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A Well-Behaved Crystallisation of a Pharmaceutical Compound

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Abstract:

Theoretical approaches to crystallisation process development were tested on a pharmaceutical development compound and resulted in a well-behaved crystallisation. The crystallisation type was selected from thermal data. Yield and productivity were fixed from the solubility curve. Solution eutectic data were used to set the specification of enantiomeric purity for the input material. Agitation and cooling parameters were established using scale-down laboratory trials. Heat transfer was the rate-limiting step for crystal growth. In-line technology was beneficial in the laboratory but not necessary on scale-up.

Introduction

The development of crystallisation processes for new organic molecules is often problematic.[1] Typical difficulties include failure to nucleate,[2] poor physical form,[3] wrong polymorph,[4] hydrates,[5] oiling,[6] and insufficient purification,[7] including chiral purification.[8] It is tempting to conclude that all new organic molecules are difficult to crystallize.

At the same time, there is an increasing understanding of crystallisation science and, specifically, of the power of combining solid-state, thermodynamic, and kinetic data.[9] There are also many new in-line techniques available to assist with crystallisation process development.[10]

3-[(4*S*)-5-Oxo-2-(trifluoromethyl)-1,4,5,6,7,8-hexahydroquinolin-4-yl]benzonitrile (compound **1**; see Figure 1) is a chiral compound with potential applications for urinary incontinence. The synthesis of compound **1** has been described elsewhere.[11]

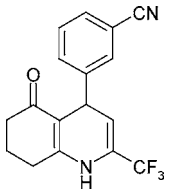

Figure 1. **Molecular structure of compound 1, $C_{17}H_{13}N_2OF_3$.**

The work described here was designed to test whether ideal solubility curves, solution eutectics, solubility data, scale-down experiments, and in-line technology were helpful in developing a robust crystallisation process for compound **1**. A further aim was to investigate to what extent this crystallisation was "well-behaved" with the ultimate goal of relating such "good behaviour" to crystal and molecular properties.

Experimental Section

Optical Microscopy: The optical micrographs were recorded digitially from an Olympus BH2 polarizing microscope, viewed under paraffin oil through partially crossed polars.

Powder X-ray Diffraction (Powder XRD): Samples were prepared on zero background silicon wafers by pressing approximately 2 mg of each sample over the wafer with a glass slide. The samples were run on a D5000 diffractometer (Brucker AXS). The samples were spun at 30 rpm to improve counting statistics. X-rays were generated using a copper long-fine focus tube operated at 40 kV and 40 mA, having a wavelength of 1.5418 angstroms.

Dynamic Scanning Calorimetry (DSC): DSC was performed using a Mettler Toledo DSC822e machine. The sample was weighed accurately into a stainless steel, medium pressure 120 μL pan with a viton seal. It was heated at 10 °C per minute from 25 °C to 140 °C, held at 140 °C for 120 min, and then heated from 140 °C to 250 °C at a slower rate of 1 °C per minute.

Solubility: The solubility of compound **1** in acetonitrile (Fisher Scientific, HPLC gradient grade) was determined by equilibration of slurries at four different temperatures, removing 5 mL samples of liquors, evaporating them to dryness, and weighing the remaining solid.

Enantiomeric Purity: Samples were analysed by HPLC using a isohexane/2-propanol/trifluoroacetic acid mobile phase and a Chiralpak AD column.

Crystallisations: Laboratory crystallisations were carried out in a 500 mL jacketed vessel fitted with a condenser, a Lasentec FBRM D600L probe, a thermocouple, and a retreat curve agitator. The Hastelloy agitator had a 5.5 cm swept

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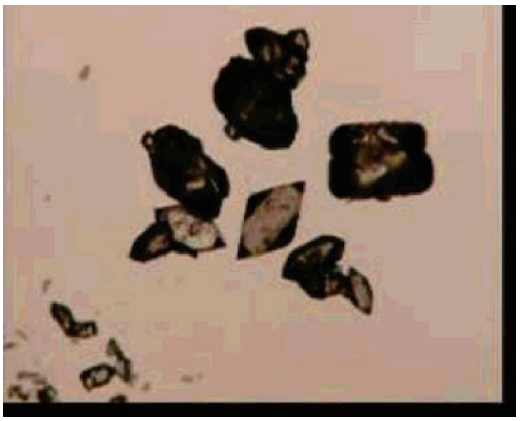

Figure 2. **Optical micrograph of compound 1. Image width is 1 mm.**

diameter, and the vessel diameter was 11 cm. The Lasentec probe was mounted via a bespoke glass top so that the probe was facing the solution flow and close to the agitator.[12] 300 mL of acetonitrile were added to 75 g of compound **1** (enantiomeric purity > 99.5%) and heated to reflux at 81 °C until the solid had dissolved, and then the mixture cooled to 5 °C before filtration. Initial problems with rapid solvent evaporation were overcome by adding a bubbler to the condenser column. Repeat crystallisations at various cooling rates and agitator speeds were carried out in the same vessel using the same material on consecutive days. The same recipe was used for multiple batches at larger scales, with the difference that the material was dissolved in a makeup vessel and then screened hot into the crystalliser before cooling.

Results and Discussion

Solid-State Characterisation. Compound **1** was characterised by optical microscopy, as shown in Figure 2.

Powder XRD was carried out on several samples of compound **1**, all of which gave the same pattern with several sharp, well-defined peaks. DSC gave one sharp peak for each sample studied. The melting temperature and heat of melting were found to be 194 °C and 112.4 J/g, respectively. There was no decomposition below the melting point. The corresponding data for the racemate were 191 °C and 100.1 J/g. By inspection, the racemate is a racemic compound and not a solid solution or a racemic mixture.[13]

The powder XRD, optical microscopy, and DSC data all indicate that compound **1** is highly crystalline and thermally stable at temperatures up to and beyond 100 °C.

To assess the appropriate crystallization type and solvent, the ideal solubility was calculated using the van't Hoff equation[14] and is shown in Figure 3.

A cooling crystallization is the easiest type of crystallisation to control and scale-up. Inspection of Figure 3 shows that a cooling crystallisation from 80 °C to 0 °C is predicted to give a yield of >90%. One constraint is that at higher solute mole fractions it will be difficult to maintain solids suspension. Thus the recommended crystallization is a cooling crystallisation from an ideal solvent with a boiling point > 80 °C and a melting point < 0 °C.

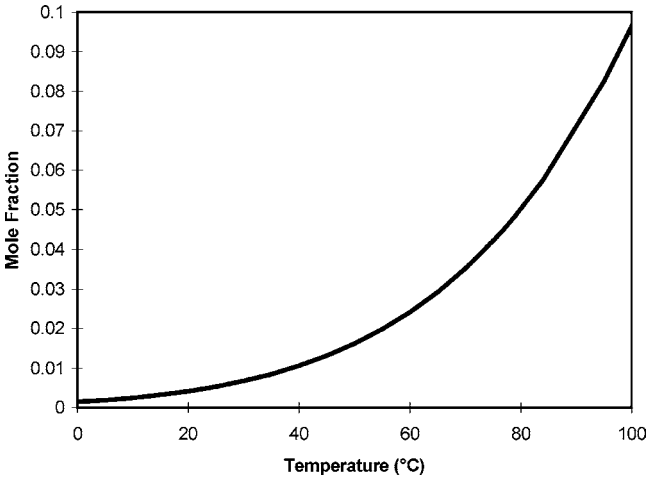

Figure 3. **Ideal solubility, expressed as mole fraction, of compound 1.**

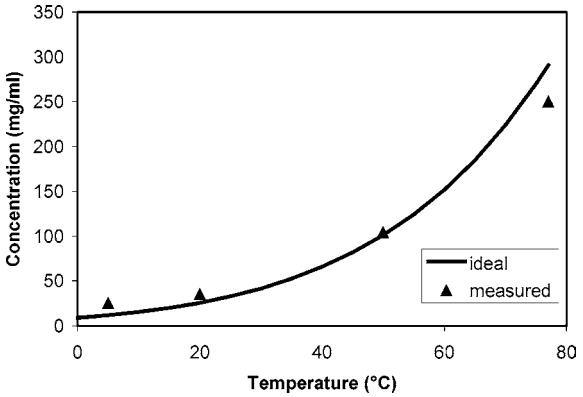

Figure 4. **Ideal and measured solubility of compound 1 in acetonitrile.**

Solution Thermodynamics. Acetonitrile has a boiling point of 81° and has the −*CN* functionality in common with compound **1**. The solubility data for acetonitrile were measured and compared with the ideal solubility. The data are shown in Figure 4.

The measured data are close to the ideal solubility. The temperature dependence of solubility in acetonitrile is strong. A cooling crystallisation between 77 °C and 5 °C will have a high yield (90%) and a high productivity (225 mg/mL). Moreover it should be easy to find other solvents with higher solubility at ambient temperatures (for cleaning) or lower solubility (for drown-out) if desired.

The degree of enantiomeric purification in this crystallization is important in setting the specification for the input material. The existence of a racemic compound implies a solution eutectic that restricts the extent of enantiomeric purification possible by crystallisation. This eutectic composition was established by a slurry experiment at room temperature in the presence of excess enantiomer and racemate. The solution eutectic was found to be at 36% enantiomer mole fraction. This information can be used to set the specification for the enantiomeric purity of the starting material.

The yield of the crystallisation has already been fixed at 90%. Therefore 10% of the desired enantiomer remains in solution. The corresponding level of the undesired enantiomer at the solution eutectic is 10 × (36/64) = 5.6%. If the level

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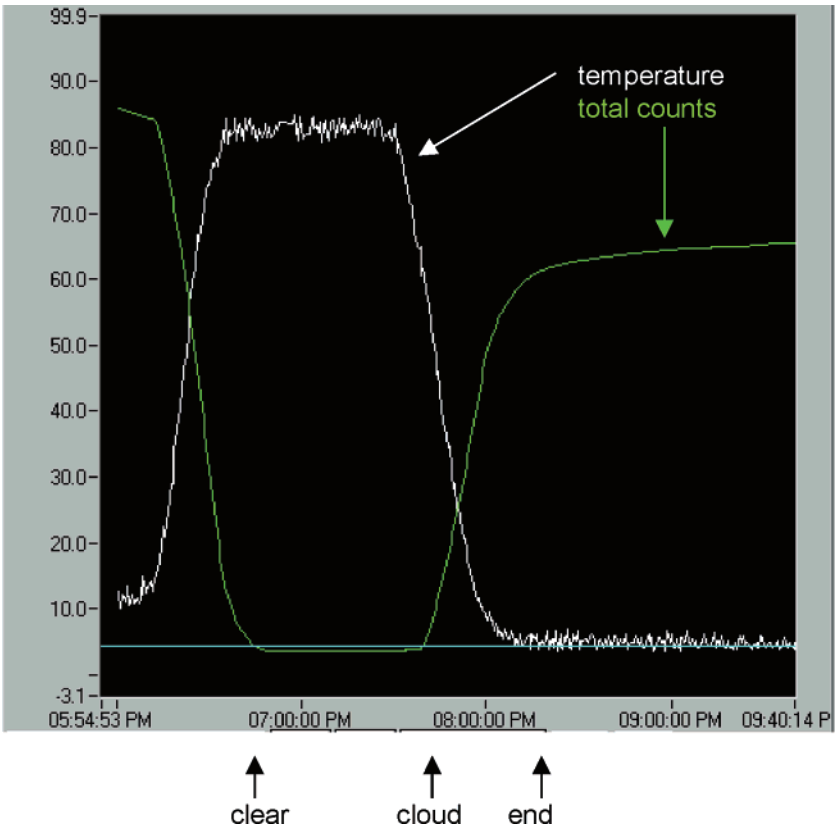

Figure 5. **Typical Lasentec data showing "clear", "cloud", and "end" points.**

of the undesired enantiomer exceeds this figure, then the racemic compound will start to crystallise and the isolated product will have an enantiomeric purity < 100%. This sets the specification for the enantiomeric purity of the input material as >94.4%.

Kinetics. The initial and final compositions for the crystallisation were fixed by the solubility study, but this gave no information about what cooling profile to use. The effect of a cooling profile was investigated using a Lasentec FBRM probe.[12] Additionally the effect of agitation rate was also investigated. This "scale-down" study was restricted to cooling rates and agitation rates which could be achieved on the large-scale vessel to be used for manufacture. The enantiomeric purity of the starting material, at >99.5%, was much higher than the critical limit of 94.4%, so enantiomeric purification in this step was not assessed.

A simple experimental design using high and low agitation rates and cooling rates was used. Typical Lasentec data are shown in Figure 5.

The data were analysed to quantify:

(1) dissolution (the "clear" point);

(2) nucleation (the "cloud" point);

(3) time to completion of crystallisation (the "end" point);

(4) evidence for attrition or agglomeration.

The results are summarized in Table 1.

Samples were taken for optical microscopy at the end of each crystallisation. A typical image is shown in Figure 6. Experiment 1 was stirred overnight to look for attrition effects. There was some adhesion of the product to the vessel walls. The mean Chord Length (CL) had decreased to 41.5 μ, and the shape of the crystals had changed as shown in Figure 6.

Table 1. **Results of four crystallisation experiments using the Lasentec**

experiment number	agitation (rpm)	cooling time (min)	clear point (°C)	cloud point (°C)	mean chord length (μ)
1	350	240	76.7	68.9	48.6
2	500	240	77.3	70.5	49.5
3	350	45	77.7	62.7	53.6
4	500	45	77.6	65.0	51.9

The clear point is constant at 77.3 ± 0.5 °C, as expected because the clear point is a measure of the thermodynamic solubility. This indicates that the solution composition remains constant and that the temperature measurement is reliable. The clear point is within 4 °C of the boiling point of the solvent. On plant scale, dissolution occurs in a makeup vessel and the hot solution is then transferred via a screening filter in to the crystallization vessel. In this process, there is very little margin for error in the screening temperature.

The "cloud" point varies with crystallisation conditions. The main effect is due to cooling rate; as expected, a wider metastable zone is observed at faster cooling. Agitation has a smaller effect, with a larger Metastable Zone at lower agitation speed. The metastable zone width of 7−15 °C is smaller than that in many other systems.[2] A more rigorous way of interpreting these data is to calculate the supersaturation at nucleation.[9] This is given by

$$S = (c_{ss} - c_{eq})/c_{eq}$$

where c_{eq} is the solubility at the nucleation temperature and

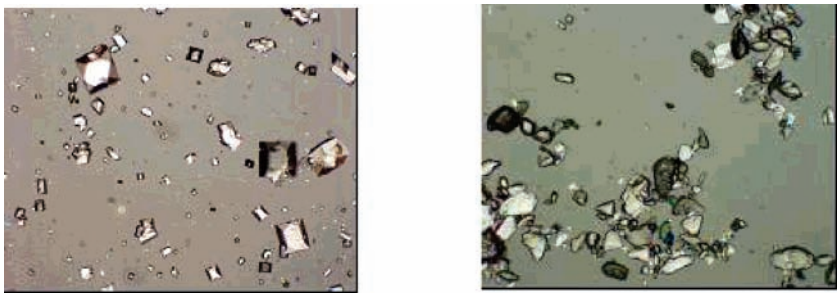

Figure 6. **Crystals of compound 1, before and after overnight stirring. Image width = 1 mm.**

c_{ss} is the solution concentration at the dissolution temperature. The calculated values of S for experiments 1, 2, 3, and 4 are 0.25, 0.16, 0.51, and 0.43, respectively.

Prolonged agitation does affect both the mean CL and shape. It may also be responsible for the small decrease in mean CL observed at slower cooling rates. Figure 6 shows a range of crystal dimensions between 20 μ and 150 μ. The mean CL 48.6 μ from the Lasentec FBRM is at the smaller end of this range.

The Lasentec data also show that growth has finished at the end of cooling, even at the faster cooling rate. The smooth increase in the "total counts" over time is consistent with the absence of additional nucleation during the crystallization, and this is confirmed by the steady increase in mean CL. This suggests that the supersaturation decreases once nucleation has occurred and is depleted by crystal growth faster than it is increased by cooling.

Inspection of Figure 5 suggests that once nucleation has occurred, the "total counts" measurement responds promptly to changes in the temperature. This was particularly noticeable at the end of the cooling period in all four runs. If the "total counts" is tracking crystal growth, then this means that crystal growth is similarly responsive to temperature. The possible rate-limiting steps for crystal growth are surface integration, mass transfer, and heat transfer. These data are consistent with heat transfer being the rate-determining step, irrespective of cooling rates in the range investigated. In such cases, a temperature probe may be sufficient to monitor the course of the crystallisation.

The occurrence of attrition is not surprising in this system given the high solids loading of 225 mg/mL at the end of the crystallisation. The combination of density difference and large crystal size means that the crystals will settle rapidly. Hence the choice of agitation rate is a delicate compromise between the need to ensure suspension, reduce attrition, and minimise adhesion of the product to the vessel walls.

Process Development. Yield, productivity, and enantiomeric specifications were set by the thermodynamic studies. This compound self-nucleates at low supersaturation (0.16−0.51), and the product is relatively insensitive to changes in nucleation point within this range. The kinetics of crystal growth were not expected to change on scale-up. As a result of this study, the conditions selected for crystallisation at a large scale (1000-L vessel) were the following:

(1) No seeding.

(2) High agitation rate − the power per unit volume was matched to the laboratory experiments.

(3) 1-h hold in the crystallisation vessel after transfer, to redissolve any material that crystallised during transfer.

(4) 4-h cooling. This was a compromise between the desire to minimize attrition, and concerns about localized cooling at the vessel walls at higher cooling rates.

(5) The hold time at the end of the cooling profile prior to discharge to the filter was restricted to 30 min to minimise attrition.

(6) No need for in-line monitoring of the process at scale.

The process was operated successfully for five batches with a total yield of 226 kg (86%) of material with the desired enantiomeric purity and physical form.

Conclusions

There is a common view in the fine chemicals industry that the basics of crystallisation are not relevant to pharmaceutical compounds because most published studies are on smaller, simpler molecules and use methods that require more time than is typically available in a process development environment. This paper is an attempt to bridge that gap by describing a real pharmaceutical case study in which the basics of crystallisation were used quickly and to good effect.

The crystallisation of compound **1** is "well behaved". The solubility in acetonitrile is close to ideal, giving a cooling crystallisation with good yield and productivity. Sufficient enantiomeric purification is obtained. The material self-nucleates at supersaturation < 0.6, so seeding is not required. Crystal growth is fast, and at achievable plant cooling rates, heat transfer is rate-limiting. The main potential source of variability was attrition, which was controlled by stipulating the total batch time. In-line technology was useful in the laboratory studies but not necessary from this compound at the 1000-L scale.

This raised the question of whether this "good behaviour" is generally accessible for similar molecular materials. There is nothing unusual about the ideal solubility of this compound, and the existence of an ideal solvent is not surprising. Good thermal stability was a prerequisite for a cooling crystallization that only contains two components. The molecule only has one flexible bond, and this may be linked to the ease of nucleation and surface integration. Further determinations of the supersaturation required for self-nucleation of more flexible molecules would help to test this hypothesis.

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