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Crystallisation Design Space: Avoiding a Hydrate in a Water-Based Process

Simon N. Black,* Andrew Phillips, and Claire I. Scott

AstraZeneca, Process Research and Development, Macclesfield SK10 2NA, England

Abstract:

Many compounds can exist in either hydrated or anhydrous crystalline forms. The demands of robust processing and consistent product performance usually mean that only one of these two forms is desired, and that mixtures are unacceptable. Where the crystallisation is preceded by a phase separation and a distillation, liquid−liquid, vapor−liquid and solid−liquid equilibria all affect the outcome. The theory behind these equilibria is presented to show how they intersect. This approach is applied to a practical example in which a nominally "nonaqueous" liquid layer is separated from an "aqueous" layer and then distilled with simultaneous crystallisation. In-line technology is used in the laboratory to assist in the definition of a "Design Space"— an area in which this complicated isolation process operates robustly at scale using simple, conventional measurements.

Introduction

Many organic compounds and molecular salts form hydrates. This can result in different pharmaceutical bioavailabilities, different physical characteristics, and different particle sizes from the anhydrate form. Some, such as lisinopril and omeprazole, are of considerable commercial importance as pharmaceuticals.

One such in-house novel drug substance has several potential forms including solvates, hydrates and an anhydrate form. The final manufacturing stage has the potential to access two of these forms: the anhydrate and the hydrate. The two figures (Figure 1 and Figure 2) show the difference in size and shape of the crystals for the two forms. These two forms have been shown to have similar bioavailability, but the anhydrate is the preferred form due to manufacturability (shorter filtration times and consistency for milling).

Generally, the simplest way to develop a robust process for avoiding a hydrate is to exclude water altogether. If water is indispensable, the relative stabilities of the hydrate and the anhydrous phases must be determined.[1,2] The thermodynamic stabilities are determined by the water activity.[3] Slurry experiments with different amounts of water have been used to determine the amount of water required to ensure or avoid hydrates,[4] and are now very common in the pharmaceutical industry. Slurry experiments and crystallisations sometimes yield mixtures of hydrated and anhydrous solid phases.[5]

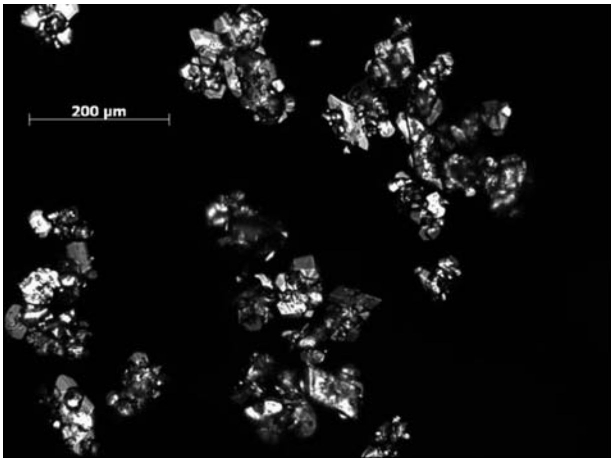

Figure 1. **Optical micrograph of hydrate crystals.**

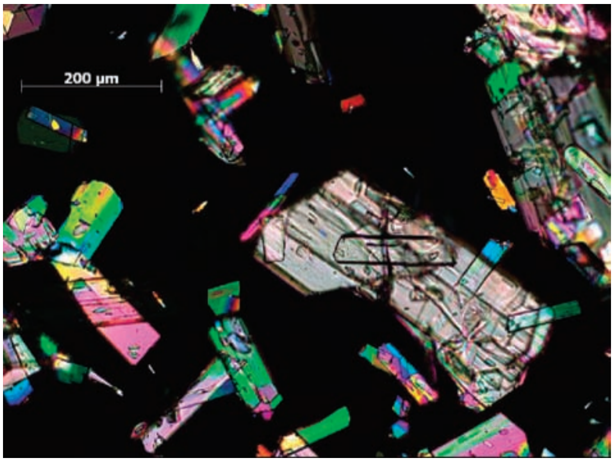

Figure 2. **Optical micrograph of anhydrate crystals.**

In a simple recrystallisation, the amount of water present is known precisely because it is the amount added to the vessel. Many synthetic procedures are more complex, incorporating separations of aqueous layers and distillations. Controlling the level of water in such procedures is more complex, requiring an understanding of more than the solid−liquid equilibrium (SLE). Liquid−liquid equilibria (LLE) provide the thermodynamic basis for separations of aqueous layers, and vapor−liquid equilibria (VLE) are required for distillations. These equilibria are well understood[6] and for most common solvents are amenable to modelling.

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* Author for correspondence. E-mail: simon.black@astrazeneca.com.

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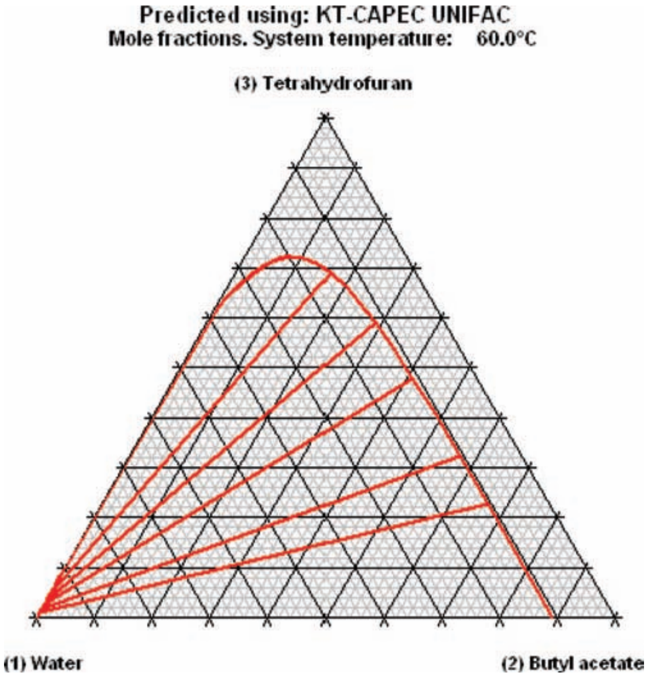

Figure 3. **Liquid−liquid equilibrium phase diagram for water, butyl acetate, and THF.**

Here we describe the design of a robust crystallisation process to prepare the anhydrous form of an API in the presence of water. The process studied involves dissolving the crude material in tetrahydrofuran, *n*-butyl acetate and water. The water layer is removed and the organic layer screened. Further tetrahydrofuran and *n*-butyl acetate are added, and the mixture is distilled, during which crystallisation occurs. The slurry is cooled, and the solid product is isolated by filtration, washed, and dried. The water activity in the solid phase is linked to the activity in the liquid and vapor phases. Ternary phase diagrams are used to explain all three equilibria.

2. Theory

2.1. Water Activity, VLE, and LLE. The water activity in a system is the ratio of the fugacity (a measure of the chemical potential) of water in the mixture compared to the fugacity of pure water in a standard state.[7] The standard state is defined as being at the temperature of interest, so by assuming an ideal gas and applying both Dalton and Raoult's laws the water activity can be calculated using the following equation where P^T is the total system pressure, P^0 the vapor pressure at the system temperature, y_w is the mole fraction of water in the vapor phase, γ is the activity coefficient of water in the mixture and x is the mole fraction. As will be shown later, x and γ can be calculated using computer modelling, and hence, the water activity can be calculated.

$$\text{Water Activity} = \frac{f_i}{f_i^0} = \frac{y_w P^T}{P^0} = \frac{x\gamma P^0}{P^0} = x \cdot \gamma \qquad (1)$$

It is common to refer to two liquid phases formed after an extraction using water as the aqueous and the organic layer. This nomenclature is misleading, as the organic layer will contain some water and vice versa. The water activity in the two phases must be equal at equilibrium, which is usually established rapidly. The concentration of water in the organic layer may be low, but it will have high (re)activity.

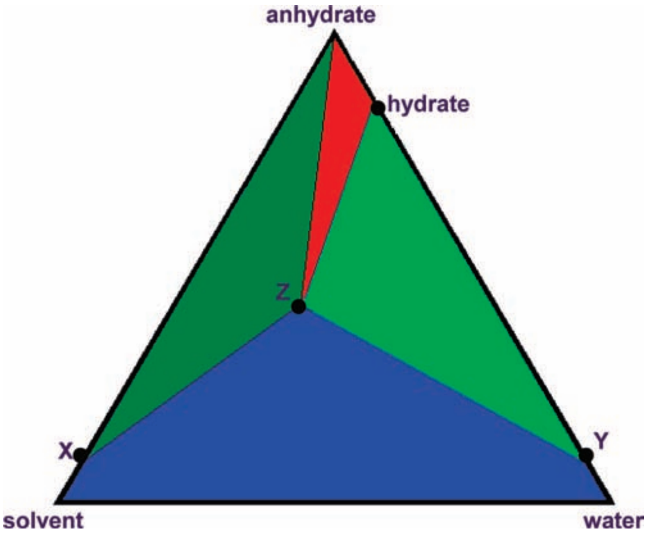

Figure 4. **Schematic isothermal ternary phase diagram for water, miscible organic solvent, and solute, where the solute forms a hydrate.**

The actual water content of each layer can be calculated using the UNIFAC functional group excess Gibbs energy model as shown in Figure 3. On this liquid−liquid phase diagram the bell-shaped region corresponds to an area of compositional space where two liquid phases are present. Inside this region the overall system composition will be located on one of the straight "tie lines". The two ends of the tie line specify the compositions of the aqueous and organic phases. Outside the bell-shaped region the system is fully miscible so that only one liquid phase exists. Without the presence of *n*-butylacetate, water and tetrahydrofuran are fully miscible.

At equilibrium, the relative humidity (RH), expressed as a decimal fraction, is equal to the water activity, both in the vapor phase and in solution.[3]

2.2. Solid−Liquid Equilibria Including Hydrate and Anhydrate Forms. The intention is to design a process to produce anhydrate only. It is important to know not only under what conditions the hydrate will form but also under what conditions hydrate and anhydrate can coexist in thermodynamic equilibrium. The application of the phase rule to such systems has been discussed elsewhere.[8] It is not possible to use two-dimensional solubility curves to represent the phase behavior of this system. For three-component systems, isothermal triangular phase diagrams are a convenient way of displaying such information.[9,10] Their use for three-liquid systems (distillation

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(7) Sandler, S. I. *Chemical, Biochemical and Engineering Thermodynamics*, 4th ed.; John Wiley & Sons: Hoboken, NJ, 2006; p 711.

(8) (a) Li, Y.; Chow, P. S.; Tan, R. B. H.; Black, S. N. *Org. Process Res. Dev.* **2008**, *12*, 264–270. (b) The phase diagram in Figure 4 makes explicit what is not clear from Figure 2 in this earlier paper: namely the position and significance of points X and Y.

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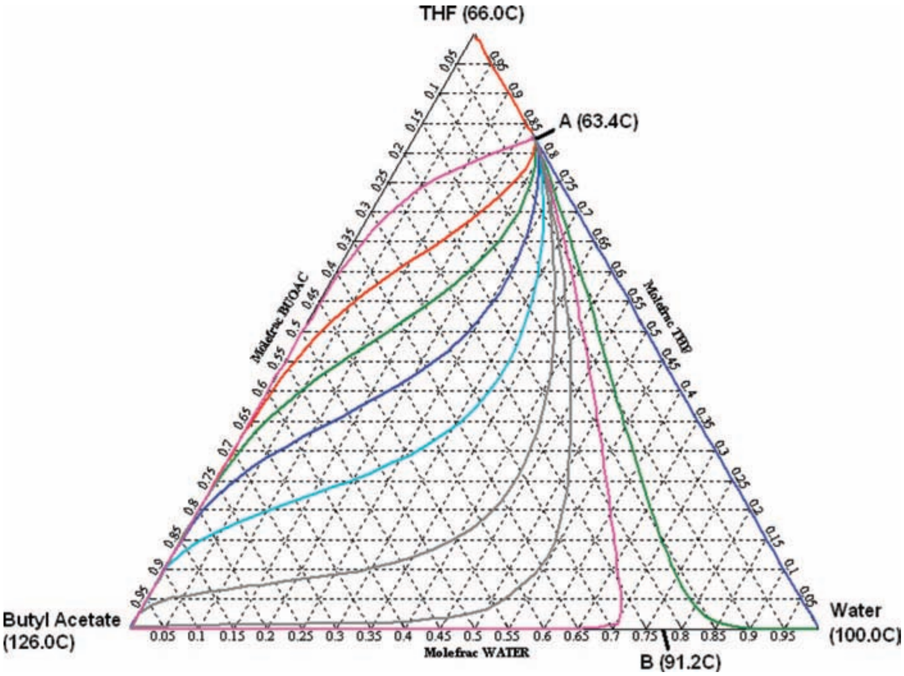

Figure 5. **Residue curve map for tetrahydrofuran, *n*-butyl acetate, and water.**

curves) and enantiomers is commonplace.[11−13] Figure 4 shows such a diagram for a system in which both anhydrate and hydrate forms exist, and there are two miscible solvents, one of which is water.

In Figure 4, the three apexes of the triangle represent pure water, pure product, and pure organic solvent respectively. The dots represent the following compositions: solid hydrate (hydrate); saturated solution in organic solvent (X); saturated solution in water (Y) and eutectic solution composition in equilibrium with mixtures of solid hydrate and anhydrate (Z). The blue region of this diagram is the region in which everything is in solution. In the dark-green region, the anhydrate is the stable phase. In the light-green region, the hydrate is the stable phase. The red region represents the range of system compositions at which hydrate and anhydrous solid can coexist in equilibrium. If the anhydrous form is desired, the process should be operated in the dark-green region of this phase diagram, and the red region should be avoided. A characteristic of the red region is that the *solution* composition (as distinct from the *system* composition) is constant and equal to Z.

It follows that at any given temperature there is one value of water activity in this system at which hydrate and anhydrate can coexist. This will correspond to one value for the relative humidity (denoted RH′). RH′ is a function of temperature but not of solvent. The water activity and RH′ at which both anhydrate and hydrate can coexist is independent of solvent, even though the corresponding water concentration may not be. This is particularly relevant for processes involving the separation of an aqueous layer. As noted above, the water activity in the remaining organic layer will be very high, *and this will favour hydrate formation*.

In general, hydrates become less stable as the temperature increases, because of their higher entropy of dissociation/dissolution. Where there is a miscibility gap between water and the organic solvent, there is an additional effect of temperature. Miscibility gaps usually decrease with increasing temperature. It follows that, at a fixed composition, the water activity is expected to decrease as the temperature increases. Therefore, there are two reasons why higher temperatures are predicted to favour anhydrous forms in such systems.

2.3. Consequences for Hydrate Formation in the Process. One way to avoid hydrate formation in the process studied is to remove the water. However, this water is essential in removing inorganic impurities to achieve the required quality of drug substance.

The three potential stages at which hydrate formation could occur in the process were identified as:

- addition of second portion of *n*-butyl acetate (antisolvent)
- crystallisation during distillation
- controlled cool and hold prior to filtration

Each of these is discussed below.

2.3.1. Addition of n-Butyl Acetate. Although precipitation of solid does occur at this stage, it redissolves on heating, and therefore it can only be a source of hydrate seed. When this solid has been tested by XRD in the laboratory, it has been shown to be the anhydrate.

2.3.2. Crystallisation during Distillation. The crystallisation occurs at approximately 82 °C, and the distillation is complete at 106 °C. Mixtures of 1:1 anhydrate/hydrate have been slurried in the process solvent composition at these two temperatures, and in both cases turnover was observed to the anhydrate. Additionally similar slurry experiments in pure water showed that at temperatures above 80 °C, the anhydrate is the more stable form. Therefore, the hydrate is not stable during the

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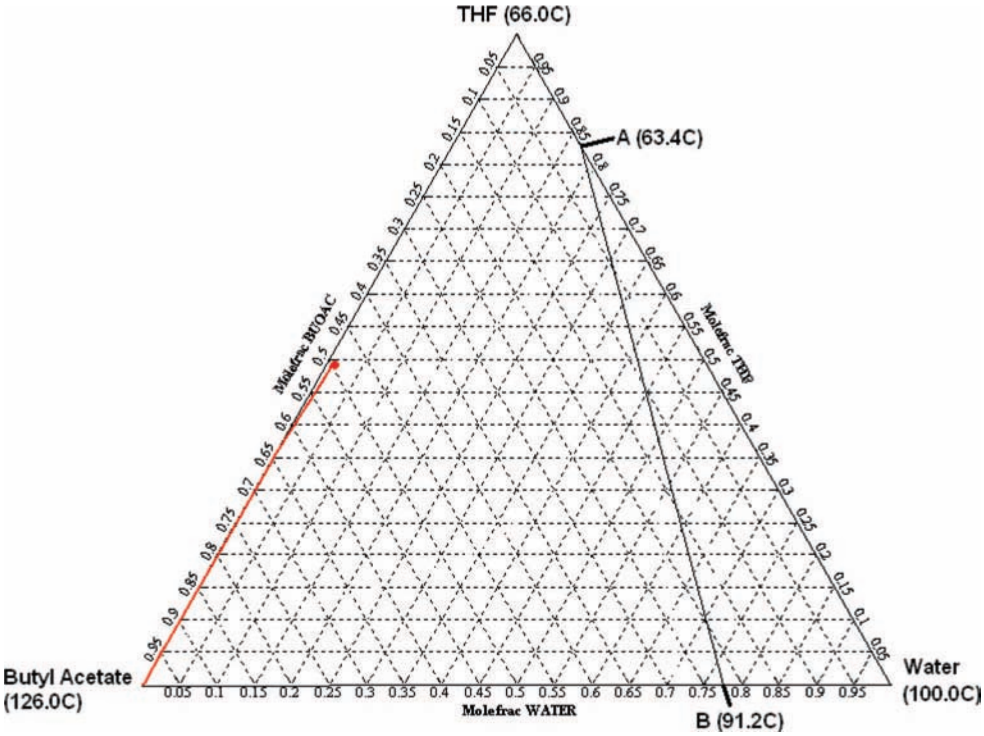

Figure 6. **Simplified residue curve map showing the course of the distillation.**

distillation, and if any seed is present from the *n*-butyl acetate addition, this will turn over to the anhydrate at this point.

2.3.3. Turnover during Cool and Hold Prior to Isolation. Having established that the anhydrate is the thermodynamically stable form at the end of the distillation, the only stage in the process where the hydrate could form is during the cool and hold at the low isolation temperature. The stability of the hydrate is dependent on the water activity in the liquid phase. This is the area that is discussed within this paper.

3. Simulation

In order to investigate the isolation with respect to the solvent and water composition, the role of the distillation first needs to be understood. The distillation end point for the process is set as a batch temperature of 106 °C. In a binary system (assuming no azeotropes) this would be enough to specify the exact composition, but in this system there is water, tetrahydrofuran, and *n*-butyl acetate, and the extra degree of freedom from the third component means that the temperature does not relate to a unique composition.

If the drug substance itself is neglected, the three-solvent system that exists during the distillation can be plotted as a residue curve map as shown in Figure 5. This figure also shows the two minimum boiling azeotropes, labelled A and B, and the boiling points of the different components in parentheses. It was generated using Aspen Properties and the NRTL (nonrandom two liquid) excess Gibbs energy model. NRTL parameters for water/tetrahydrofuran and water/*n*-butyl acetate binary pairs were available in Aspen Properties, whilst the tetrahydrofuran/*n*-butyl acetate pairing was estimated using the UNIFAC functional group excess Gibbs energy model.

The residue curve map is a two-dimensional representation of a three-dimensional shape because changes in temperature mean it is really a surface and the lines suggest the slopes. During a simple "up and over" distillation, the lines show the compositions that the batch will go through over time. The batch composition will follow a line towards the highest boiling substance or azeotrope.

The residue curves diverge from a line that links the two azeotropes. This means that there is effectively an azeotropic boundary in the system whereby, if a distillation starts with a composition on one side of that line, it is impossible to achieve a composition by distillation on the other side.

If the composition at the start of the distillation is plotted on this diagram, it lies on a line with *n*-butyl acetate at one end and the azeotrope A at the other. Since the boiling point for *n*-butyl acetate is 126 °C compared with 63.4 °C for the azeotrope, the composition in the batch will follow the line towards *n*-butyl acetate as the distillation progresses. This is easily seen in the simplified version of the residue map shown in Figure 6. The red dot shows the distillation starting composition, and by following the composition line it can be seen that as the distillation progresses the water and tetrahydrofuran are removed and the distillation tends towards pure *n*-butyl acetate.

As an aside it should also be noted that the starting composition is far away from the azeotropic boundary. This is good from a process robustness perspective, because it means that small variations in the process (e.g., a poorly controlled separation leaving additional water in the organic layer) will not push the starting composition to the other side of the boundary and so cause the distillation to tend towards a pure water end point.

As mentioned above, it is the water activity and not the water content that is important in determining whether a hydrate is stable. The activity coefficient is a function of composition, pressure and composition. Like the residue curve maps shown above, both the activity coefficient and the mole fraction can be calculated using Aspen Properties. By reference back to eq 1, the water activity is obtained from the product of these parameters and hence is plotted against the distillation temperature as shown in Figure 7.

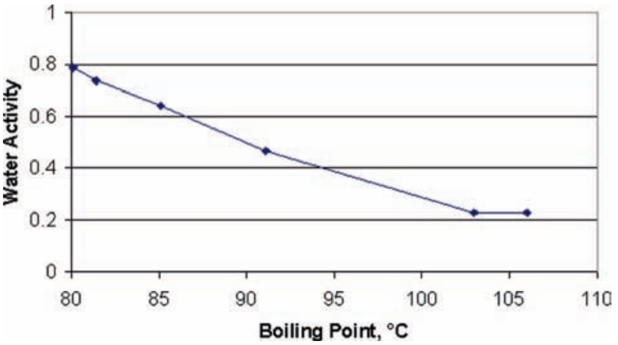

Figure 7. **Water activity as a function of batch temperature (boiling point).**

The AspenTech BatchSep software was used to predict the solvent composition in the process at the end of the distillation. It was based on the different ratios of solvent that could be present prior to distillation and different final distillation temperatures. A range of predictions was tested in the laboratory showing good agreement for the solvent levels, but more variation in the water levels. The model generated a range of solvent compositions that could be accessed during the process, which were used as part of a factorial experimental design to investigate the stability of the two forms in the isolation mixture.

4. Equipment and Experimental Methods

Gravimetric vapor sorption[14] was attempted in order to try and establish RH′ (as defined in section 2.2) directly in the absence of solvent. However, considerable hysteresis was observed, indicating that the kinetics of hydration and dehydration of this drug substance are too slow to establish equilibrium in the absence of solvent. Accordingly, slurry experiments were set up in process solvent compositions using a factorial experiment design. These experiments were carried out in a four-reactor Mettler-Toledo Autochem Multimax Reactor Box RB04-50. Each reactor is fitted with a thermocouple and a condenser, and the temperature of each reactor was controlled individually. In addition, a Lasentec focused beam reflectance measurement (FBRM) S400Q probe was present in each reactor to monitor the solvent-mediated transformations between anhydrate and hydrate.[15] The software used was WinRC for Multimax. For some of the slurry experiments at lower temperatures a separate100 mL jacketed vessel was used, fitted with a Lasentec FBRM S400Q probe, a thermocouple, and a condenser.

For each slurry experiment anhydrate (4−10 g) was charged to the reactor together with the prescribed amount of tetrahydrofuran and *n*-butyl acetate. The reactor temperature was adjusted as required, and then the required amount of water was added followed by hydrate seed. The solvent compositions used for these slurry experiments were chosen using the predicted solvent composition from the distillation model in order to mimic all the potential process conditions. The liquors were analysed prior to filtration for solvent composition (GC) and water content (moisture meter). The isolated solids were analysed for form (XRD, solid state NMR, and water content).

5. Results and Discussion

5.1. Lasentec FBRM Traces. The turnover from anhydrate to hydrate proceeded via dissolution of the larger anhydrate crystals and growth of smaller hydrate crystals. This change was detected readily by the Lasentec FBRM probe, as shown in Figure 8. As expected, the "total counts" and the "1−10 μm counts" both increase as the transformation progresses, whereas the "100−1000 μm counts" decrease.

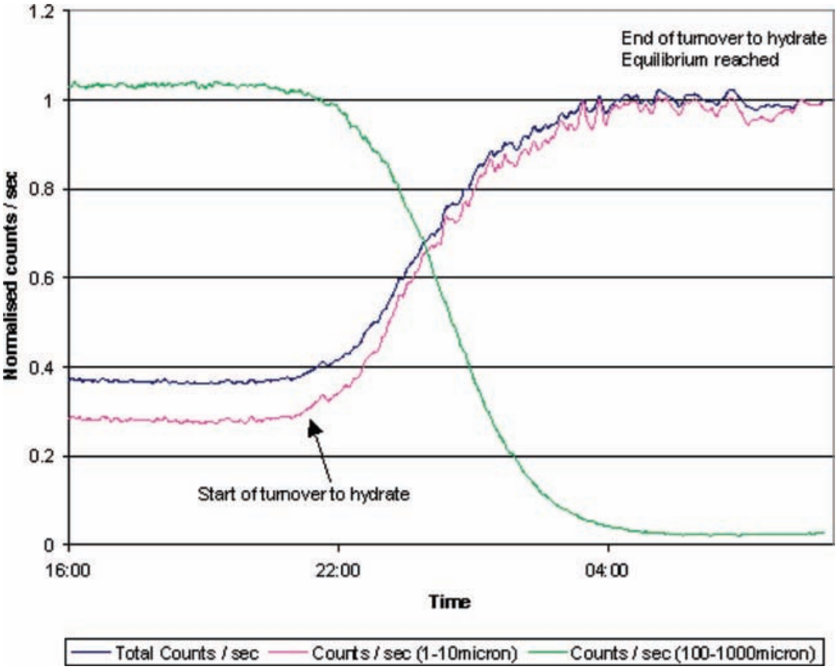

Figure 8. **Turnover from anhydrate to hydrate, as seen by the Lasentec probe.**

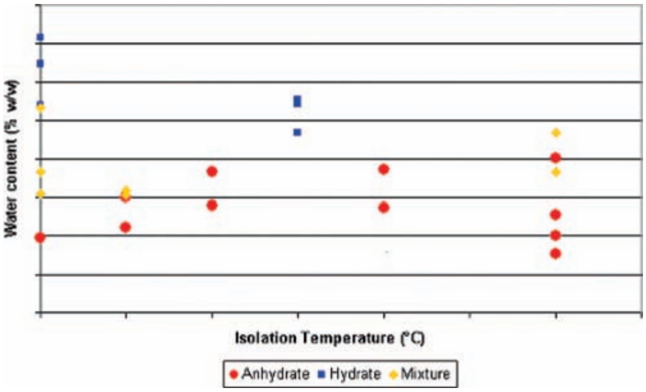

Figure 9. **Thermodynamic stability of anhydrate.**

5.2. Slurry Experiments in Process Solvents. In total 24 slurry experiments were carried out varying the solvent composition, water level, and isolation temperature. Over the solvent ranges, water levels, and temperatures investigated, the anhydrate form, hydrate form, and mixtures of the two were isolated. This provides further evidence that anhydrate and hydrate forms can be present as stable mixtures.

Statistical analysis of the experimental results showed that isolation temperature and water level were the two most important factors in determining which form was the most thermodynamically stable under the given conditions. This is consistent with the discussions above that highlight water activity as the critical factor because it is the temperature and water content that define the water activity. Hence, it follows that there is a critical water activity above which the hydrate is the most stable and below which the anhydrate will be formed.

Whilst the level of tetrahydrofuran may affect which form is more stable, the experiments showed that its contribution is not as significant as the other two factors identified. The influence of water content and isolation temperature is shown graphically in Figure 9.

5.3. Design Space. The water content, expressed as mole fraction, is related to the water activity via the activity coefficient as described in section 3. The water activity is related to the final distillation temperature as shown in Figure 7. Therefore, the data from Figure 9 can be replotted in terms of the final distillation temperature and the isolation temperature, as shown in Figure 10. Note that higher final distillation temperatures correspond to lower water contents.

Region A is the Design Space within which the process operates and within which the anhydrate is the thermodynamically stable form. Region B is the area within which the hydrate becomes the more thermodynamically stable form. The experimental results are those obtained from the slurry experiments (shown in Figure 9) and indicate the boundary at which the thermodynamically stable form changes.

This gives increased confidence that the process will produce the anhydrate form robustly and routinely as it is operated within the region in which the anhydrate is the thermodynamically stable form. This is ensured by setting the final distillation temperature at 106 °C, to control the water content. This measure of temperature was chosen rather than jacket temperature, head temperature, or distillate volume as it should be independent of scale and equipment, thus making the process robust. Additionally, the isolation temperature was set at 25 °C. At lower isolation temperatures, the undesired Region B (where hydrate may be formed) is closer to the boundary of the Design Space.

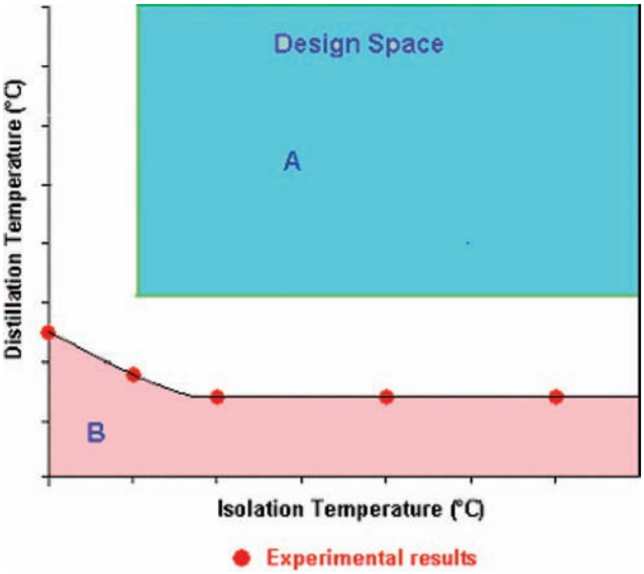

Figure 10. **Design Space for the process.**

6. Conclusion

The experimental work has successfully identified the Design Space within which this complicated process can operate with the anhydrate as the thermodynamically stable form. This has given increased confidence for manufacture.

The Lasentec FBRM probe can easily detect the turnover from the anhydrate form to the hydrate form without the need for calibration that would be required for other spectroscopic techniques. Judicious use of this inline technology in the laboratory helps to define a way of operating the process at scale without the need for inline technology.

The possibility of isolating stable mixtures of hydrate and anhydrate has been explained and observed. This is particularly important for crystallisation processes where the isolated material is used in the formulation of the drug product. This work demonstrates that relatively easy experiments can be undertaken in order to study the form of a given product and therefore ensure that the correct form or polymorph is isolated routinely and that such mixtures are avoided. The choice of these experiments was aided significantly by the understanding of the solid−liquid, liquid−liquid, and liquid−vapor phase diagrams and their interdependence.

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