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# In-Line Analysis of Impurity Effects on Crystallisation

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**Abstract:**

**The effects of impurities on crystal growth are well-known but often difficult to characterise and quantify, particularly on commercial time scales. Using urea/biuret crystallisation as a model system, an in-line Lasentec FBRM probe was evaluated as a technique for quantifying impurity effects on crystal growth rates. An in-house crystallisation was selected which showed several features similar to those of urea/biuret. The in-line Lasentec FBRM probe was also used to quantify crystal growth rates in this system. The data show that in-line probes are useful laboratory tools for studying crystal growth inhibition by impurities.**

## 1. Introduction

Impurities can affect both the rate of crystal growth and the morphology of the crystals obtained.[1−3] Traditional studies of such effects have focused on careful characterisation of the morphological changes[4] and measurements of the growth rates of individual faces.[5] The goal of this work was to find an in-line technology to measure these effects rapidly on in-house materials.

The strategy adopted was first to identify a suitable crystallisation from the literature and a suitable in-line technology. An experimental study was performed to demonstrate that the in-line technology was fit for this purpose. An in-house crystallisation was identified which was predicted to show similar effects. The in-line technology was then tested on crystallisations of this material in the presence of various levels of a known impurity.

**1.1. Model System.** The criteria for the model system were that the starting material and impurity must be commercially available, the morphology change must be large and easily recognisable in the optical microscope, and the crystal chemistry underlying the morphology change should be simple and well-understood.

The urea/biuret system meets these criteria (Figure 1). The crystallisation of urea is well studied and documented in the literature.[6] As a pure molecule, it crystallises as needles from an aqueous solution; however when biuret is added to the system, the product crystallises as block-shaped crystals.

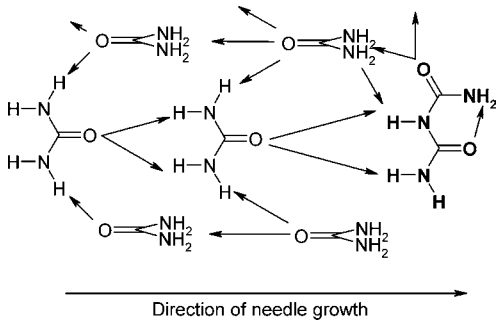


***Figure 1.*** **Diagram of hydrogen bonding in urea and the disruption caused by the introduction of biuret (bold).**


***Figure 2.*** **Chemical structures of Compound A and related impurity.**

Several methods have been used to study this system including ultrasonic attenuation spectroscopy[7] and powder X-ray diffraction.[8]

The morphology change is from needles to plates.[6] The urea crystal structure is tetragonal, with hydrogen bonds parallel to the *z*-axis. It follows that the needle axis is the *z*-axis. The biuret impurity disrupts this hydrogen bonding, "capping" the needles and changing the crystal shape to plates. Assuming that the growth rates of the other crystal faces are unchanged, it follows that crystallisation in the presence of biuret will take longer.

**1.2. In-Line Technology.** Recently there has been increased interest in using in-line technology to study the course of crystallisations.[9] Proposed techniques include techniques for monitoring the external shape of particles, the crystal structure of particles, and the solution concentration. Techniques for monitoring the crystal structure[10] of particles are not relevant here, as the effects on of the impurity on crystal structure are small. Solution concentration techniques include FTIR,[11,12] Raman,[13] and UV−vis spectroscopy.[14]

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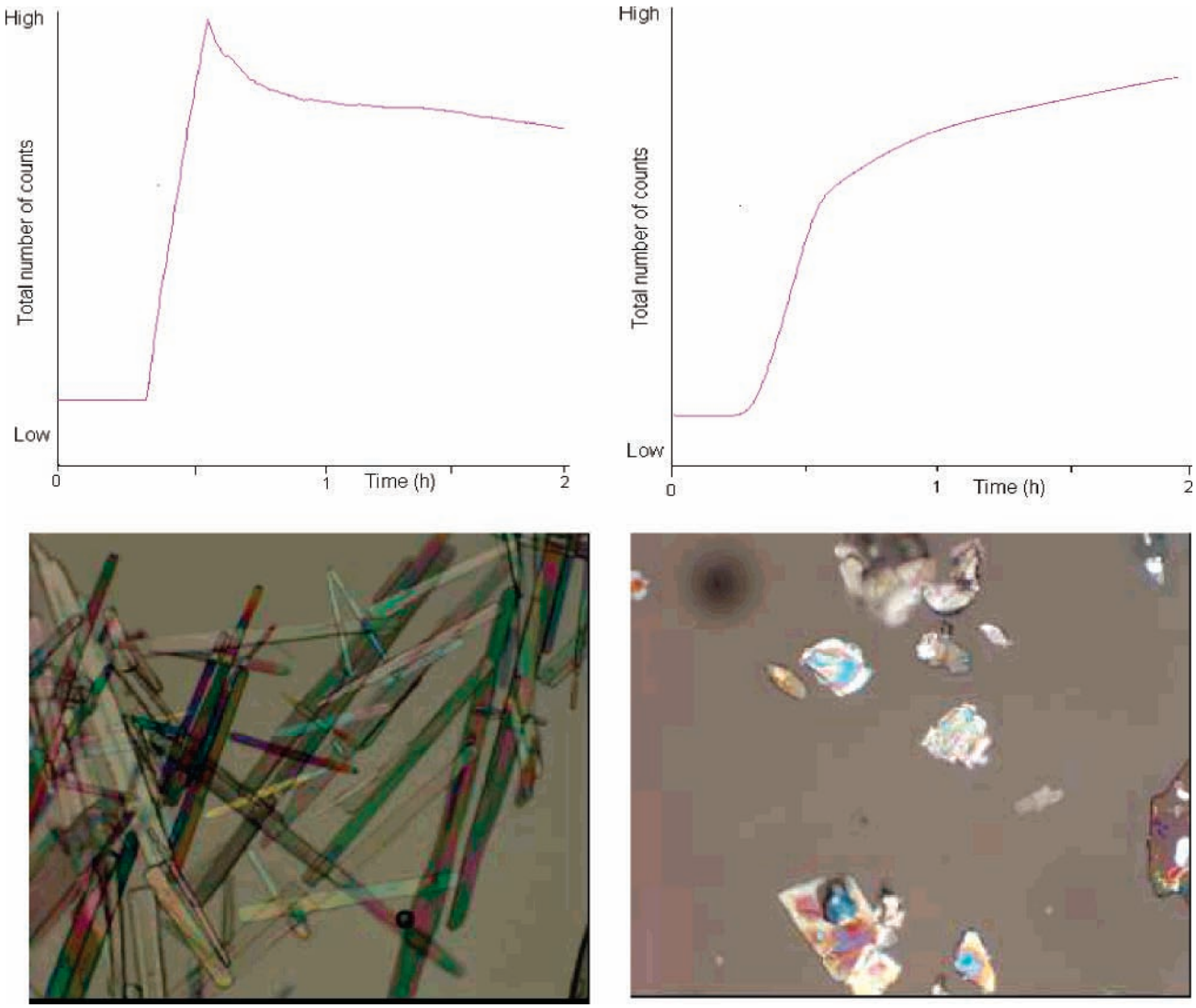


***Figure 3.*** **Lasentec FBRM data: urea (top left), urea/biuret (top right). Optical Microscopy: urea (bottom left), urea/biuret (bottom right). The width of each micrograph is 1 mm.**

All except UV−vis spectroscopy require extensive calibration, which was beyond the scope of this study. UV−vis spectroscopy was not suitable for urea.

Particle monitoring techniques fall into two categories: techniques based on in-line cameras combined with image analysis[15] and light reflectance techniques. A light reflectance technique, the Lasentec FBRM,[16] was selected for this study on the basis that it required minimum calibration and data analysis.

The Lasentec Focused Beam Reflectance Measurement probe has been used widely to study crystallisation phenomena, including oiling out[17] and polymorphic conversions.[18] The operation of the probe is discussed in detail elsewhere.[16] In brief, the probe provides a "fingerprint" of the particle size distribution every few seconds. Monitoring how this "fingerprint" varies with time allows the course of the crystallisation to be followed. Specifically it allows a rapid assessment of when the crystallisation started and when it finished.

**1.3. Compound A.** Compound A was selected for this study because the crystallisation showed similarity to the crystallisation of urea. Compound A is a carboxylic acid that crystallises as needles. A specific ester impurity has the simplified structure shown in Figure 2.

Prior to commencing this study, two hypotheses were proposed for the crystallisation of Compound A in the presence and absence of this impurity:

In the absence of impurity, the carboxylic acid groups will form hydrogen-bonded chains or dimers, similar to other carboxylic acids,[19] and these hydrogen bonds would be parallel to the needle axis, as in urea.

The impurity can accept but not donate hydrogen bonds, so it will attach to the ends of the needle and decelerate growth in this direction. As discussed above for urea/biuret, this is predicted to result in a longer crystallisation time as well as a change in morphology from needles to blocks.

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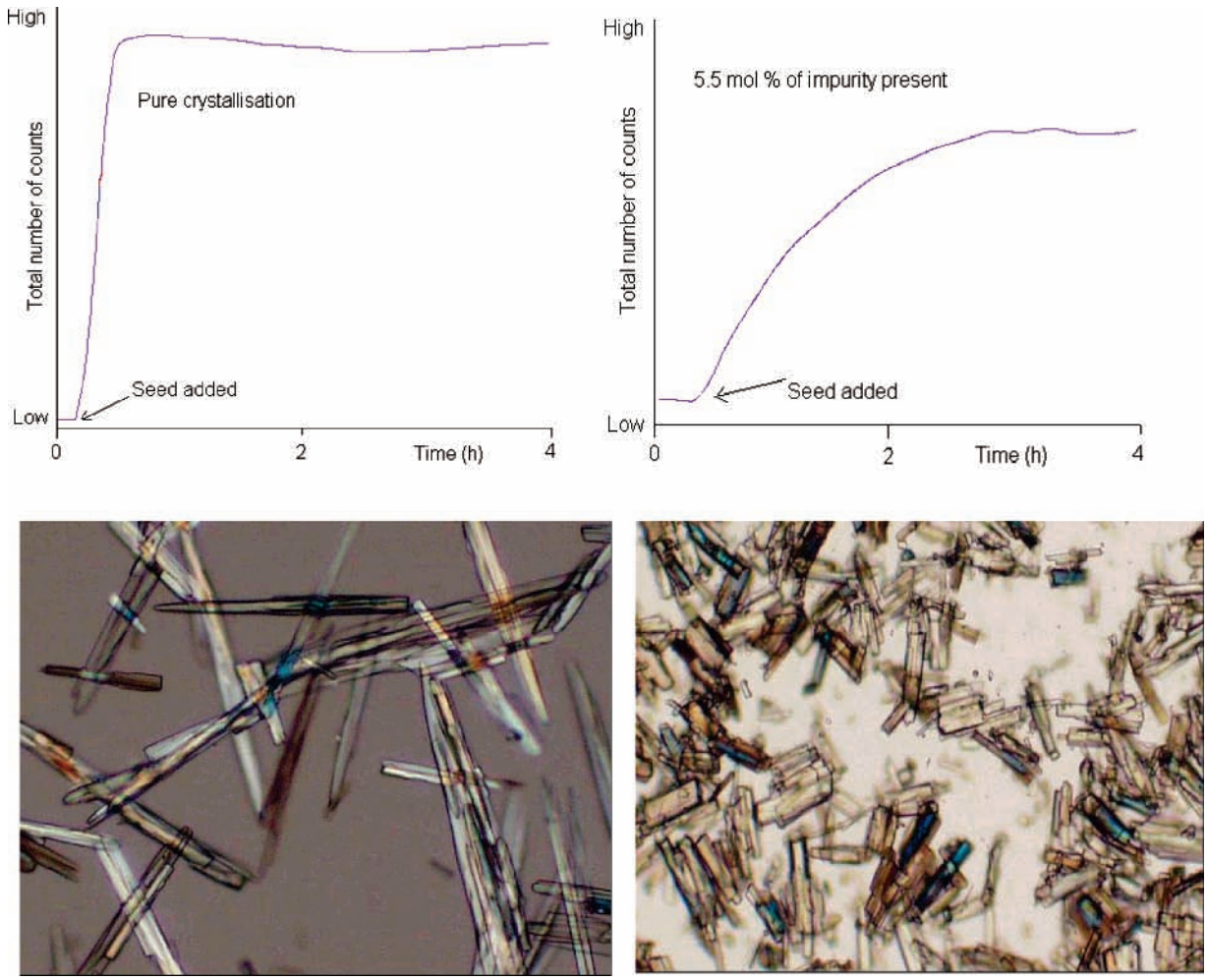


***Figure 4.*** **Lasentec FBRM data: Compound A (top left), Compound A/impurity (top right). Optical microscopy: Compound A (bottom left), Compound A/impurity (bottom right). The width of each micrograph is 1 mm.**

## 2. Equipment and Experimental Method

All the experiments detailed in this paper were carried out in a 100 mL jacketed vessel fitted with the S400Q Lasentec FBRM probe and a thermocouple. The output was analysed by plotting "total counts" as a function of time.

The urea system was investigated by dissolving analytical grade urea (<0.1% biuret) in water (0.75 relative volumes) at 50 °C. The crystallisation was induced by a cooling ramp at a rate of 10 °C/h and was monitored using the Lasentec FBRM probe. The same cooling profile was repeated using the same solution but with 8 mol % of biuret charged to the system.

The in-house case study was investigated in a manner similar to the urea/biuret system. Both the pure system and a "spiked" system containing low levels of impurity were investigated. In this case the crystallisation was initiated by the introduction of seed crystals into a solution of Compound A in a single organic solvent.

## 3. Results

**3.1. Crystallisation of Urea.** The crystallisations of both the pure urea system and the mixture containing 8 mol % biuret were easily detected by an increase in the total number of counts recorded by the Lasentec FBRM probe. For the pure urea system the crystallisation occurred at 17 °C and took approximately 15 min to reach its peak, at which point the number of counts began to decrease, possibly owing to agglomeration. There was a simultaneous temperature increase at the point of crystallisation of approximately 5 °C. The experiment was stopped after 2 h.

In contrast the system containing 8 mol % biuret crystallised at 24 °C with a simultaneous temperature increase of only 1 °C. After the initial rapid increase in the total number of counts, the rate decreased. The experiment was stopped after 2 h, at which time the total number of counts was still increasing. The data are compared in Figure 3. The final slurries were analysed by optical microscopy. The pure urea system was seen to be needles, whereas the system containing biuret was square platelike crystals. The Lasentec FBRM data and optical micrographs are shown in Figure 3.

**3.2. Crystallisation of Compound A.** The "total counts" as measured by the Lasentec FBRM in the absence of the impurity showed a very rapid crystallisation that was complete between 10 and 20 min after seeding. In comparison the system containing 5.5 mol % of the impurity took up to 5 h to reach equilibrium. This effect is even more dramatic than that seen in the urea and biuret system (see Figure 4).

As expected the crystals from the normal crystallisation were isolated as needles, but those from the impurity rich

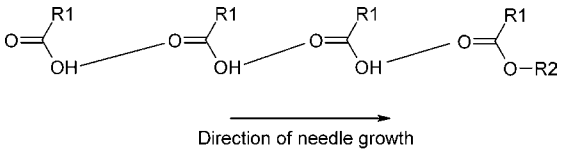


***Figure 5.*** **Model for the blocking effect of an impurity.**

system formed rod-shaped crystals. An effect on the rate of crystallisation was also detected at levels of impurity as low as 0.1 mol %, at which level the crystallisation took 40 min to reach equilibrium, but the final isolated crystals were needles.

## 4. Discussion

**4.1. Crystallisation of Urea.** The morphological change observed was consistent with that reported previously.[6] The in-line technology detected a difference between the two crystallisations in the absence and presence of impurity. Crystallisation in the presence of impurity was seven times slower. This is consistent with the observed morphological change. This study established that the Lasentec FBRM probe was a suitable in-line technology for studying impurity effects on crystal growth rate, as well as detecting nucleation and seed behaviour.

**4.2. Compound A.** The in-line technology detected a difference between the two crystallisations in the absence and presence of impurity. Crystallisation in the presence of impurity was ~20 times slower. This is consistent with the observed morphological change.

One possible molecular model for the action of the impurity is shown in Figure 5. Incorporation of a related impurity where the carboxylic acid function has been replaced by an ester terminates the hydrogen bonding along the needle axis. This would account for the formation of the rod-shaped crystals in Figure 4. This explanation could be checked against the single-crystal structure of Compound A if this becomes available.

## Conclusion

This work demonstrates the use of the Lasentec FBRM probe to detect the effect of an impurity on the rate of crystallisation, both in a well-studied system and also in a new in-house example. One area for further study is the impact of changes in morphology on the Lasentec "fingerprint".

In commercial manufacture, impurity levels often change during process development and on scale-up. This can cause changes in morphology that affect downstream processes such as filtration and drying. This work demonstrates additional potential implications for the yield and productivity. If impurity levels increase, but the time for crystal growth is not adjusted accordingly, then the yield may suffer if the batch is filtered before crystallisation is complete. Alternatively, if the impurity levels decrease, crystallisation may be completed long before the material is filtered. This is a suboptimal use of production capacity and may also result in unwanted attrition of the product. This can be avoided by in-process tests or by the use of in-line technology.

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