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Polymorphic control and scale-up strategy for crystallization from a ternary antisolvent system by supersaturation control

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KEYWORDS

Antisolvent crystallization, Scale-up, Supersaturation control, Polymorph selection, Indomethacin
Abstract

Antisolvent crystallization of indomethacin (IMC) was investigated in this work by using an acetone-methanol (66.5-33.5 wt%) mixture as solvent and water as antisolvent. Selecting the binary mixture as the solvent led to an increased yield of the batch process as the solubility of IMC is higher in the mixed solvents. Adding methanol to the solvent system mitigated the nucleation of the acetone solvate, which is dominating in the acetone-water system. Process analytical technologies (PATs) were implemented to ensure that the desired polymorph was present throughout the process. Supersaturation control (SSC) was applied as a closed-loop feedback control strategy, to achieve a rapid direct design of the crystallization process using the principles of Quality by control (QbC). The antisolvent flowrate profiles obtained by the SSC, were implemented in open-loop and used for scaling up the process by one order of magnitude. The results show how feedback control of crystallization from a ternary solvent mixture increases productivity and simultaneously ensures suppression of nucleation to obtain the desired particle size distribution (PSD) and polymorph. The direct design approach can be applied in the design and development of crystallization processes to yield the chosen solid phase of IMC when scaling from small- to large-scale.
1 Introduction

In recent decades there have been considerable research efforts directed to better understanding the crystallization process and mechanisms involved. Crystallization often serves as the final separation step in the production of active pharmaceutical ingredients (APIs),\(^1\) defining several key properties of the solid API, such as purity, crystal size and shape, polymorphic form and/or solvates.\(^2\) These characteristics have a strong effect on the final product quality including dissolution behavior and bioavailability but also on the efficiency of the down-stream operations, such as filtration and drying.\(^3\,^4\)

Exploration of the different polymorphic forms and solvates of the API is essential for a successful API development, as each form may exhibit different chemical and physical properties leading to differences in dissolution rate and stability.\(^5\,^6\,^7\) Hence, it is crucial to have a reliable control of polymorphism when developing the crystallization process of an API. The formation of a specific polymorphic form can be sensitive to process parameters, such as hydrodynamic conditions, and consequently, it can be problematic to control polymorphism when scaling up from small-scale to larger-scale experiments. To address these challenges different control strategies have been used.\(^8\,^9\,^10\)

In 2004 the US Food and Drug Administration (FDA) issued the ‘Guidance for Industry’ to encourage the implementation and use of process analytical technology (PAT) in the synthesis and processing of APIs.\(^11\) Implementing in-situ PAT tools into the crystallization process enables a more in depth understanding of the crystallization process and thereby optimized process control.\(^12\,^13\) These tools can be applied within robust feedback control strategies where real time measurements are generated and a controller adjusts the process parameters such as temperature or antisolvent/solvent flowrate to maintain or follow a desired target supersaturation, crystal form
or number of particles present. In this work, the supersaturation control (SSC) strategy was implemented. This control strategy implies following a predetermined supersaturation trajectory, using supersaturation measurement obtained from the concentration and temperature values measured in-situ. For robust polymorph control, the supersaturation setpoint generates a concentration trajectory in the concentration-solvent composition (c-X) phase diagram, which is under the solubility of the undesired metastable polymorphs. Furthermore, secondary nucleation of the given polymorph can be suppressed by having the setpoint under the metastable zone limit of the given polymorphs.

The objective of the process control is to manipulate the feeding flowrate of the antisolvent stream to keep the desired supersaturation, which was defined by considering information of the solubility and metastable zone. The supersaturation is continuously consumed by the crystal growth (which is a liquid-solid mass transfer process), therefore, the supersaturation controller must be able to dynamically compensate for this effect by pumping more antisolvent, hence, by decreasing the solubility. Various process control techniques have been applied for supersaturation control. Proportional-integral (PI) controller is the traditional continuously modulated feedback control mechanism. Thus, PI is a straightforward choice for supersaturation control, especially its advanced variants such as cascade control for improved disturbance rejection. Feedback controllers using different algorithms, including fuzzy logic controllers relying on “IF-THEN” rules (e.g. IF the supersaturation IS under the setpoint THEN feed antisolvent) were also successfully applied. A tuning-free feedforward control method was proposed which relies solely on the actual concentration and solubility curve. This is based on the assumption that the pumping system can implement the flowrate setpoint instantly.
Due to the complexity of these control strategies, application of feedback control in large production scale crystallizers can be rather complicated and challenging. However, SSC can be used as an efficient process design strategy in laboratory scale experiments and can enable the robust direct design of the crystallization process by the implementation of the recently proposed Quality-by-Control (QbC) framework.\textsuperscript{20-22} The fundamental principle of QbC is that feedback control is used to automatically identify the operating curve for the process, which then can be used as a setpoint in open-loop implementation, even at larger scales. For example, SSC can be implemented in a laboratory scale crystallization process, which will generate an antisolvent and solvent flowrate profile corresponding to the desired supersaturation trajectory in the phase diagram and the critical quality attributes of the product. Subsequently, a simplified feeding trajectory can be inferred from the flowrate profiles and this can be implemented in open-loop fashion in a larger scale process with the same initial process conditions (seed PSD, seed loading and solvent composition). The applicability, reproducibility and scalability of this concept is investigated in the current crystallization system.

Indomethacin (IMC), a nonsteroidal anti-inflammatory drug is used as the model compound, shown in Figure 1a. IMC has been reported to form seven polymorphs and several solvates\textsuperscript{23-25}, leading to significant challenges in the crystallization process as the product has to be crystallized with the desired solid form and the preferred particle size and shape. The thermodynamically most stable $\gamma$-IMC having plate like crystal shape (Figure 1c) and the metastable $\alpha$-IMC having needle-shaped crystals (Figure 1d) are most commonly observed, but also an acetone solvate may form when acetone is part of the crystallization solvent.\textsuperscript{26,27} The acetone solvate is also needle-shaped but was not observed in these experiments using the PVM. During the presence of needle-shaped
crystals, the X-ray powder diffractograms (XRD) were measured off-line confirming only the presence of α-IMC. The XRD of the three forms are easily distinguished (Figure 1b).

![Indomethacin molecule](image)

**Figure 1.** a) Structure of the indomethacin *molecule*; b) XRD diffractograms of the α-IMC, γ-IMC and the acetone solvate; c) PVM image of the γ-IMC crystals showing the plate like crystal shape; and d) PVM image of α-IMC crystals shown the needle like crystal shape.

In our previous work\textsuperscript{28,29} antisolvent crystallization was performed in a 50 mL scale. An increased productivity was gained by using a ternary solvent system, where acetone-methanol (66.5-33.5 wt\%) was used as solvent and water as an antisolvent. Several different process parameters were investigated such as initial concentration ($C_i$), seed load and amount of antisolvent.
Antisolvent was added by several injections, which may cause the bimodal distribution obtained in the particle size distribution (PSD). It was observed that seeding with the desired polymorph, in this case \( \gamma \)-IMS, was essential to obtain the desired \( \gamma \) polymorph. Furthermore, it was observed that at higher \( C_i \) of 66.7 and 200.0 mg/g solvent a low seed load would produce secondary nucleation of the undesired \( \alpha \)-IMC and acetone solvate. Seeding was found to be essential, and a seed load of 2.5 wt% of the theoretical yield was found to be sufficient to obtain the desired polymorph and was subsequently also used in this work. These previous studies were conducted in a 50 mL scale with an attenuated total reflectance Fourier-transform infrared spectroscopy (ATR-FTIR) probe to monitor the concentration, and no feedback control was implemented. Hence, the objective of this work is to implement a control strategy to ensure that only \( \gamma \)-IMC is produced. Based on the operational space established previously\(^{28}\) two constant antisolvent flowrate experiments were performed where a fast and slow antisolvent addition rate were chosen. These two preliminary experiments provide a base case. Then, the SSC strategy was implemented, and different process parameters were investigated on polymorphic control, PSD and productivity.

Finally, the implementation of open-loop operating trajectories obtained based on the application of SSC was investigated and applying the principles of QbC-based direct design, a ten-fold scale-up was successfully performed.

2 Materials and methods

2.1 Chemicals and analytical methods

For all experiments medical grade IMC was bought from Xi’an Salus Nutra Bio-Tech Inc. Acetone and methanol were obtained from Sigma-Aldrich with a purity of 99.9% and deionized water was used as antisolvent. XRD was used off-line to identify the produced polymorphs by a
Rigaku SmartLab XRD with Cu X-ray source at wavelengths $K_{\alpha 1}$ and $K_{\alpha 2}$ in the $2\theta$ range 5° to 40° with a step size of 0.02° $2\theta$ and a rate of 1.5° $2\theta$ min$^{-1}$.

2.1.1 Experiments in 500 mL reactor

For process monitoring and control three different PAT tools were used: a ParticleView V19 PVM from Mettler-Toledo with iC PVM version 7.0, a focused beam reflectance measurement (FBRM) G400 0.5-2000 μm from Mettler-Toledo with iC FBRM software version 4.3 and a Zeiss MCS621 UV/Vis spectrophotometer with attenuated total reflectance ultraviolet-visible (ATR-UV/Vis) 190-720 nm Hellma probe with Zeiss ProcessXplorer software version 1.3-Build 1.3.1.30. In the concentration determination the whole spectrum of wavelengths was used in the multivariate analysis. Off-line PSD was measured on a Malvern Mastersizer 3000 using the dry method. A tray with a hopper gap was applied and set to 1 mm with a standard venturi dispenser. The measurements were made using 4 bar air pressure, applying a 70% feed rate, 10 s background measurements and a 1-20% obscuration. The particle type was set to non-spherical. Prior to analysis the samples were filtered by vacuum filtration and left to dry overnight at room temperature.

2.1.2 Experiments in 5 L reactor

Two PAT tools were used for the scale-up experiments. The same PVM as mentioned above and a Lasentec® D600L FBRM with iC FBRM software version 4.3.

2.2 Constant feeding open-loop experiments in 500 mL

An open-loop control system uses a preset input profile in time and a local controller that implements that operating trajectory, but it does not react to the variations in the critical quality attributes or other process parameters, whereas a closed-loop control system adjusts the inputs based on the actual critical quality attributes or other process parameters (e.g. supersaturation) to
follow a setpoint in the phase diagram. The schematic overviews of the two control approaches are shown in Figure 2. The different PATs enable the monitoring of polymorphic form (indirectly by the PVM) and particle size (indirectly by the FBRM), and control of supersaturation based on concentration measurements combined with the solubility calculated based on the solvent composition. All experiments are conducted under isothermal conditions at 25 °C.

![Figure 2](https://via.placeholder.com/150)

**Figure 2.** Schematic overview of PAT tools used in a) Open-loop control and b) Closed-loop control. In a) the lines and diamonds in the crystallizer represent different polymorphs.

All small-scale crystallization experiments were carried out in a 500 mL jacketed glass reactor equipped with an overhead stirrer. Antisolvent addition was achieved using a MasterFlex peristaltic pump. It was chosen to perform two constant antisolvent addition flow rates at 1 and 5 mL/min. IMC was dissolved in the acetone-methanol (66.5-33.5 wt%) mixture to obtain a concentration of 66.7 mg/g solvent at 25 °C with a stirring rate of 300 RPM. Before the antisolvent addition began the solution was heated to 30 °C to insure complete dissolution and then cooled to 25 °C. Sieved γ-IMS in the 125-180 μm sieve fraction and a seed load of 2.5 wt% (of theoretical crystal product yield) was applied in the experiments. Antisolvent addition was shortly paused at
a wt% of 28 (antisolvent composition within the solvent system) to add seeds, after which it was continued to reach 40 wt%. In all experiments it was desired to reach 40 wt% of water. Both experiments were stopped at 4 hours. Samples were taken every 30 min after seed addition and analyzed by XRD. Based on the initial results it was found that formation of the undesired $\alpha$-IMC was observed during the antisolvent addition but transformation into the stable $\gamma$-IMS would happen by the end of the experiment.

### 2.3 Supersaturation measurement and control

The supersaturation (SS) is expressed as the ratio between the concentration of the solution ($c$) and the solubility ($c^*$) at the given solvent/antisolvent composition in the crystallizer and is expressed by:

$$S = \frac{c}{c^*} \quad (1)$$

It was previously shown that the solubility as a function of the antisolvent content for this particular system could be expressed as:\textsuperscript{29}

$$c^* = 217.6 - 8.845 \cdot X + 0.08757 \cdot X^2 \quad (2)$$

where $X$ is the antisolvent weight fraction within the solvent system. As mentioned earlier the SSC strategy implies the use of a constant supersaturation setpoint and based on this setpoint a specified trajectory can be followed in the $c$-$X$ phase diagram. This requires real time solute concentration measurement, hence, spectroscopic tool calibration. A quick calibration technique was employed, which consists of a 0.2 mL/min solvent addition to a slurry of $\gamma$-IMC in an acetone-methanol-water mixture from 40 wt% water to the desired setpoint and the UV spectra was recorded using a Zeiss ATR-UV/Vis spectrophotometer. The entire spectrum from 190-720 nm was used for the multivariate analysis and calibration. Because of the slow feeding it can be assumed that the concentration followed closely the solubility, therefore, in the knowledge of
solubility Eq. (2), the actual concentration profile of the experiment becomes available. The absorbance was found not to be influenced by the solvent system composition, only by the solute concentration and therefore a relation between the absorbance and concentration could be established. The traditional univariate calibration method relying on following the absorbance or derivative absorbance at one wavelength failed to provide accurate calibration. Instead, a partial least square regression (PLS) based calibration model was established using two components with a $R^2$ of 0.9966 with an error of 0.9989. Two components were chosen based on cross validation.

PLS is a basic tool of chemometrics; it is a linear multivariate model where a certain wavenumber range of the spectrum (in this work the whole spectrum) is used for the analysis, in contrast with the traditional univariate methods. By that it not only over-performs the univariate calibration techniques, but in certain cases it is an enabling technology. The PLS based calibration and concentration calculation was carried out using the Matlab PLS tool on the full UV spectrum and was used to attain in-situ supersaturation calculation in real time in different experiments.

According to the Eq. (2), the solubility is a function of antisolvent concentration within the solvent system ($X$). The antisolvent (water) concentration is calculated as:

$$X(t) = 100 \cdot \frac{m_{A,0} + m_{A,t}}{m_{A,0} + m_{S,0} + m_{A,t}}$$

(3)

where $m_{A,0}$, $m_{S,0}$ are the antisolvent and solvent mass initially present in the crystallizer, whereas $m_{A,t}$ is the mass of antisolvent added to the system at the time $t$. The value of $m_{A,t}$ is expressed as a function of implemented flowrate profile:

$$m_{A,t} = \rho_A \int_0^t F(t) dt$$

(4)

where $\rho_A$ is the antisolvent density. Thus, this is an inferential control system, which uses the implemented antisolvent flowrate profile for the calculation and control of supersaturation. Hence,
the accurate pump operation is crucial for the overall system operation. The combination of pump and tubing was carefully calibrated, and the same calibrated system was used in all experiments.

Proportional–integral (PI) controller was employed to control the relative supersaturation, Eq. (1), throughout the process. The standard PI is a linear controller and is well suited to control linear time invariant systems. However, the supersaturation consumption rate might change throughout the crystallization process. In the case of IMC crystallization, it was observed that the large IMC crystals undergo significant attrition (shown in Figure 3), which creates new particles to induce secondary nucleation that can contribute to the consumption of supersaturation. In addition, numerous studies correlate the growth rate with the absolute supersaturation \( (c - c^*) \) which, however, naturally changes throughout the process as the relative supersaturation is kept constant.\(^{32}\)

![Micrographs showing attrition](image)

**Figure 3**: Micrographs showing attrition where a) is a microscope images and b) is a PVM image recorded during an experiment.

A gain-scheduling adaptive PI controller was developed which accounts for the increased supersaturation consumption by the new particles produced by attrition as well as for the slowdown
of growth rate due to the decrease of absolute supersaturation as the process evolves. The gain scheduling strategy is given by the equation:

\[ K_C(t) = K_{C,0} \frac{\Delta c(t)}{\Delta c(0)} \cdot \frac{N(t)}{N(0)} \]  

(5)

where \( K_{C,0} \) is the controller gain constant and \( K_C \) is the effective gain adjusted continuously as a function of concentration and as the relative number density evolves. \( \Delta c \) denotes the absolute supersaturation \( (\Delta c = c - c^*) \) and \( N \) is the FBRM count. The first fraction of Eq. (5) adjusts the controller gain as a function of ratio of actual to initial absolute supersaturation, whereas the second fraction compensates for the increased supersaturation consumption by attrition/nucleation.

According to the experiments, this gain scheduling strategy compensated effectively for the process nonlinearity and allowed controller tuning by \( K_{C,0} \) for broad operating domain. In addition to the gain scheduling, integral windup was also employed.

The standard operating procedure of the antisolvent crystallization process for \( \gamma \)-IMC production is described below.

1. Solid IMC was added to an acetone-methanol mixture corresponding to the solubility of IMC at 25 °C, and the temperature was raised to 30 °C to ensure complete dissolution, which was confirmed by the FBRM.

2. The temperature setpoint was lowered to 25 °C and kept for approximately 30 minutes for temperature stabilization, and then antisolvent was added gradually to achieve the desired SS setpoint.

3. Crystalline \( \gamma \)-IMC seeds were added, and the SSC was turned on.

4. After finishing the antisolvent addition, one hour equilibration time was applied for complete supersaturation depletion.
Different operating conditions were investigated and a summary of these are shown in Table 1. These parameters are selected to show the effect of surface area of the seeds, effect of supersaturation setpoint and effect of initial concentration ($C_i$) on the PSD and process time.

**Table 1.** Overview of experimental plan and operating parameters for the antisolvent crystallization in 500 mL scale.

<table>
<thead>
<tr>
<th>Exp. no</th>
<th>Initial concentration ($C_i$) (mg/g solvent)</th>
<th>Seed load (wt%)</th>
<th>Seed size (μm)</th>
<th>SS setpoint</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66.7</td>
<td>2.5</td>
<td>125-180</td>
<td>1.2</td>
<td>94.1</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>45-63</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>45-63</td>
<td>2.0</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>2.5</td>
<td>45-63</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
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<td>2.5</td>
<td>45-63</td>
<td>2.0</td>
<td>97.07</td>
</tr>
<tr>
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<td>200.0</td>
<td>2.5</td>
<td>45-63</td>
<td>2.0</td>
<td>98.04</td>
</tr>
</tbody>
</table>

2.4 Robustness and scalability experiments

Based on the SSC experiments presented in Table 1 it was chosen to investigate the robustness and scalability of experiment 6. A trajectory was designed based on the antisolvent addition profile created by the SSC algorithm and shown in Figure 4.
Figure 4. Trajectory obtained from the antisolvent addition profile of experiment 6. The actual supersaturation and the desired SS setpoint are also shown throughout the process.

Duplicates were performed using this trajectory in the 500 mL scale using the same procedure as in the previous section but implementing the trajectory instead of the SSC algorithm. Hence, the experiment is an open-loop experiment. The same flowrate trajectory was increased 10-fold and was used for the scale-up experiment. The large-scale crystallization experiments were carried out in a 5 L jacketed glass reactor equipped with an overhead stirrer and applying multi-point feeding to reduce the mixing time. All other process parameters were kept the same as in the 500 mL experiment and duplicates were made. The set-up is shown in Figure 5.
Figure 5. 5 L scale set-up: 1-thermoregulator, 2-FBRM probe, 3-temperature probe, 4-PVM probe, 5-peristaltic pump, 6-antisolvent bottle, 7-solvent bottle, and 8-computer with control algorithms.

3 Results and discussion

3.1 Constant feeding open-loop experiments at 500 mL scale

In this study two preliminary open-loop experiments were performed with a constant antisolvent flowrate of 1 and 5 mL/min. These experiments were conducted to investigate how the process proceeded in the 500 mL scale with continuous antisolvent addition. In Figure 6 the FBRM counts and the antisolvent addition profiles for the two antisolvent addition rates are shown together with the product PSD. In previous work a bimodal distribution was obtained from the injection type antisolvent addition, meaning that antisolvent was not added continuously but added three times by a syringe with a 30-minute interval. In this work the antisolvent is added continuously which resulted in an improved PSD being unimodal for both constant antisolvent additions rates. This indicates that the addition type of antisolvent has a significant influence on the PSD. A sudden increase in the FBRM count was observed after the addition of seeds, indicating secondary nucleation. The onset of the secondary nucleation, denoted by the FBRM count/s, was observed approximately 10 min after seed addition at the antisolvent addition rate of 5 mL/min, whereas the
increase of the FBRM count happened about 45 minutes after seeding for the experiment with an antisolvent addition rate of 1 mL/min. Based on the point of nucleation the antisolvent/solvent ratio is similar for the two experiments. In both experiments the maximum peak count becomes similar (approximately 30,000 #/s), which suggests that once the metastable zone limit for secondary nucleation was crossed intensive nucleation happens, regardless of the antisolvent feeding rate. This highlights the importance of keeping the supersaturation within the metastable zone to ensure the desired γ-IMC throughout the entire experiment. Additionally, the final count was also very similar in both experiments at approximately 10,000 #/s.

**Figure 6.** FBRM total counts and antisolvent profiles over time for two open-loop experiments at an addition rate of 1 mL/min in a) and 5 mL/min in b). Three and four samples were taken throughout the two experiments at times indicated by the numbers 1-4. In c) the PSDs of the seed and final products of the two experiments are shown where unimodal distributions are observed.

Throughout the experiments three or four samples were taken and denoted by 1-4 in Figure 6. These samples were analyzed by XRD, which confirmed the presence of α-IMC in sample 2 and a conversion to the stable γ-IMC in 3 and 4 also indicated by the sudden drop in FBRM count/s. Microscope pictures were captured and compared to the PVM pictures shown in Figure 7 for the
5 mL/min addition rate. From both the PVM and the microscope images it is shown in sample 2, that the undesired and typical needle-shape α-IMC is present. The needle-shape α-IMC crystals contribute more in the FBRM count/s than the plate like γ-IMC. In the case of the high aspect ratio of the needle-shaped crystals the count increases during the growth of the long needles resulting in the steep increase in the count. At a certain point the breakage rate tends to be faster than the growth rate causing an additional increase in count. Hence, the steep increase in FBRM count/s was due to nucleation of the unwanted α-IMC. In the other samples only the desired γ-IMC with a plate like structure was observed.

![Micrographs of the samples](image)

Figure 7. Micrographs of the samples, where picture with suffix ‘a’ are microscope images and those with suffix ‘b’ are PVM images of the 4 different samples obtained during the 5 mL/min antisolvent addition as shown in Figure 6.

### 3.2 Supersaturation control

Based on the preliminary constant feeding open-loop experiments, secondary nucleation of the undesired polymorph was observed using both fast and slow addition rates. The presence of undesired polymorphs can lead to contamination of the final product and batch-to-batch variation.
in product quality. It was therefore the aim of this work to optimize the antisolvent crystallization process to ensure solely the formation of γ-IMC throughout the entire process. This can be achieved by controlling the supersaturation using SSC. The SSC implies the use of a constant supersaturation ratio. Therefore, a benefit of this method is that secondary nucleation of undesired polymorphs can be avoided by choosing a supersaturation ratio below the solubility curve of the undesired polymorph.4

The effect of seed surface area on the process time was investigated previously at a supersaturation setpoint of 1.2. 28 Two different seed sizes with the same seed load of 2.5 wt% were compared and it was desired to reach an antisolvent concentration of 40 wt%. A twofold increase in supersaturation consumption was observed when the seed surface area was increased by a threefold and only the desired polymorph was observed throughout the entire experiment. At this supersaturation setpoint of 1.2 the duration of the experiments exceeded 2 days while only reaching an antisolvent concentration of 27.6 wt%. The experiments were therefore stopped and the desired concentration of 40 wt% antisolvent was not reached. Based on the decrease in process time it was decided to continue with the smaller seed size for the remaining experiments.

The aim of the next experiments was to investigate if the desired antisolvent concentration could be reached by increasing the supersaturation setpoint to 2.0 and 2.2. By increasing the supersaturation setpoint, the concentration of antisolvent was reached at a process time for the setpoint 2.0 of 2.9 hours and for the setpoint 2.2 it was 3 hours. The concentration profiles for both setpoints are shown in Figure 8 showing that the supersaturation could be maintained throughout both experiments. When the desired antisolvent concentration was reached the SSC-control was stopped and one hour equilibration time was applied for complete supersaturation depletion. At the 40 wt % antisolvent concentration a vertical line is observed in the concentration profiles which
was the supersaturation depletion. Additionally, only the desired polymorph was identified, and the product PSDs were recorded for all SSC experiments and were found to be unimodal.

Figure 8. Concentration profile of the SSC experiments with supersaturation ratio setpoints 2.0 and 2.2.

SSC conducted at three different initial concentration ($C_i$) were conducted and compared. Previously, the experiments were conducted at a $C_i = 66.7$ mg/g solvent which in the following experiments was increased to 133.3 and 200.0 mg/g solvent with a supersaturation setpoint of 2.0. There was no significant change in the process time when increasing the $C_i$ and there was no observation of the undesired $\alpha$-IMC. At a high supersaturation there is an increased chance of agglomeration which was observed at the $C_i = 200.0$ mg/g solvent. Agglomeration causes a broadening in the PSD due to the presence of larger particles (the agglomerates). When the agglomeration becomes significant a bimodal distribution will appear which was confirmed by a slightly bimodal product PSD for as shown in Figure 9a. Figure 9b shows the microscope images of the individual seed crystals (without agglomeration), whereas in Figure 9c the PVM image clearly showes the formation of agglomerates.
Figure 9. a) PSD of the product crystals obtained using three different initial concentrations ($C_i$) with the same process parameters. A bimodal PSD is clearly observed at the highest $C_i$ due to agglomeration; b) microscope image of the seeds; and c) PVM image showing agglomerated particles.

The productivity of the antisolvent crystallization of the different initial concentrations was calculated by Eq. (6):

$$P = \frac{C_i - C_f}{\Delta t}$$  \hspace{1cm} (6)

where $P$ is the productivity, $C_i$ the initial concentration before antisolvent addition, $C_f$ the final concentration and $\Delta t$ is the batch time. The yield ($Y$) was calculated by Eq. (7):

$$Y = \frac{C_i \cdot m_{s,0} - C_f \cdot (m_{s,f} + m_{A,f})}{C_i \cdot m_{s,0}} \cdot 100$$  \hspace{1cm} (7)

where $m_{s,0}$ is the solvent mass initially present in the crystallizer, whereas $m_{A,f}$ and $m_{s,f}$ is the mass of antisolvent and solvent at the end of the process. Comparing the productivity shown in Table 2, a four-fold increase in the productivity is obtained when increasing the $C_i$, while
simultaneously maintaining the desired polymorph and reaching an antisolvent concentration at 40 wt%. An increase is also observed in the yield when increasing the initial concentration. In previous work the productivity was reported for the open-loop experiments with an \( C_i \) of 133.3 and 200.0 mg/g. Comparing the productivity and yield obtained from the open-loop experiments with the productivity and yield obtained in this work, the implementation of the SSC is shown to have a significant effect on increasing both the yield and productivity. The productivity was increased with 26 % at the initial concentration of 133.3 mg/g solvent and with 252 % at an initial concentration of 200 mg/g solvent. When the feedback strategy was implemented a higher antisolvent concentration of 40 wt% was achieved while maintaining the desires polymorphic form \( \gamma \)-IMC, which was not possible in the previous work. Previously it was only possible to reach an antisolvent concentration of 28.5 wt% for the \( C_i \) at 133.3 mg/g solvent and 23 wt% for \( C_i \) of 200.0 mg/g solvent to maintain the desired polymorph, thus the lower final concentration of the antisolvent resulted in a poorer productivity and yield. The results from this work highlight that applying SSC not only ensures polymorphic control but also achieves an increased yield and productivity as an increased antisolvent concentration can be reached without inducing the nucleation of the undesired solid forms when applying a feedback strategy.
Table 2. Productivity of antisolvent crystallization of IMC at different initial concentrations ($C_i$).

<table>
<thead>
<tr>
<th>$C_i$</th>
<th>66.7 mg/g</th>
<th>133.3 mg/g</th>
<th>200.0 mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Productivity (mg/g/min)</td>
<td>0.35</td>
<td>0.82</td>
<td>0.65*</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>90.2</td>
<td>95.1</td>
<td>61.6</td>
</tr>
<tr>
<td>Initial (wt%) at seeding</td>
<td>32.5</td>
<td>25.3</td>
<td>16.6</td>
</tr>
<tr>
<td>Final (wt%)</td>
<td>40.0</td>
<td>40.0</td>
<td>28.5</td>
</tr>
</tbody>
</table>

*Previous work

3.3 Reproducibility and scalability of the direct design approach

The importance of reduced batch-to-batch variability in pharmaceutical manufacturing is emphasized by both industry and regulatory agencies. To achieve this on an industrial scale, open-loop temperature or antisolvent/solvent strategies are applied. Based on the antisolvent addition profile obtained from the SSC experiment at the initial concentration of $C_i = 200.0$ mg/g solvent a simplified trajectory was made, as shown in Figure 4. This trajectory was implemented directly, and a set of replicates were made to investigate the reproducibility. Concentration profiles and FBRM counts/s obtained from the SSC experiment at the $C_i = 200.0$ mg/g solvent, and the first of the two duplicate open-loop experiments conducted based on the simplified antisolvent trajectory are shown in Figure 10. There is a good agreement between the concentration (Figure 10 a), FBRM count/s (Figure 10 b) profiles and the PSD (Figure 10c) which indicates that reproducibly of using a trajectory based on the original SSC experiment was very successful.
Figure 10. Comparison of the SSC experiment performed at the initial concentration 200.0 mg/g solvent and the experiment by direct implementation of the antisolvent trajectory obtained from the SSC experiment; a) concentration profiles; b) FBRM profiles; and c) PSDs of seed and final products of the SSC experiment and of the repeated experiments obtained by the direct implementation of the antisolvent trajectory.

The open-loop trajectory was magnified by a factor of ten and the crystallization process was implemented on 5 L scale, to investigate the scalability of the direct design approach. Comparing the FBRM profiles and the product PSDs shown in Figure 11, a good agreement is observed between the two scale-up experiments and the original SSC experiment performed in the small scale. At 1.5 hours a decrease in the FBRM count was observed in the second scale-up which is caused by agglomeration as no sedimentation was observed in the vessel. Similar PVM images are observed as in Figure 9 c. The good agreement between the profiles indicate the direct design approach is scalable and significant reproduction of the PSD can be obtained. In addition, the shape of the evolution of the FBRM count/s during the process at larger scale is also very similar to that at the 500 mL scale (Figure 10b).
Figure 11. a) The FBRM counts/s profiles obtained from the scale-up experiments in a 5 L scale; b) the PSDs obtained from the scale-up experiments at 5 L scale and the SSC experiment at 500 mL scale at an initial concentration of 200.0 mg/g solvent.

Secondary nucleation and breakage rates are significantly impacted by the stirring and hence the specific turbulence kinetic energy.34,35 An improvement of the scale-up experiments can be achieved by regarding these kinetics. During the scale-up the stirring rate of the small-scale experiments (300 RPM) was applied directly in the large scale, without scaling for the turbulence kinetic energy conditions. To minimize the nucleation/attrition rates, adjustments of the stirring conditions (stirrer type and speed and the baffles) can be done. However, the quick scale-up using the principles of direct design for high productivity of the desired polymorphic form production was successfully achieved.

4 Conclusions

In previous work and in the primary open-loop experiments in this work, nucleation of the undesired α-IMC polymorph was observed. Therefore, the objective of this work was to reach a
40 wt% of antisolvent concentration while maintaining the desired polymorph throughout the whole experiment. To do so, the feedback control strategy supersaturation control (SSC) was implemented and the effect of several operating parameters were investigated on process time and particle size distribution (PSD). A significant impact of the seed surface area on process time was shown at a supersaturation setpoint of 1.2. The seed surface area was increased by a threefold causing a twofold decrease in process time. However, the desired concentration of 40 wt% antisolvent was not reached due to very slow supersaturation consumption at the given setpoint of 1.2 and the experiments were stopped at a process duration of two days. Increasing the supersaturation setpoint to 2.0 and 2.2 improved the process duration and the desired antisolvent concentration was reached within 3 hours for both supersaturation setpoints. Additionally, the influence of the initial concentration ($C_i$) was investigated at a supersaturation setpoint of 2.0. It was possible to obtain a unimodal PSD in all SSC experiments, except at the highest $C_i$, where agglomeration caused a bimodal distribution and only the desired $\gamma$-IMC was produced throughout all SSC experiments. The implementation of the supersaturation feedback strategy showed a significant increase in productivity compared to not implementing a feedback strategy.

In addition, the objective was also to investigate the implementation of open-loop operating trajectories, obtained from the experiments with SSC, and use these to facilitate rapid scale-up according to the principles of direct design and quality-by-control (QbC). A trajectory was formed based on the antisolvent flowrate profile obtained from the SSC experiment at the $C_i = 200.0$ mg/g solvent and was shown to be very reproducible. Subsequently, the trajectory was scaled magnified by ten and was found to be robust at reproducing the same product characteristics as found in the small-scale. The obtained results highlight how a feedback control of antisolvent crystallization from a complex ternary solvent mixture not only can ensure polymorphic control but can also
increase productivity to help obtain good PSD while ensuring that the desired polymorph is obtained at different scales.

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References


(20) Zhou, G. X.; Fujiwara, M.; Woo, X. Y.; Rusli, E.; Tung, H. H.; Starbuck, C.; Davidson, O.;


180–196.
Manuscript title: Polymorphic control and scale-up strategy for crystallization from a ternary antisolvent system by supersaturation control

Author list: Iben Ostergaard, Botond Szilagyi, Zoltan K. Nagy, Heidi Lopez de Diego, Haiyan Qu

Synopsis:

A scale-up strategy based on the principles of direct design and Quality by Control (QbC) was applied and investigated using supersaturation control (SSC). Antisolvent crystallization from a ternary solvent system was applied using Indomethacin as the model compound. The results are a proof-of-concept showing that the direct design approach is reproducible and scalable.
Figure 1. a) Structure of the indomethacin molecule; b) XRD diffractograms of the α-IMC, γ-IMC and the acetone solvate; c) PVM image of the γ-IMC crystals showing the plate like crystal shape; and d) PVM image of α-IMC crystals shown the needle like crystal shape.
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135x84mm (600 x 600 DPI)
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169x116mm (96 x 96 DPI)
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Figure 2. Schematic overview of PAT tools used in a) Open-loop control and b) Closed-loop control. In a) the lines and diamonds in the crystallizer represent different polymorphs.

98x65mm (150 x 150 DPI)
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97x85mm (150 x 150 DPI)
Figure 3: Micrographs showing attrition where a) is a microscope images and b) is a PVM image recorded during an experiment.

338x254mm (96 x 96 DPI)
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152x103mm (95 x 95 DPI)
Figure 4. Trajectory obtained from the antisolvent addition profile of experiment 6. The actual supersaturation and the desired SS setpoint are also shown throughout the process.
Figure 5. 5 L scale set-up: 1-thermoregulator, 2-FBRM probe, 3-temperature probe, 4-PVM probe, 5-peristaltic pump, 6-antisolvent bottle, 7-solvent bottle, and 8-computer with control algorithms.

84x84mm (600 x 600 DPI)
Figure 6. FBRM total counts and antisolvent profiles over time for two open-loop experiments at an addition rate of 1 mL/min in a) and 5 mL/min in b). Three and four samples were taken throughout the two experiments at times indicated by the numbers 1-4. In c) the PSDs of the seed and final products of the two experiments are shown where unimodal distributions are observed.
Figure 6. FBRM total counts and antisolvent profiles over time for two open-loop experiments at an addition rate of 1 mL/min in a) and 5 mL/min in b). Three and four samples were taken throughout the two experiments at times indicated by the numbers 1-4. In c) the PSDs of the seed and final products of the two experiments are shown where unimodal distributions are observed.

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84x84mm (600 x 600 DPI)
Figure 7. Micrographs of the samples, where picture with suffix ‘a’ are microscope images and those with suffix ‘b’ are PVM images of the 4 different samples obtained during the 5 mL/min antisolvent addition as shown in Figure 6.

338x254mm (96 x 96 DPI)
Figure 7. Micrographs of the samples, where picture with suffix ‘a’ are microscope images and those with suffix ‘b’ are PVM images of the 4 different samples obtained during the 5 mL/min antisolvent addition as shown in Figure 6.
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338x254mm (96 x 96 DPI)
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260x177mm (96 x 96 DPI)
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338x254mm (96 x 96 DPI)
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259x174mm (96 x 96 DPI)
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338x254mm (96 x 96 DPI)
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258x175mm (96 x 96 DPI)
Figure 8. Concentration profile of the SSC experiments with supersaturation ratio setpoints 2.0 and 2.2.
Figure 9. a) PSD of the product crystals obtained using three different initial concentrations (C_i) with the same process parameters. A bimodal PSD is clearly observed at the highest C_i due to agglomeration; b) microscope image of the seeds; and c) PVM image showing agglomerated particles.
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338x254mm (96 x 96 DPI)
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282x192mm (96 x 96 DPI)
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83x83mm (600 x 600 DPI)
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