Organic Process Research & Development **2003**, *7*, 983−989

Phase Transitions in Supersaturated Drug Solution

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Abstract:

In this contribution we present two cases of phase transitions, in which the ability to control the reproducible formation of the desired physical form requires a control of crystallization parameters and a deep understanding of the phase diagram.

The different stages of the solution-mediated phase transition, i.e., dissolution of the metastable phase and nucleation and growth of the stable phase, were studied for irbesartan, a pharmaceutical compound. The influence of crystal sizes and habits and of additive on the kinetics of dissolution and growth has been shown.

The second case of phase transition describes a liquid−liquid phase separation which is metastable with respect to the crystallization of the two polymorphs F_I and F_{II} of $C_{35}H_{41}Cl_2N_3O_2$ in an ethanol/water mixture. Thermodynamic stability of the phases toward each other with temperature and the impact of the liquid−liquid phase separation on crystallization have been investigated. Our results show that a deep control of the crystallization parameters and the understanding of the phase diagram lead to the achievement of the desired polymorph, in a reproducible manner. Moreover, the dilute solution studied was shown to be nonideal since it was correlated with the existence of the metastable liquid−liquid demixing which was observed and characterized. In our experiments the liquid−liquid phase transition prevented the drug from crystallizing, while it changed the medium and the conditions of crystallization, which consequently affected the process.

1. Introduction

Many industries, such as food, agrochemicals, and pharmaceuticals, are frequently confronted with the presence of multiple crystal polymorphs.[1−4] Indeed, polymorphism means different physicochemical properties of the solid, which have possible consequences on the processing, the physicochemical stability of the active substance alone and in its formulations, and on the bioavailability of the considered pharmaceutical compound. An example, in 1998, was Abbott's ritonavir, marketed for AIDS treatment as Norvir, which developed problems with appearance of the new less soluble, stable form which had different physicochemical properties with respect to the form registered with the U.S.Food and Drug Administration.[5]

The complexity of the molecules to be crystallized and the necessity of good productivity often lead to the use of a solvent mixture in the crystallization process, which causes a rather complicated crystallization medium, at least a ternary system, mixture of two solvents and a solute. A better understanding of the crystallization process is essential to control nucleation and growth, and thus the phase, quality, and size of crystals. With that aim, it becomes clear that the important stage is the determination of the phase diagram. In the phase diagram there is a region where two coexisting liquids can be observed, which corresponds to a miscibility gap in the phase diagram. This liquid−liquid phase separation (LLPS), or demixing, may have an impact on the crystallization process. If the LLPS appears in the metastable zone for crystallization, a competition between the LLPS and the crystal formation might occur, crystallization might thus be hindered or accelerated. Recent works[6−9] suggest that a metastable LLPS can affect nucleation. Nucleation was thus expected to be different above and below the coexistence or binodal curve. Experimental results and simulation calculations seem to indicate that nucleation is enhanced in the vicinity of this curve.[7,10−12] LLPS is known in colloid physics

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10.1021/op034089f CCC: $25.00
Published on Web 11/21/2003

and in the protein area as a gas−fluid[13,14] and a fluid−fluid transitions[6,15−17] respectively.

In this contribution we present two cases of phase transitions, in which the ability to control the reproducible formation of the desired physical form requires a control of crystallization parameters and a deep understanding of the phase diagram.

The first case is the study of dissolution and pseudopolymorphic transition of irbesartan, where the effects of crystal sizes and habits and of additive are discussed. The second case describes a LLPS which is metastable with respect to the crystallization of the two polymorphs of a drug.

2. Materials and Methods

2.1. Materials. The pharmaceutical compounds studied are organic molecules with the following basic formula: $C_{25}H_{28}N_6O$ (irbesartan) and $C_{35}H_{41}Cl_2N_3O_2$. The first compound is used in the treatment of hypertension and presents a solution-mediated phase transition (SMPT) of phase A into phase B in water. Phase A is trigonal ($R\bar{3}$),[18] whereas B is triclinic ($P\bar{1}$),[19] this compound is an organic molecule with an unsaturated N cycle and the transformation of A into B is a tautomeric transformation in liquid state isolated in solid state, called a desmotropy (Figure 1). The second compound crystallizes two polymorphs, F_I and F_{II}, but the transformation of F_I into F_{II} had not been observed thus far. F_I is monoclinic, whereas F_{II} is orthorhombic. The crystallization process imposes the solvent: an ethanol/water mixture (54.2/45.8% weight). Note that solubility of the polymorphs is high in ethanol but very low in water.

2.2. Solid Characterization. The crystals were observed under a scanning electron microscope (SEM) JEOL 6320F. The SEM photographs clearly show differences in the crystal habits of irbesartan form A and B, Figure 2, a and b, respectively. Figure 2c shows platelet crystals, and Figure 2d shows needle habits of polymorphs F_I and F_{II}, respectively, of $C_{35}H_{41}Cl_2N_3O_2$. In this study all the solid phases were characterized by X-ray diffraction INEL CPS 120.

2.3. Phase Diagram and Transformation. Dissolution and water-mediated desmotropy of irbesartan were performed in a batch crystallizer of 0.8 L at constant temperature widely described in a previous work.[20] This crystallizer is a double-jacketed glass vessel equipped with three wall baffles to prevent the solution from rotating in the crystallizer. Solution stirring is ensured by a stainless steel stirrer equipped with a mixel TT propeller type at a stirring rate of 300 rpm. Both are covered with halar(ECTFE) coating to avoid chemical interactions with the stirrer. At the beginning of the dissolution experiment, crystal seeds of irbesatan form A were poured into the crystallizer previously filled with pure water. To determine the concentration as a function of time we measured the conductivity variation of the solution. Metrohm 660 conductimeter (Metrohm Herisau, Switzerland) with an open geometry measurement cell (constant cell of 0.57 cm^{-1}) was used. If not specified in the text, the dissolution experiments were carried out with the crystal seeds presented in Figure 2a.

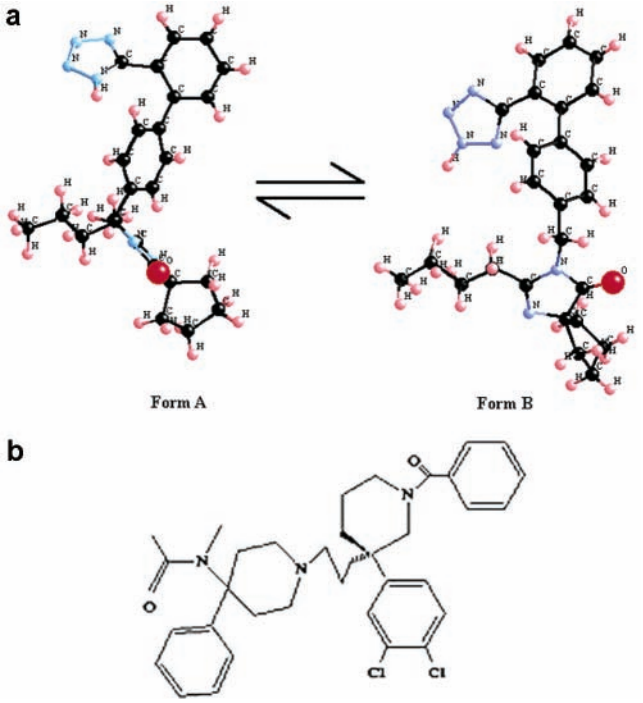

Figure 1. **(a) Tautomeric transformation of irbesartan form A into form B from crystallographic data. (b) Structure of $C_{35}H_4Cl_2N_3O_2$.**

The technique used to determine the solubility of the stable as well as the metastable polymorphs of $C_{35}H_{41}Cl_2N_3O_2$ versus temperature was the bracketing technique.[21,22] This technique consists of observing the growth or the dissolution of small single crystals seeded in solutions at known concentrations, under optical microscope (Nikon, Diaphot), at given temperatures. Using the experimental setup previously described[23] (Figure 3), the temperature in the solution is monitored by Peltier effect (±0.1 °C), and the crystal temperature equilibrium is measured. When we measure the solubility of the metastable polymorph, the stable form does not spontaneously nucleate; thus, the concentration within the solution

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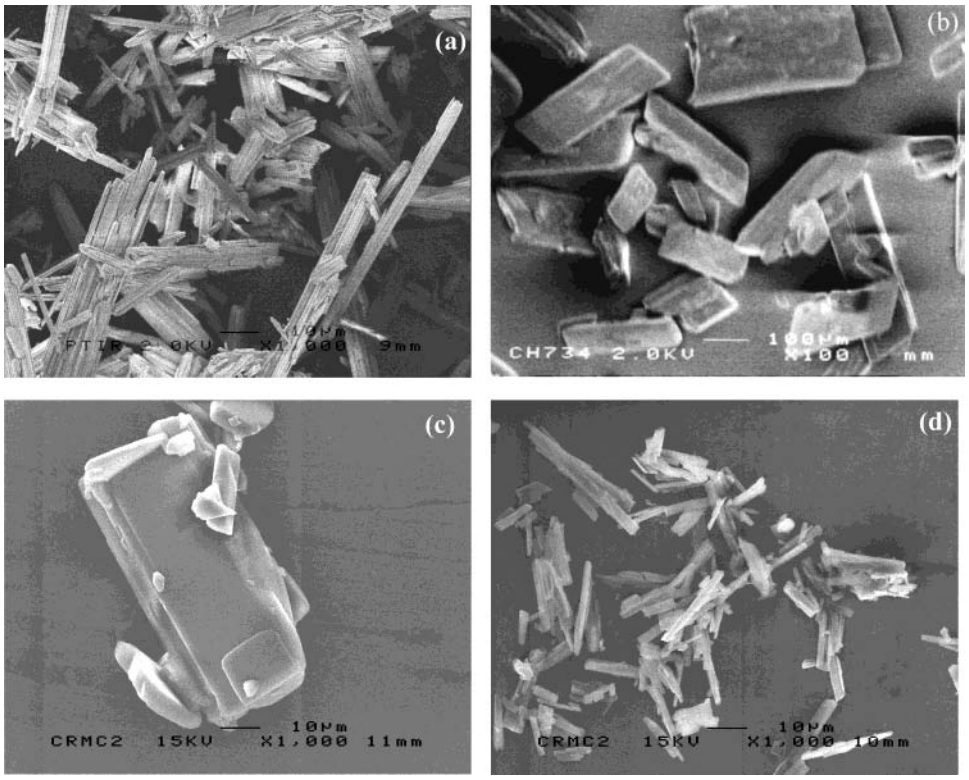

Figure 2. **SEM photographs of irbesartan form A (a) and form B (b), and polymorphs of $C_{35}H_{41}Cl_2N_3O_2$, F_I platelet (c) and F_{II} needle (d) habits.**

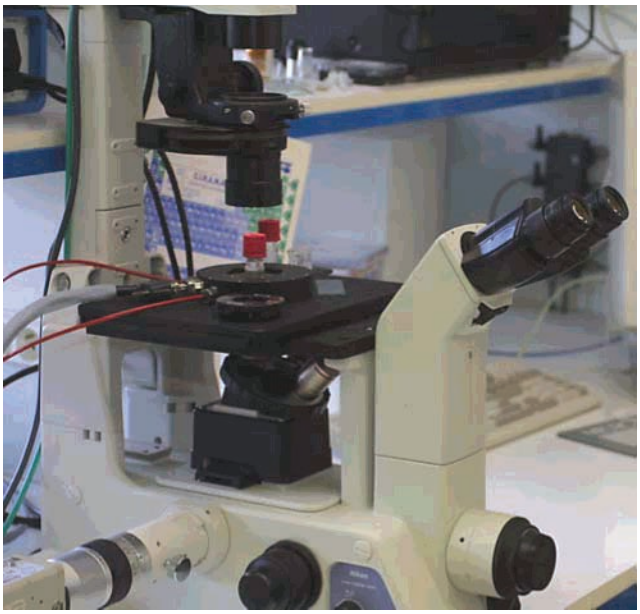

Figure 3. **Quiescent thermostated cell by Peltier effect placed under a microscope equipped with a camera.**

remains constant throughout the experiment. The temperature range for the solubility measurements was 10−57 °C.

This setup was also used to observe and to characterize the liquid−liquid demixing. The coexistence curve for the liquid phases, also called the T_{L-L} boundary (L−L for liquid−liquid), was determined through light-scattering intensity measurements. To determine the spinodal temperature of each solution used, we extrapolated the temperature dependence of the reciprocal intensity, I^{-1}, of the light

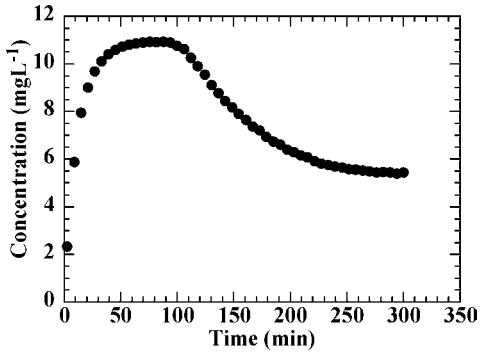

Figure 4. **Variation of concentration versus time due to the solution-mediated phase transition of form A into form B for a mass concentration of 50 mg·L^{-1} at 40 °C in pure water.**

scattered at 90° to the temperature for which I^{-1} reaches zero.[16] In this work we present the isoplethe section of the ternary phase diagram.

3. Results and Discussion

3.1. Dissolution and Desmotropic Transition of Irbesartan. Here is presented a laboratory study of the SMPT of irbesartan. Mechanisms and effects of some crystallization parameters are discussed.

3.1.1. Dissolution and Desmotropic Transition of Irbesartan in Pure Water. Figure 4 shows the variation of concentration versus time due to the SMPT of form A into form B, for an initial solid concentration of 50 mg·L^{-1} at 40 °C in pure water. As shown in a previous report[2] the different stages observed in Figure 4 correspond to the dissolution of form A (increase in the concentration). When the apparent solubility of the metastable form A is reached,

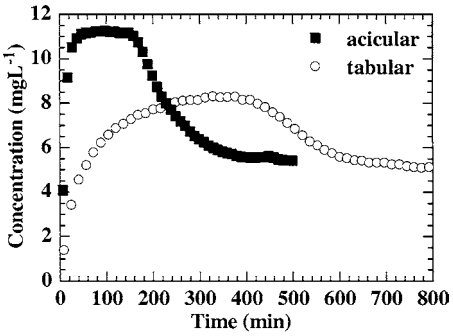

Figure 5. **Variation of concentration versus time for acicular and tabular crystal habit of irbesartan form A for a mass concentration of 100 mg·L^{-1} at 40 °C in pure water.**

the dissolution of form A strictly compensates form B nucleation and growth (presence of a plateau at 11 mg·L^{-1} corresponding to the apparent solubility of form A at 40 °C). Then dissolution of form A cannot compensate anymore for the growth of form B, the concentration decreases until it reaches form B solubility (5 mg·L^{-1} at 40 °C). It is noteworthy that this behaviour is characteristic of SMPT, for instance the setting of plaster, gypsum or $CaSO_4 \cdot 2H_2O$, which is obtained by a SMPT of $CaSO_4 \cdot 0.5H_2O$, presents the same transformation curve.[24,25]

When mass concentration of form A increases from 50 to 100 mg·L^{-1}, the length of the plateau increases, and the total time of the transformation increases from 280 to 405 min (Figures 4 and 5). These results correspond to the fact that when mass concentration of form A increases, the amount of form A available to compensate the diminution of the concentration in solution due to the growth of form B is greater; therefore, the plateau is much longer.

Another interesting point is that the overall kinetics of the SMPT is controlled either by the dissolution kinetics of the metastable form or by the growth kinetics of the stable form or by both. The process which kinetically controls the SMPT can be determined[26] from the shape of the transformation curve, Figure 4 in our example. The SMPT of form A into form B is controlled by the growth of the form B at 40 °C in water (Figure 4).

3.1.2. Influence of the Crystal Habits and of Additive on the Dissolution and Desmotropic Transition of Irbesartan. As the SMPT uses the concept of dissolution, nucleation, and growth, all the factors usually met in crystallization from solution play a role: solvent, temperature, hydrodynamics, crystal sizes and habits, additives, etc.

Here we show the influence of crystal sizes and habits and of additive on the SMPT of irbesartan. Figure 5 shows the differences in the overall kinetics of the SMPT of form A into form B, when larger tabular crystals are used instead of smaller acicular crystals (Figure 2a). The transition lasts 700 min instead of 400 min. This is due to a dissolution rate of tabular crystals lower than that of acicular crystals.

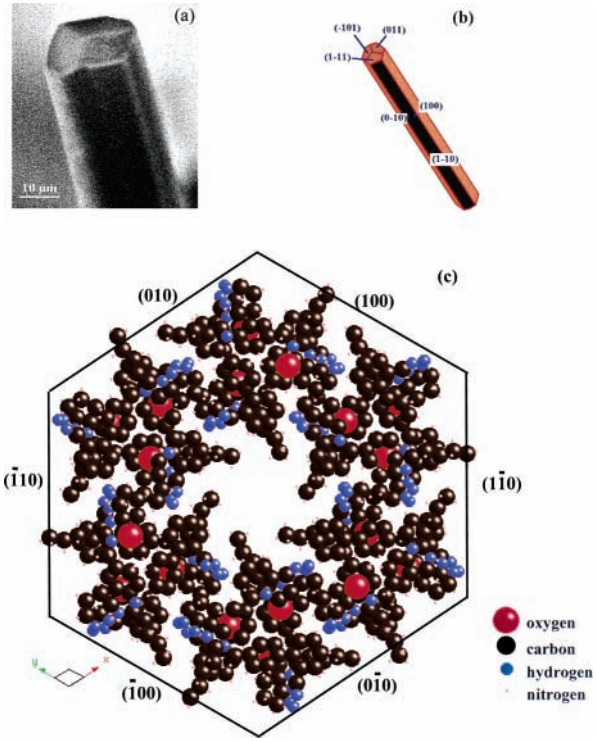

Figure 6. **(a) Experimental morphology obtained for crystals of irbesartan form A grown in water, (b) scheme of the experimental morphology, and (c) packing arrangement of irbesartan molecules viewed along the *c*-axis.**

Because of this lower dissolution rate, the plateau has a lower value. In that case, the diminution of both dissolution rate and plateau concentration values reveals a dissolution-controlled process.[26]

The use of additives to control SMPT is very promising, and many reports deal with such an approach.[27−30] By using the concept of "tailor-made" additives, molecules can be selected from examination of crystal structure and indexation of the experimental morphology of irbesartan form A (Figure 6).[2] Two forms have to be considered, the {100} lateral faces and the {111} terminal faces of the needle. The weak solubility of crystals of irbesartan form A in water (about 11 mg·L^{-1} at 40 °C) and their aggregation in water are due to the hydrophobic nature of the {100} form. These results, together with a previous work[31] in which we evidenced that the first step in the dissolution process of irbesartan form A is disaggregation of the powder lead us to use a surfactant, 50 ppm of dodecylamine chloride (DAC), to accelerate the dissolution (Figure 7). The dissolution of form A is accelerated, and the apparent solubility of form A is increased about

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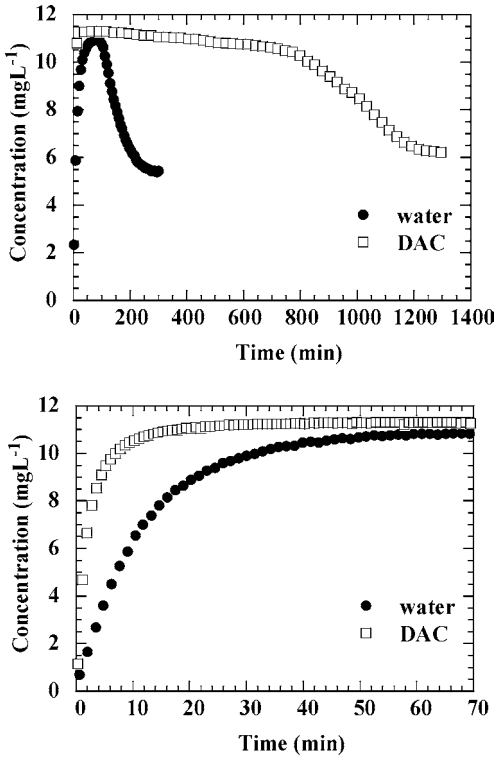

Figure 7. **(a) Variation of concentration versus time due to the SMPT of form A into form B for a mass concentration of 50 mg·L^{-1} at 40 °C in pure water and in the presence of 50 ppm of DAC, (a) the whole process and (b) the first stage.**

10%. It is also interesting to note that the growth rate of form B is slowed, and the whole process lasts 1300 min in the presence of DAC instead of 300 min in pure water. The surfactant has a double effect; it accelerates the dissolution of form A and hinders the growth of form B.

3.2. Polymorphism and Liquid−Liquid Phase Separation of $C_{35}H_{41}Cl_2N_3O_2$. The second case studied concerns a more complicated system, in which two polymorphs have been identified. The use of a solvent mixture is at the origin of LLPS or demixing which affects the crystallization process, with sometimes a poor nucleation ability which may be avoided by seeding.[21] Thus, in this part we will describe polymorph selection and influence of LLPS on seeding.

3.2.1. Isoplethe Section of the Phase Diagram of $C_{35}H_{41}Cl_2N_3O_2$. Figure 8 shows the T_{L-L} boundary, spinodal curve, and solubility of polymorphs F_I and F_{II} in ethanol/water mixture (54.2/45.8% weight). The temperature range corresponds to that used in the industrial crystallization process. This diagram exhibits four regions: one homogeneous region (region I: one liquid) and three two-phase regions (region II: one liquid + one solid FI; region III: one liquid + one solid FII; region IV: two liquids), the two solid phases correspond to the two polymorphs FI and FII. The region IV is divided into two sub-regions by the spinodal curve in which the mechanisms to set off demixing are different (IV(a) and IV(b)).[14]

The graph shows that the polymorphs F_I and F_{II} make an enantiotropic system with a crossover temperature of transition noted T_p. Under this temperature the polymorph F_I is thermodynamically stable, but above T_p, the form F_I becomes metastable with respect to the form F_{II}. T_p was estimated to

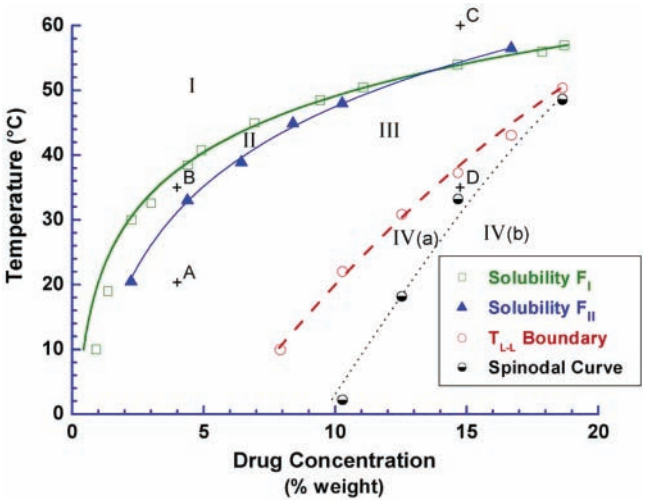

Figure 8. **T_{L-L} boundary, spinodal curve, and solubility of polymorphs F_I and F_{II} in mixture ethanol/water (54.2/45.8% weight).**

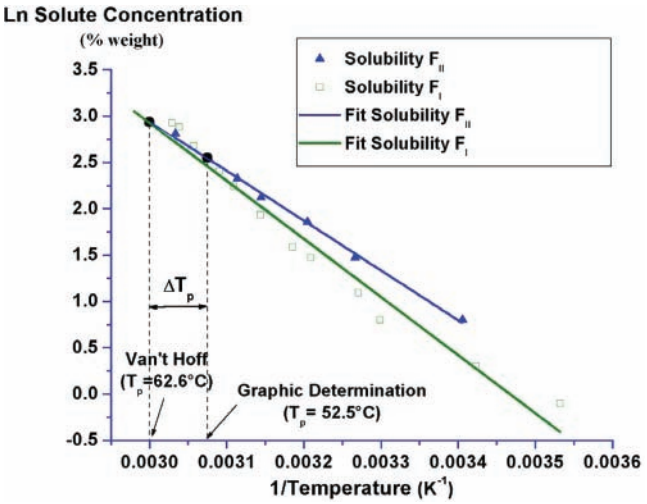

Figure 9. **Solubilities of polymorphs F_I and F_{II} in mixture ethanol/water(54.2/45.8% weight) versus the inverse of the absolute temperature. The solid lines are empirical fits to the data.**

be 52.5 ± 1 °C by graphic determination, this is the reason the transformation of F_I into F_{II} had never been observed previously, since all prior studies were conducted well below T_p.

The solubility variation with temperature of any solute in any solvent is commonly represented by the van't Hoff plot[32] (Figure 9). In our study, the van't Hoff fit gave a transition temperature of 62.6 °C. There is a difference of about 10 °C (Figure 9) with respect to the transition temperature estimated by graphic determination; this showed that the van't Hoff plot was clearly inappropriate here. According to Grant et al.,[33] this nonlinearity of the van't Hoff plot is particularly relevant to drugs and other hydrophobic substances in water and in other self-associated solvents over the temperature range of approximately 0−50

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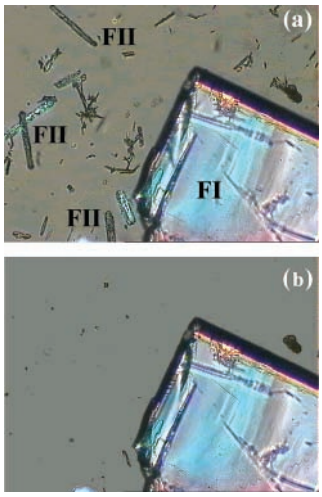

Figure 10. **In situ observations under optical microscopy, of polymorphs F_I and F_{II} in different phase diagram areas. (a) F_I and F_{II} in solution at point A in Figure 8, and (b) F_{II} crystals have completely dissolved and F_I has grown at point B in Figure 8.**

°C. That is why these authors suggested that it was preferable and normally adequate to assume that the apparent partial molar enthalpy of solution, which is independent of temperature only for ideal solutions, is a linear function of temperature. With this assumption, the solution has to be considered as nonideal.

Consequently, this result reminds pharmaceutical scientists of the danger to erroneously attribute the nonlinear solubility behaviour as a phase change in the solid state, such as polymorphism or solvate formation. The slope discontinuity is not necessarily due to the existence of a new polymorph, but it may also be the result of the "nonideality" of the solution.

3.2.2. Polymorph Selection. The understanding of the phase diagram and the experimental setup, quiescent thermostated cell by Peltier effect placed under a microscope (Figure 3), lead to the achievement of the desired polymorph, in a reproducible manner. Our study was aimed at obtaining only one polymorph, for instance F_I, in solution. Thus, when the solution of this drug molecule was concentrated up to 4% weight at 20 °C, (point A in Figure 8), both polymorphs were in suspension (Figure 10a). When the solution was heated to 35 °C (point B in Figure 8) form F_{II} dissolved while F_I remained stable as shown in Figure 10b. As the solubility curves of F_I and F_{II} cross at 52.5 °C, it is easy to select either polymorph by slightly changing the temperature.

3.2.3. Liquid−Liquid Phase Separation and Crystallization. A solution of this pharmaceutical compound at a concentration of 14.6% weight at 60 °C (point C in Figure 8) was cooled to 35 °C (point D in Figure 8). A cloud appeared in the solution, despite a supersaturated solution, this cloud was not due to an amorphous precipitation, gelation, or crystallization of one polymorph but to the appearance of droplets in solution (Figure 11a). The solution separated into two coexisting liquid phases of different compositions, with different densities; one of the phases will be solute- and ethanol rich, and the other will be water rich (the complete characterization of the phase diagram will be

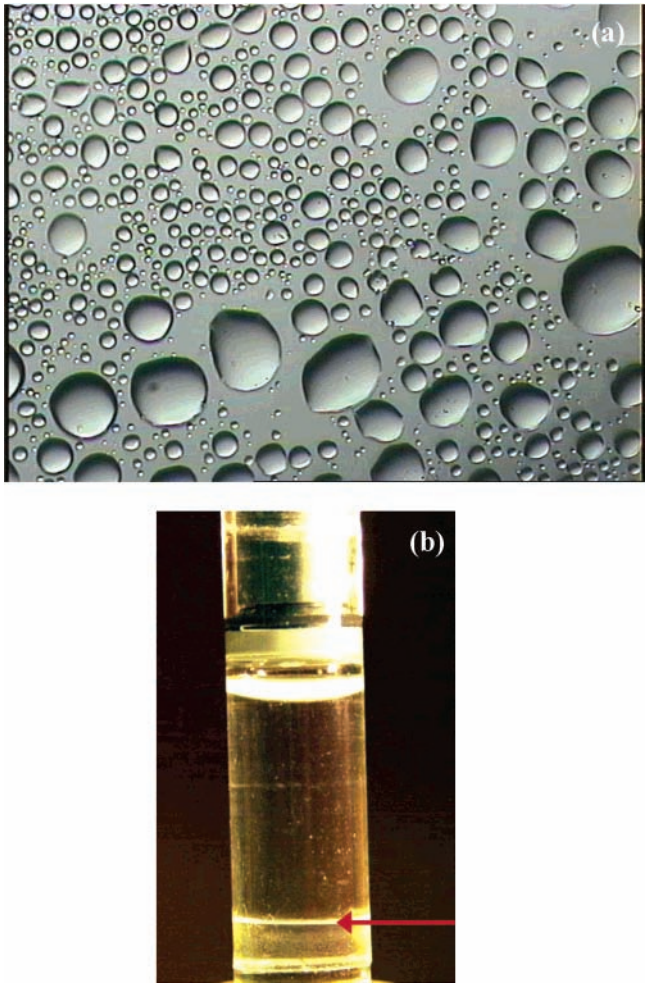

Figure 11. **Photographs of drug solution concentrated to 14.6 wt % in mixture ethanol/water (54.2/45.8 wt %), point D in Figure 8. (a) In situ observations under optical microscopy, of appearance of droplets in the drug solution at 35 °C and (b) photograph of drug solution at 35 °C after 15 min. (The arrow indicates the limit between the two phases.)**

presented in another report in preparation).[34] In a quiescent solution, we observed the decantation of the droplets (Figure 11b), whereas in a stirred medium we observed an emulsion. As shown in Figure 8 (point D), this phase separation occurred in the supersaturated area of the phase diagram with respect to the two solid phases F_I and F_{II}, and at 35 °C F_I is the stable form and F_{II} is the metastable form. This metastable LLPS can significantly affect the crystallization by changing its kinetics. For instance, in a case of seeding with crystals of F_I at point D (Figure 8), crystals which are the stable phase can coexist with the metastable phase, i.e., the droplets (Figure 12a). In Figure 12b, after 12 h, droplets have increased their size by both growth and coalescence. The coalescence of droplets was confirmed by their decreasing number (Figure 12b). Crystals were still growing, and we observed a nucleation of droplets by an heterogeneous mechanism (Figure 12, b and c). At the end of the crystallization process, in the isothermal experiment, the solute concentration reached the solubility of F_I by crossing

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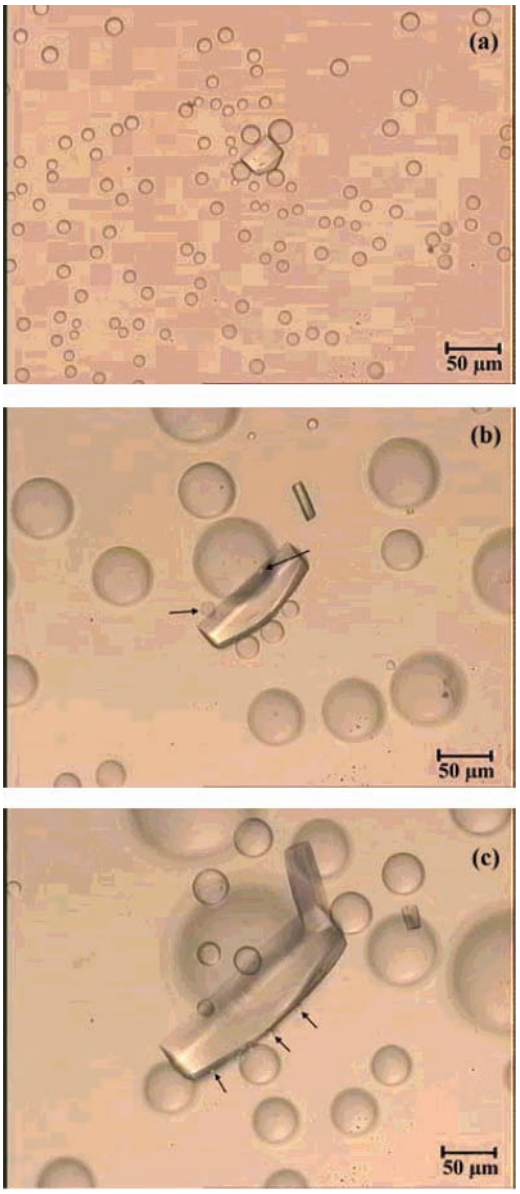

Figure 12. **In situ observations under optical microscopy of seeding with polymorph F_I of drug solution concentrated to 14.6 wt % in mixture ethanol/water (54.2/45.8 wt %) at 35 °C; (a) $t = 0$, (b) $t = 12$ h and (c) $t = 22$ h. (The arrow indicates the heterogeneous nucleation of droplets onto crystal surface).**

the liquid−liquid coexistence curve so that droplets disappeared, crystals grew at the expense of the droplets. Despite the large supersaturation, the crystallization was hindered, and the suspension took a long time to reach equilibrium.

The scale-up of such a process will be uneasy because of the presence of an emulsion and of a ternary phase diagram. It will be difficult to extrapolate the behavior of the suspension of crystals and droplets without further characterization of the system. In the scale-up procedure the most widely used criterion for crystallization process is based on constant power input per unit volume.[35] In the case of emulsion,[36] scale-up at constant power per unit volume produces smaller drops.

We thus conclude that the existence of a LLPS is correlated with the "nonideality" of the solution. The relevance of this LLPS for crystallization is evident because of the composition changes in both liquid phases. That means, at least, that supersaturation and viscosity are affected during the process. The probability of forming a miscibility gap or liquid−liquid demixing increases with the number of components in the system.[37] Thus, the use of a solvent mixture for the sake of the process could lead to a liquid−liquid demixing, and crystallization might thus be hindered.

4. Conclusions

The different stages of the solution-mediated phase transition, i.e., dissolution of the metastable phase and nucleation and growth of the stable phase, were studied for irbesartan, a pharmaceutical compound. The influence of crystal sizes and habits and of additive on the kinetics of dissolution and growth has been shown.

For a system having a liquid−liquid phase separation which is metastable with respect to the crystallization of the two polymorphs, F_I and F_{II} of $C_{35}H_{41}Cl_2N_3O_2$ in an ethanol/water mixture, thermodynamic stability of the forms with each other with temperature was investigated. Thermodynamic stability of the phases towards each other with temperature and the impact of the liquid−liquid phase separation on crystallization have been investigated. Our results show that a deep control of the crystallization parameters (temperature, supersaturation, solution composition, etc.) and the understanding of the phase diagram lead to the achievement of the desired polymorph, in a reproducible manner. Moreover, the dilute solution studied was shown to be nonideal since it was correlated with the existence of the metastable liquid−liquid demixing which was observed and characterized. In our experiments the liquid−liquid phase transition prevented the drug from crystallizing, while it changed the medium and the conditions of crystallization, which consequently affected the process.

Acknowledgment

We are indebted to Sanofi-Synthélabo for financial support, M. C. Toselli for technical assistance, and F. Farnarier for her help in the manuscript correction. We acknowledge the suggestions the reviewers made to clarify this paper.

Received for review June 30, 2003.

OP034089F

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