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Water Activity-Mediated Control of Crystalline Phases of an Active Pharmaceutical Ingredient

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Abstract:

A systematic investigation of the polymorph−hydrate system for Compound I was carried out with the objective of understanding the phase relationships between the different forms as it relates to crystallization conditions. The ternary phase diagram was determined from solubility and KF measurements of the supernatant liquor for Compound I−water−ethanol mixtures. Water concentrations were converted to water activities using the NRTL-RK model as implemented in ASPEN Properties. These water activities were then used in defining phase boundaries between anhydrous and the various hydrated forms of Compound I. Since the critical water activity at the phase boundaries between anhydrous and hydrated forms in water−cosolvent systems is independent of the nature of the cosolvent it can be used to extrapolate the water concentrations defining ternary phase boundaries in any other cosolvent−water system. This was demonstrated in the cases of acetonitrile−water and dimethyl acetamide−water. *Triple points* (anhydrate−hydrate−solvent) were estimated in these two cosolvent−water systems. Two representative crystallizations in these crystallization solvents produced a hemihydrate in 15% acetonitrile−water, and the tetrahydrate in 15% dimethyl acetamide−water, both of which were predicted by the phase diagrams in these systems. The importance of this work lies in obviating the need for phase equilibria measurements in every cosolvent−water system used in crystallization processes. Additionally the crystal structure of hemihydrate was solved by single-crystal X-ray diffraction, and the binding mode of water in the lattice elucidates the thermal and hygroscopicity behavior of this form. In addition the crystal structure unambiguously identified the hemihydrate and enabled the design on an appropriate crystallization process incorporating a_w as a major variable.

Introduction

Pharmaceutical compounds display a rich diversity in crystal forms such as anhydrate, hydrates, solvates, and cocrystals and polymorphs of each of these.[1] One crystal form is typically chosen for further development into the drug product on the basis of solubility, morphology, dissolution rate, thermal stability, and other factors.[2,3] In cases where both anhydrous and hydrated forms can exist as stable solids under typical conditions of processing, storage, and use, the choice of form may be determined by the ease of isolation through crystallization and the kinetics of conversion from anhydrous to the hydrate in an aqueous medium or by considerations of bulk behaviour, for example during tableting operations.[4] Robust crystallization processes involve extensive optimization to improve yield, productivity, impurity rejection, and crystal shape and size control. The variables that can be optimized in the design of such processes include solvent type and composition, temperature, and specific adsorbents to remove select impurities. In order to ensure that the desired crystal form is obtained as the final product, it is crucial to understand the effects of such key variables on phase equilibria.

The role of water activity (a_w) in solid-state stability is also well recognized.[5−7] a_w-based design is useful in determining storage conditions due to its direct correlation with relative humidity.[8] It is also recognized through the solvate rule that at higher a_w (i) hydrates are more stable than the anhydrous form and (ii) higher hydrates are more stable than lower hydrates.[9] A straightforward way to ensure production of the anhydrous form, if desired, is to crystallize under anhydrous conditions. Frequently, however, water is an essential component of the solvent system due to advantages offered in terms of salt or impurity rejection, and due to the fact that it is often the best antisolvent for lipophilic molecules. Incorporating water in the crystallization process can, however, complicate the phase equilibria by enabling the isolation of stable, yet undesirable, hydrates.

One of the most interesting types of solid−liquid phase equilibrium that occurs in the crystallization of pharmaceuticals is that involving anhydrous−hydrate−cosolvent−water. In addition to the state variables of temperature and pressure, water activity assumes the role of a state variable controlling the crystallization of the appropriate form.[5,6] It is possible to preferentially crystallize either the anhydrous or hydrated forms of a compound simply by tuning the water activity of the solvent system.[10] Coupled with temperature, interesting phase behavior can be observed in systems that are liable to form hydrates in addition to anhydrous poly-

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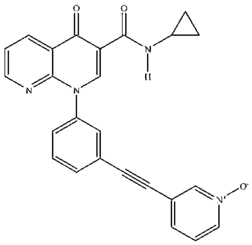

Figure 1. **Chemical structure of Compound I.**

morphs. It is crucial to keep in mind that the variable that is most directly relevant to crystallization in such systems is water *activity* rather than water *concentration*. As will be evident in this work, this is simply because the activity of water in a system can be translated across solvent systems without the need for any additional experimental measurements in more than one cosolvent−water system. For the purposes of this work, only solute concentrations in the infinite-dilution limit of the solute will be considered. The main objective of this paper is to elucidate the phase relationships that exist in a polymorph−hydrate system of Compound I (see Figure 1). Unique crystal forms of Compound I were isolated under different crystallization conditions. These included both anhydrous forms and hydrates, and the occurrence of these forms was found to be a sensitive function of the water activity in the solvent system. The solid−liquid phase equilibrium was measured in one cosolvent−water system. This was followed by computation of the water activities in that system. This enabled the definition of phase boundaries that delineated the conditions of stable existence of different hydrates and anhydrous forms of Compound I in terms of water activity. This information was used to determine the water concentrations that marked the boundaries in two different cosolvent−water systems

The crystal structure of Form B hemihydrate has been solved, and correlations between binding modes of water in the lattice and the physical properties of Form B will be elucidated.

Materials and Methods

X-ray Powder Diffraction (XRPD) Measurements. X-ray diffraction measurements were carried out on an X'Pert Pro (Panalytical Inc., Natick, MA) with a Cu-LFF source of wavelength 1.5418 and operating at 40 kV and 50 mA. Data was collected in the 2−40° *2θ* range.

Water Activity Computations. The activity of water in solvent−water mixtures was calculated using the NRTL-RK (non-random two-liquid-Redlich−Kwong) model as implemented in the ASPEN Properties software program.[11] Nonidealities in the liquid phase are treated through the NRTL framework, while the RK formulation accounts for the vapor-phase properties. This involved the computation of the vapor−liquid equilibria for the solvent mixtures at 25 °C. The liquid-phase activity coefficient, the total pressure, and vapor-phase mole fractions were computed as a function of water mole fraction. The activity was then calculated as

$$a_w = \gamma_w x_w$$

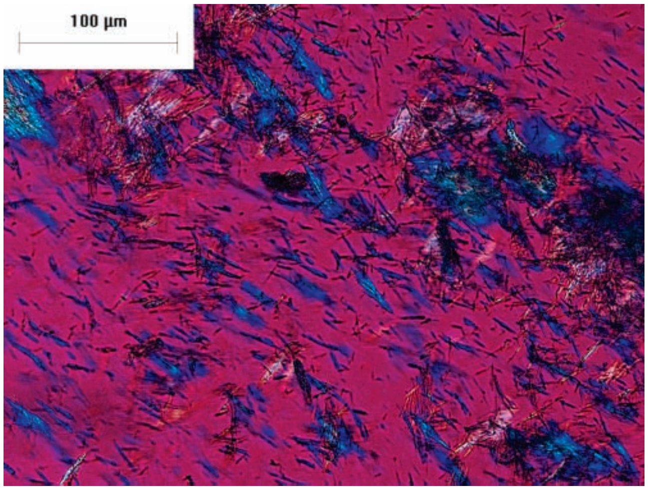

Figure 2. **Optical micrograph of Form A crystals.**

where a_w is the activity, γ_w the activity coefficient, and x_w the mole fraction of water in the mixture.

Solubility Measurements. For all solids, an excess was equilibrated with 2 mL of solvent in flame-sealed glass tubes and placed in water baths at various temperatures for a time ranging from 2 to 3 days. After temperature equilibration, the glass tubes were placed within metallic tubes containing water at the same temperature and were quickly centrifuged. The glass tubes were then opened and the supernatant transferred to volumetric flasks. Warmed pipettes were used to transfer supernatants in experiments conducted at higher temperatures. Dilutions were prepared appropriately, and concentrations were analyzed by chromatography, and solids, by X-ray diffraction.

Thermal Analysis. Thermogravimetric analysis was carried out in a TGA7 (Perkin-Elmer) instrument with N_2 as purge gas from 20 to 300 °C in an open aluminum pan.

Moisture Sorption. Isothermal moisture sorption isotherms were measured in a VTI balance (VTI, Hialeah, FL). A known weight of sample was placed in the sample pan along with an empty reference pan. About 15−20 mg of sample was used for each run. A drying step at 60 °C for 120 min was incorporated at the beginning of the runs. The moisture uptake was monitored from 5% to 95% relative humidity (RH) with an equilibrium criterion of 0.001 wt %/min. The kinetics of water absorption was monitored to ensure that equilibrium was attained at each RH.

Results and Discussion

Crystal Forms of Compound I. Compound I (free base) was chosen for development since it had adequate bioavailability and all of its salt forms were found to disproportionate rapidly in aqueous systems. The typical morphology of an anhydrous form of Compound I, Form A, is needle-like (Figure 2). It is nonhygroscopic [Supporting Information] and exhibits a detonation temperature without an obvious melting event [Supporting Information].

Subsequently, another crystalline form of Compound I, Form B, with plate-like morphology (Figure 3), was discov-

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(11) *ASPENPlus*, Version 2002; ASPENTECH: Cambridge, MA.

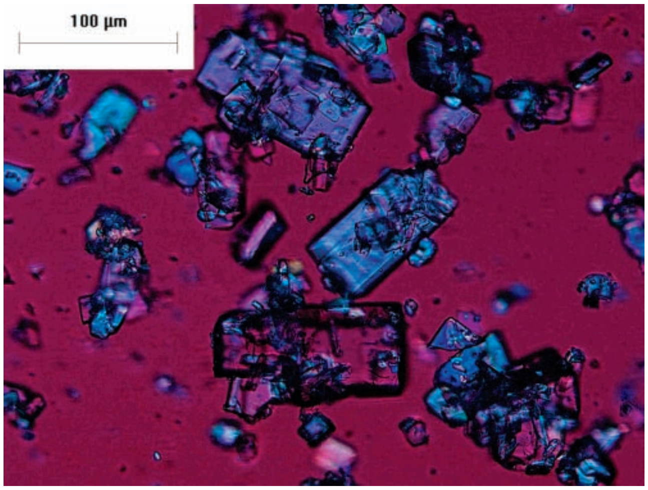

Figure 3. **Optical micrograph of Form B crystals.**

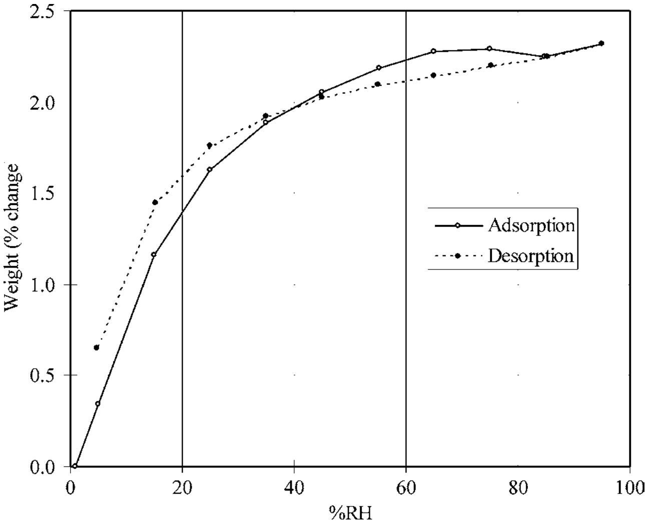

Figure 4. **Hygroscopicity profile of Form B hemihydrate.**

ered. The moisture sorption profile of Form B after a drying step at 40 °C is shown in Figure 4. The dried solid absorbs a maximum of 2.3% water at 95% RH (theoretical hemihydrate is 2.0%) in a continuous manner (Figure 4).

The equilibrium water content of this phase depends on the relative humidity. Above 75% RH a hemihydrate is formed. The form obtained upon drying will be referred to as Form C.

Thermogravimetric analysis of Form B indicated that the water is completely lost only at ~200 °C [Supporting Information]. Further, Figure 5 shows the XRPD patterns of two samples, one containing 0.6% water (which had been absorbed during the XRPD experiment) and one containing 2.0% water.

The former clearly shows peaks shifts attributed to dehydration of the latter especially at higher angles ($>15°$ 2θ). The combination of the energetics of water loss and XRPD patterns points to the conclusion that the crystal lattice can incorporate varying amounts of water accompanied by small changes in unit cell dimensions. This will be discussed in detail in the next section.

A slurry of Form A or B in water results in the formation of a tetrahydrate (Form D), which exists only in equilibrium

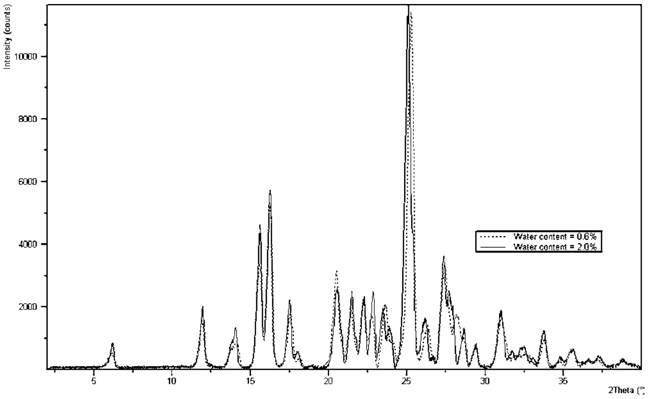

Figure 5. **XRPD patterns of samples containing 0.6% and 2.0% water.**

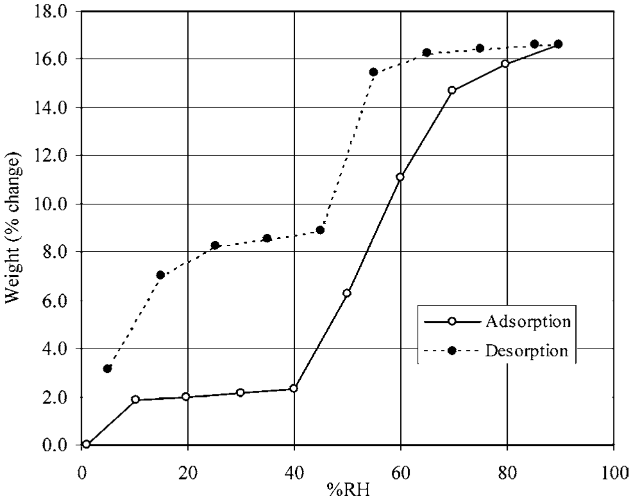

Figure 6. **Hygroscopicity profile of the tetrahydrate.**

with water. It is interesting that the hygroscopicity profiles of both Forms A and B do not show the production of the tetrahydrate even at high RH. This is most probably due to a kinetic barrier to the nucleation and growth of the higher hydrate in the solid state. Exposure of the tetrahydrate to varying RHs (The absorption steps are preceded by a drying step at 60 C° under N_2 flow.) in a moisture balance results in the curve shown in Figure 6.

The tetrahydrate loses all its water of hydration upon drying to form a dehydrate, Form E. Upon exposure to increasing amounts of moisture, Form E converts to a hemihydrate (Form F) between 15% and 45% RH followed by the formation of Form D at higher RH. Upon desorption, Form D dehydrates to a dihydrate (Form G) between 35% and 15% RH and a monohydrate, Form H, at 5% RH. At lower RH another anhydrous form, Form I, is obtained. Form I is unstable under ambient conditions and hydrates quickly to Form H under ambient conditions. This cycle of moisture absorption/desorption shows the importance of kinetics in the isolation of different hydrates and anhydrous forms for Compound I. A concise pictorial representation of the phase relationships is provided in Figure 7.

Development work subsequently focused on the relationships between forms A (anhydrous form), B (hemihydrate), and D (tetrahydrate). This choice was driven by the observation that Forms A and B were physically and chemically

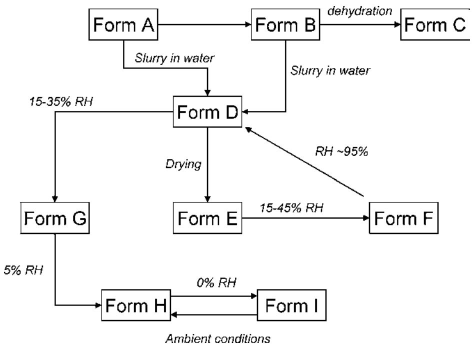

Figure 7. **Phase relationships in Compound I.**

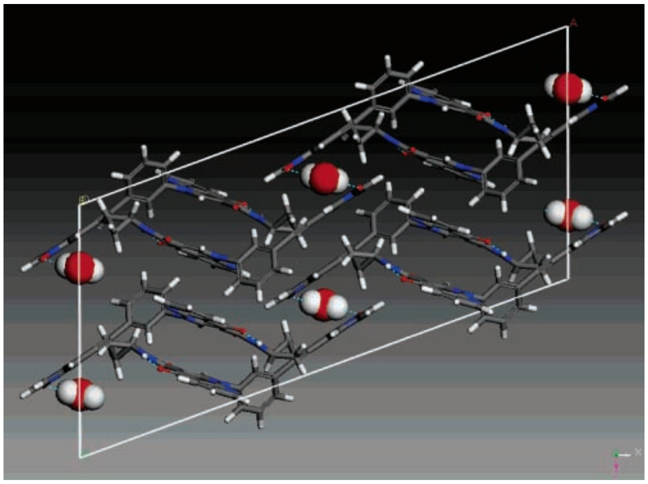

Figure 8. **Single-crystal structure of Form B hemihydrate. The water molecules are rendered as CPK structures.**

stable under ambient conditions for at least 2 years and the tetrahydrate form is the stable phase in water, making these phases of particular importance to product development.

Crystal Structure of Form B Hemihydrate. A better understanding of lattice changes in Form B due to water content can be obtained by considering the single-crystal structure that has been solved for the hemihydrate and that is shown in Figure 8. Even though the hemiydrate is thermodynamically stable above 75% RH, it was found to be kinetically stable under ambient RH as measured by water content of a sample stored in a vial over a period of 2 months. Single-crystal X-ray analysis, however, was carried out at 100 K to prevent any loss of lattice water during the structure-solution process. Form B hemihydrate crystallizes in the monoclinic $C_{2/C}$ space group with unit cell parameters of $a = 31.9524$ Å, $b = 8.7675$ Å, $c = 15.5264$ Å, and $\beta = 109.96°$. The molecules of Compound I are packed in a herringbone motif with one water molecule bridging two drug molecules at the N−O sites. No evidence of channeling is observed. In fact, the binding motif and placement of the molecules is suggestive of a strong intermolecular interaction between the drug and water molecules. This is also reflected in the weight loss behavior on the TG and the extent of the endotherm observed on the DSC. Complete dehydration can only be effected at temperatures as high as 200 °C. Upon dehydration, noticeable shifts in peak positions are observed at $2\theta = 17.1°$, 23.1°, 24.8°, 25.0°, 25.9°, and 27.6°. The *hkl* planes *5 1 −1*, *6 0 −4*, and *3 1 3* corresponding to three of these peaks, 17.1°, 24.8°, and 25.0°, are visualized in Figure 9. These planes are observed to cut through the hydrogen bonds between water and the N−O group on Compound I. Therefore, upon release of water, significant changes can be expected in the peak positions corresponding to these planes. This phenomenon is indeed observed in the X-ray pattern in Figure 4 as a general shift to higher 2θ or smaller d-spacings.

Process Development. Large-scale crystallization efforts to produce anhydrous Form A, sometimes resulted in the production of Form C (upon drying), and the production of either form was found to be dependent on the water content in the crystallization solvent. In order to develop a robust crystallization process to produce anhydrous Form A, the solid−liquid equilibria in anhydrous and aqueous solvent systems were investigated. It is well-known that the relative stability of anhydrous polymorphs can be estimated from the solubilities of the forms in any solvent system. In general, the anhydrous form with the lower solubility would have a lower free energy and hence is more stable than the form with a higher solubility. The solubilities of the anhydrous forms in dehydrated ethanol were measured at various temperatures. Throughout the temperature range between 5 and 35 °C, Form A was found to be more stable than Form C (Figure 10).

XRPD of the excess solids isolated at the end of the solubility experiment confirmed the preservation of the individual crystal forms. Consequently, it is advantageous to choose Form A for development. These solubility experiments only explain the relative stabilities of *anhydrous Forms A and C in anhydrous solvent* systems. Since it was observed that Form C converts to Form B under ambient conditions given sufficient time, a more thorough investigation including water activity was carried out.

It was pointed out that a continuous lattice change accompanies absorption of water by Form C or desorption of water by Form B, as observed in the vapor sorption experiment. Thus, there exists a continuum of phases, depending on water activity. However, for purposes of process development and our main arguments in this work we will consider this continuum of phases as a single phase.

Stability Relationships between Forms as a Function of Water Activity. There are at least three ways in which the relative stabilities or stability regimes of different crystal forms as a function of water activity can be determined:

(1) by measuring the equilibrium solubility of each of the crystal forms over the entire range of water activity and by confirming the identity of the resultant solid phases by X-ray diffraction at the end of each measurement. In this case, a metastable form may or may not convert to the most stable form, depending on whether a kinetic barrier exists in the absence of seeding. Subsequently, when plotting a phase diagram, only the solubility of the most stable form is plotted as a function of a_w.

(2) by measuring the solubility of a physical mixture of all possible crystal forms as a function of water activity and by confirming the identity of the resultant solid phases by X-ray diffraction. This method is more robust then method

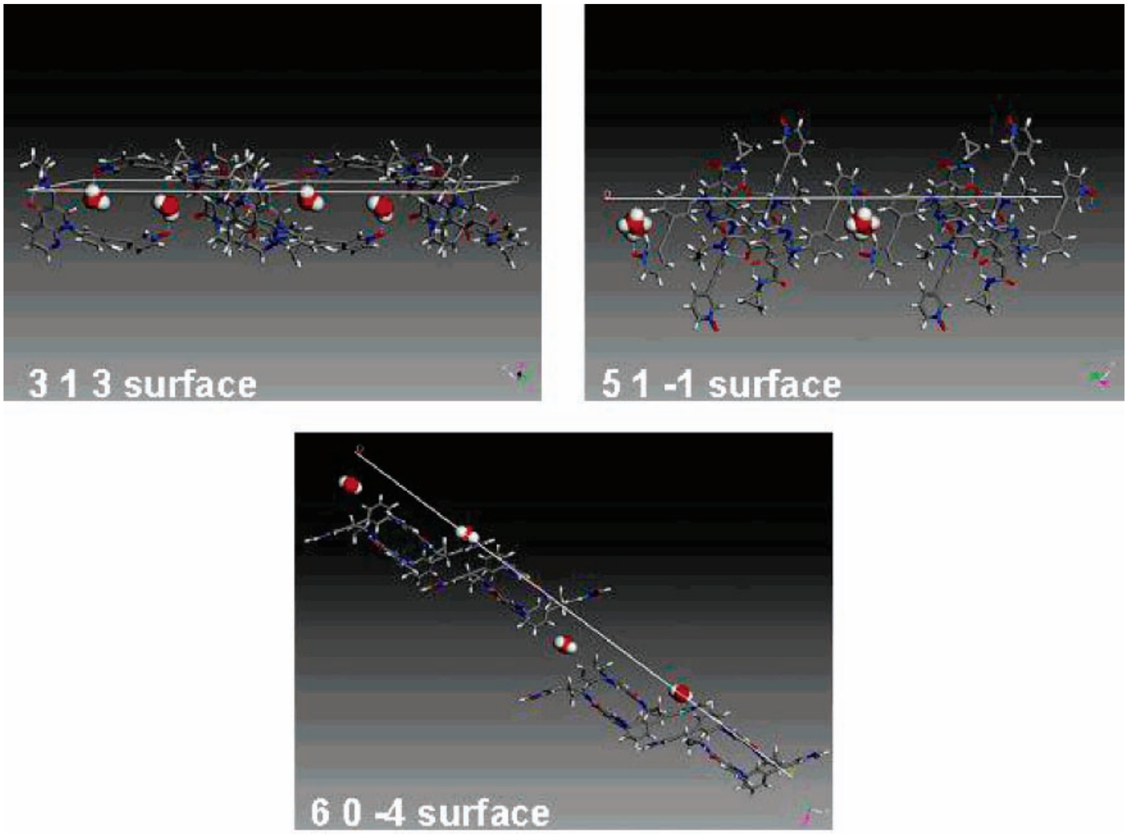

Figure 9. **Three *hkl* planes corresponding to the most prominent shifts in peak positions in the powder X-ray patterns upon dehydration of Form B hemihydrate. The planes are represented as white lines. The relative orientation of the different surfaces is not intended to reflect actual locations in the unit cell and is just for visualization purposes.**

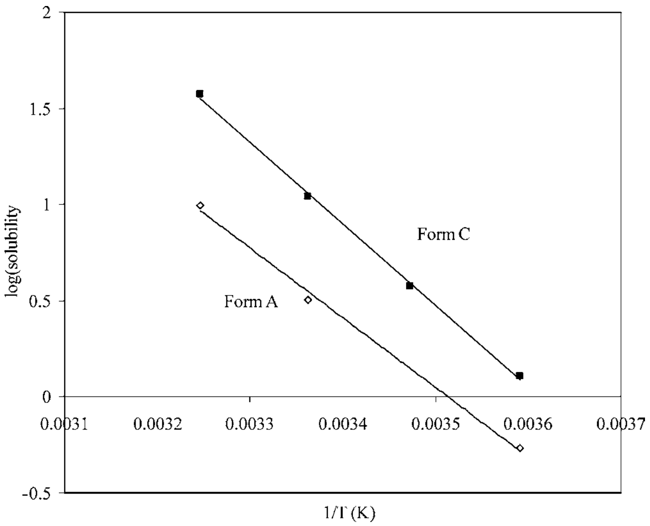

Figure 10. **van't Hoff plot for Forms A and C in dry ethanol.**

1 since metastable forms have a greater chance of converting to the most stable forms through the presence of seed of the most stable form.

(3) by equilibrating an excess of a mixture of forms (anhydrous and hydrate or lower and higher hydrate) whose phase boundaries are required, in *anhydrous* solvent and measuring a_w of the mother liquors.[12]

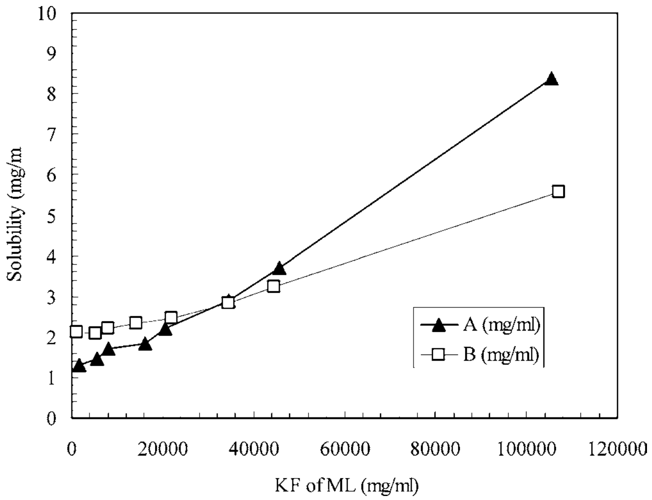

Figure 11. **Solubilities of Forms A and B as a function of water % in ethanol. *X*-axis represents water content measured by Karl Fisher (KF) titration of the mother liquors (ML).**

In this study, a combination of methods 1 and 2 was employed. The individual solubilities of Forms A and B were measured in water−ethanol mixtures of varying concentrations. The individual solubilities of Forms A and B were measured in water−ethanol mixtures of varying water concentrations.

Figure 11 shows the solubility of Forms A and B or concentration in solution of Compound I as a function of water content in mother liquors.

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[12] Crocker, L. S.; Ge, Z.; Abrahim, A.; Hartman, R.; Xu, J. *Org. Process Res. Dev.* **2003**, *7*, 958.

Table 1. **Slurry turnover in (a) water−ethanol mixture at 25 °C, (b) at 70 °C, (c) water−dimethyl acetamide at 25 °C and (d) at 60 °C**

(a) Water−Ethanol Mixture at 25 °C			(b) Water−Ethanol Mixture at 70 °C		
water vol %	a_w	final form	water vol %	a_w	final form
0	0	A	0	0	A
2.5	0.10	A	2.5	0.12	A
5	0.19	B	5	0.21	A
7.5	0.28	B	7.5	0.30	B
10	0.35	B	10	0.37	B
20	0.58	B	20	0.60	B
40	0.81	tetrahydrate	40	0.82	B+tetrahydrate
60	0.90	tetrahydrate	60	0.90	tetrahydrate
80	0.95	tetrahydrate	80	95	tetrahydrate
100	1	tetrahydrate	100	1	tetrahydrate

(c) Water−Dimethyl Acetamide at 25 °C			(d) Water−Dimethyl Acetamide at 60 °C		
water vol %	a_w	final form	water vol %	a_w	final form
20	0	B	20	0.47	B
25	0.48	B	25	0.57	B
30	0.58	B	30	0.66	B
35	0.66	B	35	0.73	B
40	0.72	tetrahydrate	40	0.78	B
50	0.83	tetrahydrate	50	0.86	B+tetrahydrate
60	0.89	tetrahydrate	60	0.91	tetrahydrate
80	0.96	tetrahydrate	80	0.96	tetrahydrate
100	1	tetrahydrate	100	1	tetrahydrate

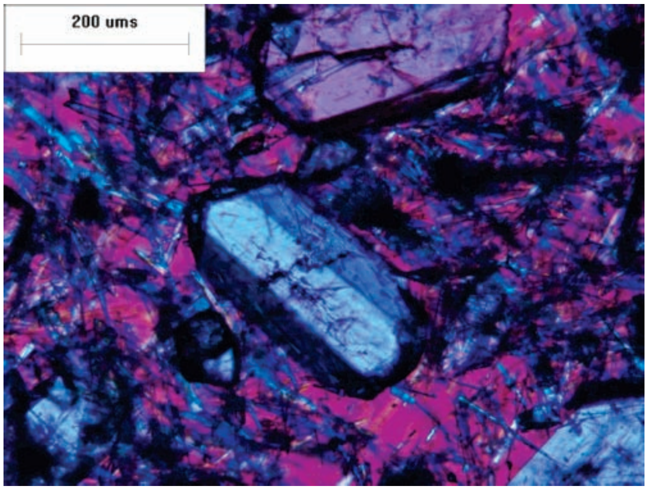

Figure 12. **Coexistence of Forms A and B in 3.2 vol % water in ethanol solution after 1 year. The needles are Form A, while the plates are Form B.**

The solubility curves of Forms A and B cross over at a water concentration of 3.2% (v/v) in ethanol, corresponding to a solubility of 2.8 mg/mL at 25 °C. This theoretically represents the triple-phase point where thermodynamic equilibrium would exist between Form A, Form B, and saturated solution. Assuming infinite dilution of the solute, this concentration translates to a water activity of 0.09 at 25 °C. If a mixture of the forms is prepared under these conditions both forms could potentially survive indefinitely in equilibrium with each other and the saturated solution. This is visually shown in Figure 12 where the needles of Form A were found to coexist with plates of Form B after 1 year in an ethanol solution containing 3.2% water at 25 °C.

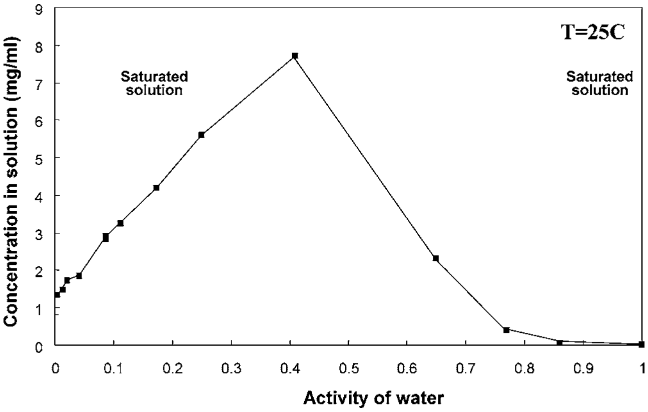

Figure 13. **Solubility curve of Compound I as a function of water activity at 25 °C.**

Equimolar mixtures of A, B, and tetrahydrate were also slurried in increasing amounts of water in ethanol. Results are shown in Table 1a where independent slurry experiments from low vol % water experiments are also included. Conversion to Form B is observed between 2.5% and 5% water and to the tetrahydrate between 20% and 40% water, i.e., Form A is the stable phase below $a_w = 0.1$; Form B is stable in the region $0.09 < a_w < 0.4$, whereas the tetrahydrate is the stable solid phase for $a_w > 0.4$. A graphical representation is depicted in Figure 13.

Effect of Cosolvent and Temperature on Triple-Phase Point. The advantage of reducing the phase diagrams in aqueous systems to activities instead of concentrations is clearly apparent when one considers that this activity can be translated to other water-cosolvent systems, *at the same temperature*, in a straightforward manner. This is particularly useful if (i) multiple cosolvent systems have to be screened for purposes such as impurity rejection, increasing yield and productivity, or in altering the morphology or habit of the crystals from the crystallization process and (ii) multiple forms including anhydrous and hydrates exist for the compound being crystallized and a particular solid phase is to be targeted; for example, in the present case, the desirable solid phase was the anhydrous Form A. Table 1 also shows the results of slurry experiments in water−ethanol at 70 °C (part b), water−dimethyl acetamide at 25 °C (part c) and water−dimethyl acetamide at 60 °C (part d). At 70 °C in water−ethanol between 5 and 7.5% water is required to transform to Form B as opposed to 3.2% at 25 °C, and between 40 and 60% water is required to convert to tetrahydrate compared to 20−40% at 25 °C. A similar trend is observed in water−dimethyl acetamide where Form B is stable to a much higher water activity at 70 °C than at 25 °C. The transition between Form B and tetrahydrate occurs in the region $0.58 < a_w < 0.81$ in water−ethanol at 25 °C and in $0.66 < a_w < 0.72$ in water−dimethyl acetamide at the same temperature. Thus, with increasing temperature, the transition between anhydrous to a hydrate and between a lower hydrate to a higher hydrate occurs at higher water activities, and the transition point seems to be relatively insensitive to cosolvent at the same temperature.

Crystallizations were carried out in two different solvent systems as part of process development, (i) 15/1/5 (v/v/v) DMAC−AcOH−water and (ii) 15% (v/v) water−acetonitrile. In these cases, the first solvent system was able to reject Pd in the process stream very effectively, whereas the second crystallization solvent system offered the best impurity rejection. These crystallizations, however, produced Form B and the *tetrahydrate* form, respectively. With the knowledge of the phase diagram expressed in water activities, it was possible to immediately predict the solid phase that would be produced—*under thermodynamic equilibrium conditions*—in both cases. The calculated water activity in the first case is 0.195 and in the second case 0.65. Form B is produced in the first case, while the tetrahydrate form D is produced in the second. This is indeed observed from the crystallization processes.

Thus, it is possible to design suitable solvent systems to ensure the crystallization of the appropriate form, once the thermodynamic phase diagram is known in one solvent−water system. This is accomplished by calculating the water activity at the transition points in any one solvent−water system and translating this water activity into water concentration in any other solvent−water system. This greatly reduces the number of experiments that have to be carried in order to establish the stability regimes for different solute−water−cosolvent systems. The only approximation involved in the calculations is the assumption of the infinite dilution limit for the solute. The maximum solute concentration in this study was ~10 mg/mL or 0.02 mol/L. The concentration at the triple point is ~0.002 mol/L at 25 °C in the ethanol−water system.

Peculiarities of the Crystalline Forms of Compound I. It was noted in the beginning that Form A was nonhygroscopic, even though several hydrates of Compound I have been discovered. This phenomenon is not uncommon and is driven by the high activation energy required for hydrate formation in the solid state when exposed to water in the vapor phase as opposed to liquid water. Slurrying of Compound I in hydro/alcoholic or other aqueous solutions of sufficient water activity is required for the formation of hydrates. Whereas Form A did not form hydrates in a moisture sorption experiment, Form C was found to hydrate in a continuous manner upon exposure to different RH levels, but only up to a hemihydrate, Form B. A water slurry of either Form A or B is required to form the tetrahydrate, the crystalline phase in equilibrium with saturated solution in water. An estimate of the relative humidity corresponding to the transition points between anhydrous and hydrated forms can be obtained very simply as outlined by Sacchetti et al.[7] However, this estimate is of limited practical utility in the case of molecules such as Compound I due to hindered kinetics in the solid state even by incorporating, for example, seed of the hydrate.[13]

Practical Issues in Isolating Hydrates. Even though the form chosen for development in this program was anhydrous, it is equally plausible to develop a hydrate, for example, Form B. However, the following factors should be borne in mind when developing hydrates. Using a combination of thermal analysis and water content measurements (Karl Fischer titration) a general idea of the nature of the hydrate can be obtained. This is particularly important since hydrates have been classified into various types,[14,15] isolated-site stoichiometric hydrates, nonstoichiometric channel hydrates, and ion-coordinated hydrates. These have been referred to as Class I, II, and III hydrates, respectively. Such definitions are, however, to be considered only as operational descriptions. For example, the structure of Form B would classify it as a Class I hydrate purely on the basis of the location of the water molecules. However, its adsorption−desorption behavior would classify it as a Class II hydrate since there is a continuous change in lattice, depending on water content. Further, it was already stated that Form B has been found to be kinetically stable as a hemihydrate for at least 2 months (up to which time data was collected). These considerations are important in isolating Form B from a crystallization process. To ensure robust production of Form B, the drying could be implemented under *humid conditions* with an RH of at least 75%. It is well-known to those who practice crystallization that humid-drying (for example using a N_2 stream with an RH of ≥75%) often accelerates removal of solvents such as alcohols and acetonitrile due to the affinity of such solvents to water in the drying stream. Thus, it is possible that an accelerated and robust isolation process could be developed with knowledge of the type of hydrate and its adsorption−desorption behavior.

Channel hydrates pose various other problems in isolation. Due to the variability in water content with RH and the weak interactions between water and the drug molecule, not only

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must humid drying be carried out, but consideration should also be given to storage and the setting of specifications of water content in the solid phase. These considerations fall outside the scope of this work and will not be discussed any further.

Conclusions

This work aims to elucidate some general principles of hydration in pharmaceutical development by analyzing the relationships of the crystal forms in Compound I. These include the following:

(i) The critical parameter in designing suitable crystallization processes in systems characterized by both anhydrous and hydrated forms is the *activity* of water rather than *concentration* in the aqueous solution.

(ii) The production and stabilization of hydrates or anhydrous forms requires the existence of the appropriate water *activity* in the environment.

(iii) The transformation of an anhydrous form to a hydrate is often limited by the restricted mobility in the solid state as often experienced in a moisture sorption experiment. Frequently, slurrying in aqueous solutions may be required to form hydrates.

(iv) Considerable resources can be saved by expressing the phase equilibria in anhydrous−hydrate systems in terms of water activity. This is because, once the phase boundaries are established in one cosolvent−water system, the activity boundaries can be simply converted to water concentrations in any other cosolvent−water system. The only approximation involved in these calculations is the assumption of infinite dilution of the solute which is very reasonable at the solubility levels observed in this study.

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Supporting Information Available

The physical properties of Form A, crystallization data of Form B in CIF format, and a diagram illustrating the phase relationships between different forms of Compound I. This material is available free of charge via the Internet at http://pubs.acs.org.

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