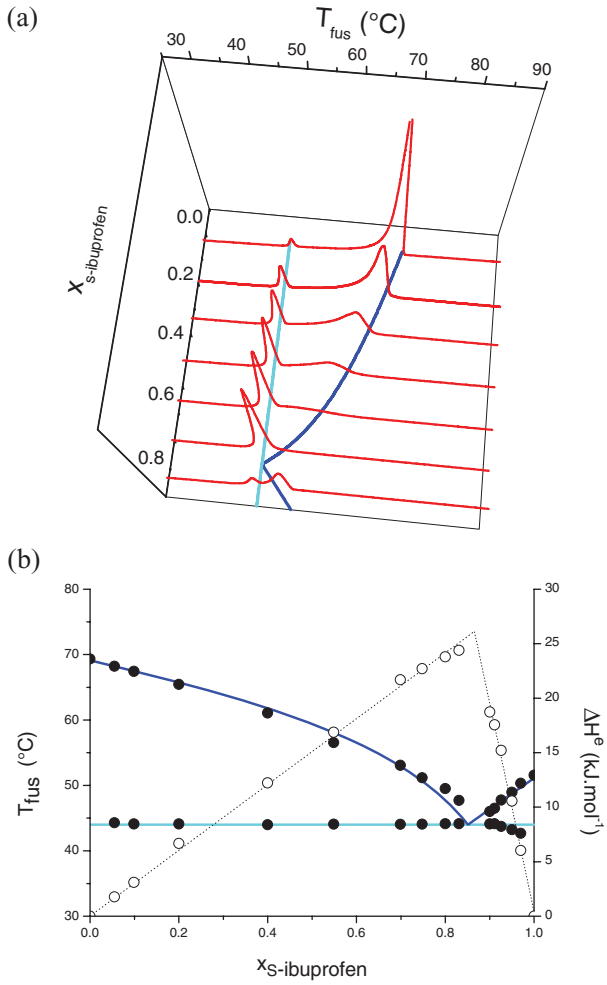


Figure 5. (a) 3D representation of selected DSC thermograms obtained for the S-ibuprofen/stearic acid mixtures (red curves). Endothermic transformations give signals pointing up. (b) The corresponding T–x phase diagram (left axis). The Tammann plot is represented by the open circles and dotted lines (right axis). The eutectic and liquidus curves are represented in cyan and blue, respectively.

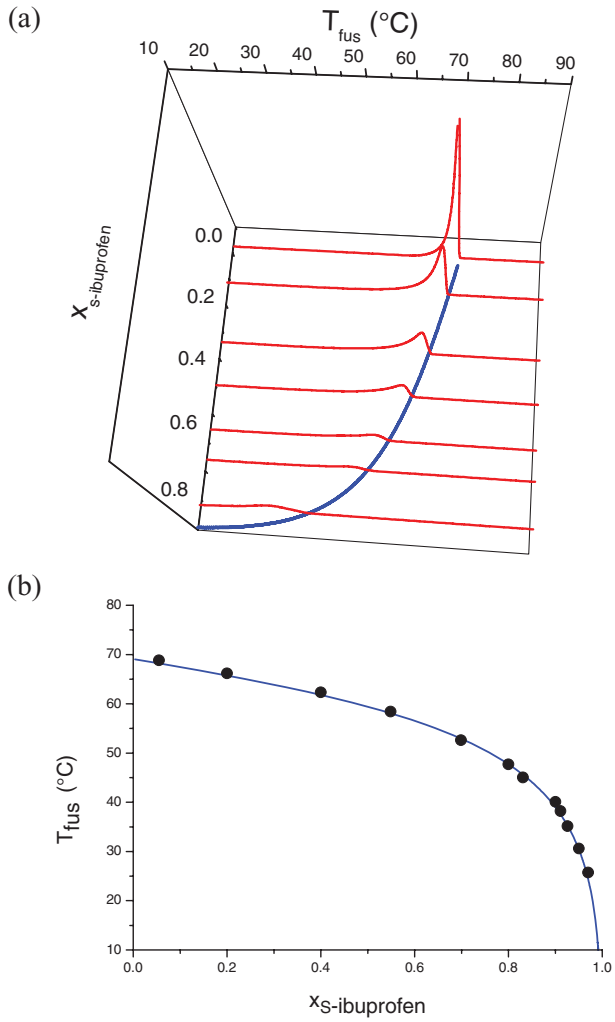


Figure 6. (a) Three-dimensional representation of selected DSC thermograms (red curves) obtained for the S-ibuprofen/stearic acid mixtures and recorded upon heating after cooling from the molten state. Endothermic transformations give signals pointing up. (b) The corresponding T–x phase diagram. The liquidus curve is represented in blue.

recrystallization never occurred even for samples annealed at room temperature for $1\frac{1}{2}$ year (results not shown). We demonstrate here that this behavior of S-ibuprofen is not altered even in the presence of stearic acid. The latter conjecture, proposed on the basis of the thermal and visual experiments, was confirmed by X-ray studies. Indeed, 3 days after being melted at 80°C and then annealed at room temperature, the S-ibuprofen/stearic acid mixtures presented only X-ray diffraction signals corresponding to pure stearic acid.

The broad peak between 15° and 20° in 2θ is due to the presence of an amorphous phase corresponding to the liquid mixture in the sample. Moreover, for binary samples with high S-ibuprofen concentration ($x > 0.759$), when comparing the experimental X-ray diffraction patterns (Fig. 8) with the calculated ones (Fig. 9), especially around 2° and 22° in 2θ, we observed that the stearic acid recrystallized into two polymorphs, namely the C- and E_m-forms. We propose here that the presence of ibuprofen in the liquid state may induce polymorphism during the stearic acid recrystallization process. These structural data allow explaining why the $E_m \rightarrow C$ transition at around 45°C has not been observed with the thermal experiments as might be expected (Fig. 6). Indeed, for S-ibuprofen compositions lower than the eutectic composition, the C-form of stearic acid is predominant as compared with the E_m-form, the latter being converted into C with a small transition enthalpy (~3 kJ mol^{-1}). For S-ibuprofen compositions higher than the eutectic composition, the solubility temperatures are lower than 45°C. Accordingly, whatever the molar ratio, the

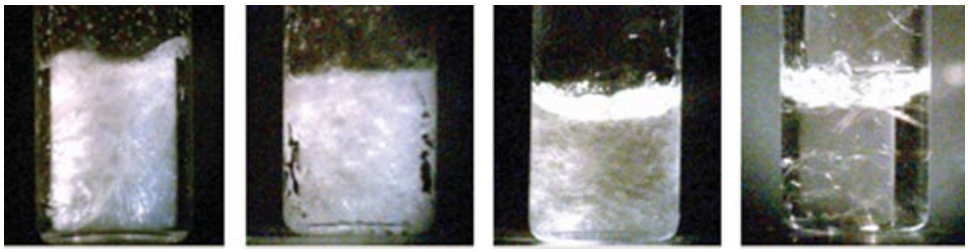


Figure 7. Pictures of glass vials containing mixtures of S-ibuprofen and stearic acid. S-ibuprofen molar ratios: 0.000, 0.501, 0.944, and 0.959, from left to right, respectively.

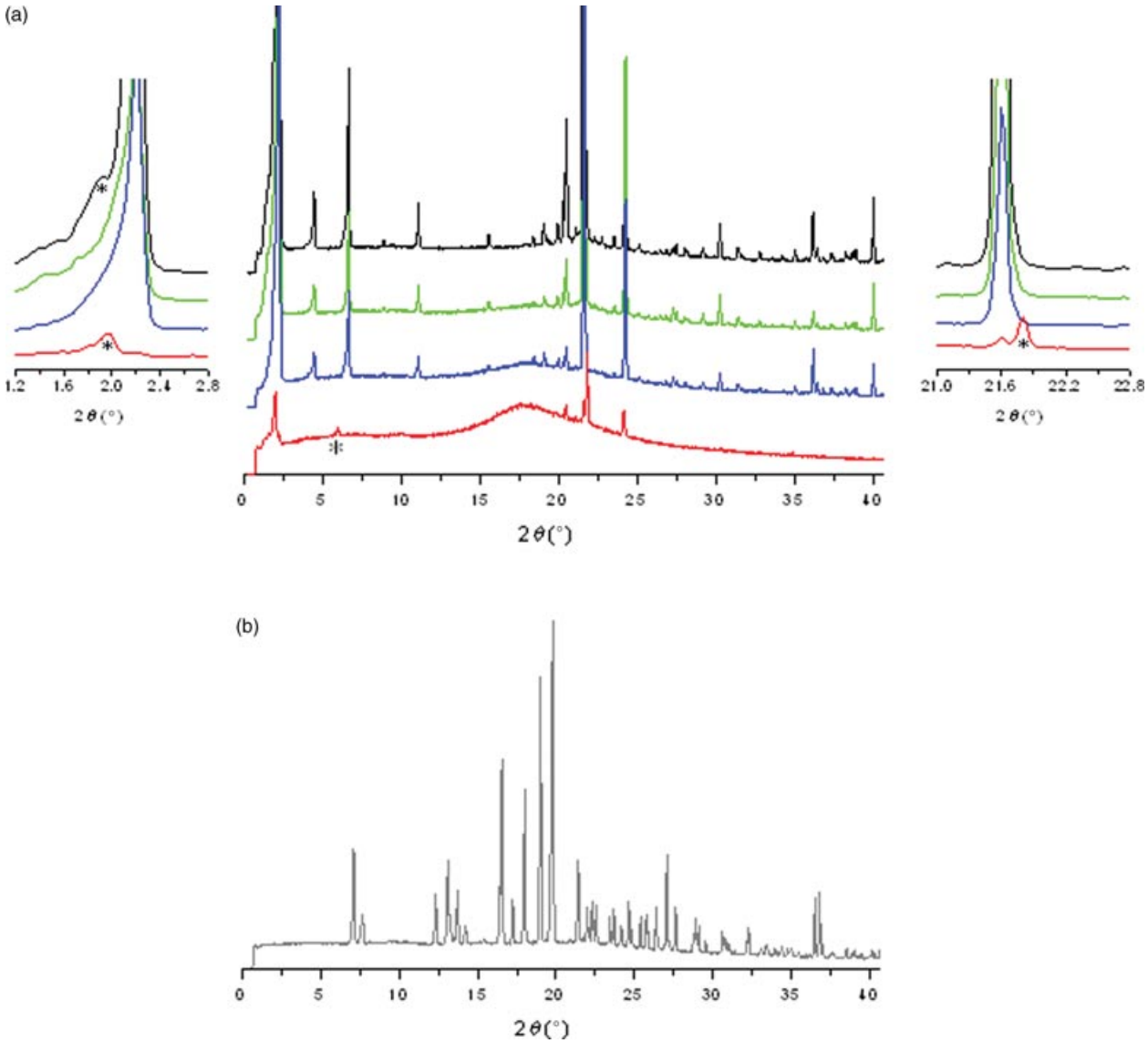


Figure 8. Experimental XRPD of (a) selected S-ibuprofen/stearic acid mixtures and (b) pure S-ibuprofen. The patterns were shifted for clarity. (a) S-ibuprofen molar ratios: 0.000 (black), 0.334 (green), 0.501 (blue), and 0.929 (red). The samples were analyzed 3 days after being melted at 80°C directly in the capillary, and then annealed at room temperature. (Insets) Corresponding patterns focused between 1.2° and 2.8° (left) and between 20.8° and 22.8° (right). The ∗ indicates the signal corresponding to the stearic acid E_m-form.

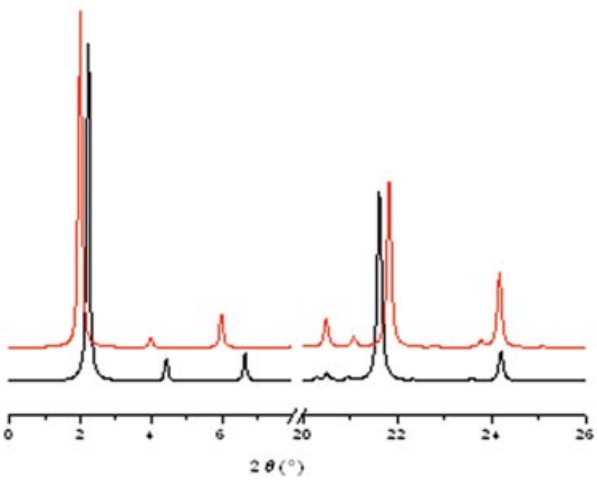


Figure 9. Calculated XRPD patterns of C- (black) and E_m-(red) stearic acid polymorphs; from Refs. 13 and 15, respectively. The patterns were shifted for clarity.

solubility curve proposed in Figure 6 is not affected by the so-considered solid–solid transition.

Interestingly, we found out that the S-ibuprofen/stearic acid mixtures may totally recrystallize by external mechanical actions (homogenization or conditioning). In this case, stearic acid polymorphism also occurs during recrystallization (results not shown). The nature and the proportions of the polymorphic forms are random. As stearic acid presents at least six polymorphs, it can be assumed that a S-ibuprofen/stearic acid solid dispersion prepared from the homogeneous melt would lead to nonreproducible batches. Consequently, different properties of the solid dispersions such as dissolution rate, bioavailability, and so on could be expected. All these results taken together provide a good justification for the S-ibuprofen/stearic acid mixture preparation from the solid versus liquid state from a pharmaceutical point of view. Besides, it has to be noticed that the behavior of S-ibuprofen mixtures with stearic acid should hold true for the mixtures containing R-ibuprofen instead.

The RS-ibuprofen/stearic acid system was also studied upon heating–cooling steps. Contrary to S-ibuprofen, the racemic compound has a strong tendency to recrystallize as can be predicted from the Patterson ratio[33] determined as 1.77 by Romero and Rhodes.[27] However, the recrystallization rate of the racemic compound seems to be random and depends on the degree of dissociation in the molten state.[19,28] Dwivedi et al.[23] showed that in the liquid state, RS-ibuprofen is largely dissociated into its enantiomers. Therefore, upon cooling, the nondissociated part of RS-ibuprofen may recrystallize. As far as the enantiomers resulting from the resolution are concerned, our study shows that they do not recrystallize upon cooling. As a consequence, the cooling step leads at least to four components in arbitrary proportions. Owing to the nonreproducibility of the experimental results, the study of such a quaternary system proves rather complicated.

CONCLUSION

We demonstrated that the use of stearic acid as an excipient is highly justified because the complete immiscibility between RS- or S-ibuprofen and stearic acid in the solid state indicates that no specific interactions exist between stearic acid and ibuprofen. In addition, from the molten state, the recrystallization of the corresponding pharmaceutical mixtures is incomplete. This is why the solid dispersion between ibuprofen and stearic acid should be performed from the solid state. Moreover, during stearic acid recrystallization, polymorphic forms are formed and stabilized, which leads to batch to batch nonreproducible phases. The studies presented here allow a better understanding of the API/excipient interactions for an adjusted formulation approach.

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