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Published in:
Organic Process Research & Development

DOI:
10.1021/acs.oprd.9b00052

Publication date:
2019

Document version:
Accepted manuscript

Citation for published version (APA):

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Org. Process Res. Dev., Just Accepted Manuscript • DOI: 10.1021/acs.oprd.9b00052 • Publication Date (Web): 02 Apr 2019

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Antisolvent Crystallization of Indomethacin from Ternary Solvent System with High Productivity, better Polymorphism and Particle Size Control

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For Table of Contents only

![Graph showing solubility of a compound in Acetone - Methanol (66.5 - 33.5 wt%) as a function of water content (Wt%). The graph indicates different solubility levels at various water contents and highlights critical points such as $C_{eq.1}$ and $C_{eq.2}$. Unseeded and seeded crystallization processes are also depicted.](image-url)
ABSTRACT

Antisolvent crystallization of Indomethacin (IMC), a nonsteroidal anti-inflammatory drug, from a ternary solvent system (acetone–methanol–water) has been investigated in this work. Acetone–methanol (66.5-33.5 wt%) binary mixture was selected as a solvent based on the solubility of IMC reported earlier. Water was selected as an antisolvent based on the solubility of IMC measured in acetone–methanol–water mixtures at 25 °C. Unseeded and seeded antisolvent crystallization was carried out for two initial concentrations of IMC ($C_{0,1}$ and $C_{0,2}$) with stepwise addition of antisolvent. The acetone solvate of IMC was crystallized during the unseeded experiments, while the desired $\gamma$-IMC was obtained with a bimodal particle size distribution (PSD) during the experiments seeded with $\gamma$-IMC. A significant increase in the productivity was observed because of increased crystal yield and faster crystallization kinetics as compared to the crystallization processes reported earlier for the production of $\gamma$-IMC. Finally, the feasibility of IMC particle size tuning through the solvent-antisolvent (dissolution-growth) addition cycles was demonstrated successfully.

KEYWORDS Indomethacin, solubility, antisolvent crystallization, polymorphism, particle size distribution
1. Introduction

Crystallization is a widely used purification technique for manufacturing of active pharmaceutical ingredients (APIs) as well as intermediates. Crystallization being a final step in the manufacturing of APIs plays an important role in obtaining the desired critical quality attributes of APIs, which are very important for subsequent formulation processes and performance of the final drug products.\(^1\) The critical quality attributes of APIs that are important for the drug product performance includes chemical purity, optical purity, solid form (crystalline or amorphous), particle size and shape. Generally, the amorphous form of APIs exhibit better dissolution properties, which are important to achieve high bioavailability for drugs with low aqueous solubility.\(^2,3\) However, the crystalline form is mostly preferred over the amorphous form for development of drug products due to the stability issues associated with the amorphous form.\(^4\) The amorphous form of an API is a metastable form and tends to crystallize upon storage, which may change its physical properties such as solubility, dissolution rate etc. leading to a change in bioavailability.\(^3\) When it comes to the use of crystalline form for the drug product development, polymorphism plays an important role. There are several examples of the API polymorphs exhibiting significantly different physical and chemical properties leading to the varied dissolution properties as well as stabilities.\(^5-7\) Therefore, the selection and reliable production of a suitable polymorph of an API is very important for pharmaceutical industry. Similarly, the particle size and shape of APIs are crucial quality attributes that are known to influence not only the downstream processing such as filtration or drying, but also the formulation processes and drug product attributes such as the rate of drug release, bioavailability etc.\(^8-11\) Therefore, control of polymorphism and particle size and shape during crystallization of APIs assumes great significance for the pharmaceutical industry. Moreover, it is also important for the pharmaceutical...
industry to produce APIs of the desired qualities with high productivity that will dictate the economy of the process. While the critical quality attributes of APIs could be a complex function of crystallization parameters such as solvents, method of supersaturation, degree of supersaturation (cooling, evaporation, anti-solvent addition rate etc.), operating temperature, impurities or additives, agitation etc., the productivity of the process strongly depends on the solvent. The selection of a solvent with high solubility of an API to be crystallized is very important to obtain high crystal yield as well as to decide the volume of the crystallizer.\textsuperscript{12} While seeding with the target polymorph is most commonly used technique to obtain desired polymorph, many different strategies such as direct nucleation control, temperature cycling, crystal growth combined with in process comminution have been reported earlier for particle engineering.\textsuperscript{13–20} In this work, we investigate the use of ternary solvent system in order to obtain desired polymorph with favorable particulate properties and high productivity. Abu Bakar et al. have demonstrated the direct nucleation control (DNC) approach to control the particle size distribution of glycine during antisolvent crystallization from water-ethanol mixture. The DNC approach involved controlling the number of nuclei by dissolving the excess nuclei and increasing the number or allowing growth of constant number of nuclei with addition of solvent and antisolvent, respectively.\textsuperscript{13} We also investigate the possibility of manipulating particulate properties through dissolution-growth cycles by strategic addition of solvent-antisolvent in this work.

Indomethacin (IMC), a nonsteroidal anti-inflammatory drug, is selected in this work as a model compound. IMC is known to exhibit five polymorphs and several solvates.\textsuperscript{21} However, $\alpha$-IMC and $\gamma$-IMC are the most commonly obtained among five polymorphs. These two IMC polymorphs are monotropically related to each other: $\alpha$-IMC (mp $149–154 \, ^\circ\mathrm{C}$) is a metastable and $\gamma$-IMC (mp $158–161 \, ^\circ\mathrm{C}$) is the thermodynamically most stable form. It has also been reported that $\gamma$-IMC
crystals exist as rhombic plates while α-IMC crystals have a fine short needlelike shape.\textsuperscript{22} Although the solubility of α-IMC is higher than that of γ-IMC, the use of metastable α-IMC for formulation of the drug products is avoided due to the possibility of transformation into γ-IMC during unfavorable storage conditions. In addition, the needle shaped crystals are known to have issues with the downstream processing such filtration, powder flow ability, compression etc. Therefore, we aim to obtain the most stable γ-IMC with a unimodal size distribution and high productivity in this work. In our previous work, we have performed seeded cooling crystallization of IMC from ethanol. Desired γ-IMC was obtained in the seeded experiments, however, the yield of IMC was very low due to lower solubility of IMC in ethanol and longer batch times up to 20 h were observed.\textsuperscript{23} Therefore, antisolvent crystallization of IMC with acetone-methanol (66.5-33.5 wt\%) binary mixture as a solvent were investigated in this work based on the high solubility of IMC in the solvent reported earlier.\textsuperscript{24} First, the solubility of IMC in acetone-methanol-water mixtures of varying water composition was measured at 25 °C. This was followed by unseeded and seeded antisolvent crystallization of IMC from acetone-methanol-water for two initial concentrations of IMC ($C_{0,1}$ and $C_{0,2}$) at 25 °C. Finally, a seeded antisolvent crystallization experiment was repeated with a cycle of solvent-antisolvent addition to demonstrate the effect of dissolution-growth on particle size distribution of the end product.

2. Materials and Methods

2.1 Chemicals

Methanol, acetone and acetonitrile of CHROMASOLV grade (purity \(\geq 99.9\%\)) obtained from Honeywell Specialty Chemicals were used in this work. IMC of purity \(\geq 99\%\) purchased from Shanghai Hungsun Chemical Co., Ltd. was used after a recrystallization step. Ultrapure MiliQ water obtained from a Purelab Chorus (ELGA) water purifier system was used.
2.2 Solubility Measurement of Indomethacin

The classical isothermal technique was used to measure the solubility of $\gamma$-IMC in ternary mixtures of acetone–methanol–water at 25 °C. The different compositions of solvent mixtures as shown in Figure 1 were used for the solubility measurement. The procedure for solubility measurement involved preparation of a suspension with an excess amount of solute in 2 mL of solvent contained in a 10 mL glass vial. Sealed vials were maintained at constant temperature under magnetic stirring for 24 h to attain equilibrium. A detailed description of the apparatus used for the measurements is provided by Malwade and Christensen. At the end of the equilibrium, the saturated solution was separated from the excess solid phase with a syringe and 0.2 µm PTFE filters, appropriately diluted, and analyzed by High Pressure Liquid Chromatography (HPLC) to determine the concentration of IMC. A Dionex UltiMate 3000 HPLC system equipped with a ZORBAX Eclipse XDB-C18 reverse phase column (dimensions 150 × 4.6 mm, particle size 5 µm, Phenomenex, Denmark) maintained at 35 °C and a diode array detector (DAD-3000) was used for the analysis of samples. The samples (1 µL injection volume) were eluted with the mobile phase (Acetonitrile with 0.1% formic acid) flow rate of 0.8 mL/min for 5 min and the chromatograms were recorded at 320 nm wavelength. The solid phase was analyzed by X-ray Powder Diffraction (XRPD) to ascertain any possible phase change during the solubility measurement. A Rigaku MiniFlex600 benchtop X-ray diffractometer equipped with Cu-Kβ radiation source operating at 40 kV and 15 mA, a graphite monochromator, and NaI scintillation detector was used for analysis of solid phase samples. Four repetitions were performed for each measurement.
Figure 1. The composition of acetone-methanol-water mixtures used for the solubility measurement of IMC.

2.3 Antisolvent Crystallization of Indomethacin

Antisolvent crystallization of IMC was performed in an EasyMax102 workstation (Mettler-Toledo AutoChem) equipped with two 100 mL reactors, an overhead stirrer, and a solid-state thermostat enabled cooling/heating jacket. An Attenuated Total Reflection – Fourier Transform Infrared (ATR-FTIR) probe (ReactIR15, Mettler-Toledo AutoChem) equipped with an AgX probe interface (6 mm × 1.5 m Fiber), a DiComp (Diamond) probe tip, and a liquid-nitrogen-cooled MCT detector was used to monitor IMC concentration in a calibration free manner. The spectra were collected in the wavenumber range of 3000 – 650 cm\(^{-1}\) with a resolution of 8 cm\(^{-1}\). Each spectrum consisted of 256 scans. In order to remove the background effects such as a baseline drift and to obtain a better signal to noise ratio, second derivative of the spectra was used for extracting the signal for IMC. A peak at 1322 cm\(^{-1}\) was found to be responsive to the IMC concentration; therefore, it was used to estimate the IMC concentration in the liquid phase. An exemplary FTIR spectrum of IMC in acetone-methanol-water mixture at 25 °C and its second derivative is provided.
in the Supporting Information (Figure S1). The experimental conditions for antisolvent crystallization of IMC are shown in Table 1. Unseeded and seeded antisolvent crystallization experiments were performed with two different initial concentrations of IMC ($C_{0,1}$ and $C_{0,2}$). The procedure included preparation of a solution of initial concentration by dissolving appropriate amount of IMC in 30 g of acetone-methanol (66.5-33.5 wt%) mixture and maintaining the solution at 30 °C to ensure the complete dissolution. The solution was then cooled to 25 °C followed by the stepwise addition of antisolvent. In case of seeded antisolvent crystallization experiments, the seeds of $\gamma$-IMC were added immediately after the first addition of antisolvent to avoid dissolution of seed crystals. Seed loads equivalent to 0.75, 1.5, 3, and 4% of the theoretical yield were used.

The theoretical yield of IMC is calculated by using following formula:

$$Theoretical\ yield = (C_0 \times m_0) - (C_{eq} \times m_{eq})$$

Where, $C_0$ (g/g solvent) is the initial concentration of IMC, $m_0$ (g) is the initial mass of solvent, $C_{eq}$ (g/g solvent) is the equilibrium concentration of IMC at final solvent composition, and $m_{eq}$ (g) is the mass of solvent at equilibrium after addition of antisolvent. $C_{eq}$ is estimated from the solubility data measured in this work. Seeds of $\gamma$-IMC were prepared by recrystallization of IMC from acetonitrile and consisted of a sieve fraction of a range 71–125 µm. A constant overhead stirrer speed of 300 rpm was maintained throughout the experiments. The calculation of IMC yield was based on the initial and final concentration of IMC determined by HPLC. IMC crystals obtained at the end of the experiment were dried and analyzed by XRPD and a laser diffraction particle size analyzer (LS 13 320, Beckman Coulter, Inc.) to determine the polymorph and crystal size distribution, respectively.

Table 1. Experimental plan and operating parameters for antisolvent crystallization of IMC from acetone-methanol-water at 25 °C.
2.4 Implementation of Dissolution-Growth Cycles

Temperature cycling is a widely used strategy to tune the particle size and shape through the dissolution and growth cycles during crystallization of APIs. In this work, we have investigated the feasibility of solvent-antisolvent addition cycles to effect the dissolution-growth cycles to optimize the particle size distribution of IMC. Effective application of dissolution-growth cycles through the addition of solvent-antisolvent needs a better understanding of the crystallization mechanisms such as crystal growth, secondary nucleation, breakage, attrition etc. occurring during the process. In addition, the required amount of solvent and antisolvent, the timing of addition and the number of cycles strongly depend on the understanding of these mechanisms. Advanced Process Analytical Technology (PAT) tools such as Focused Beam Reflectance Measurement (FBRM) combined with ATR-FTIR are necessary to extract such information and subsequently to develop the strategy for effective solvent-antisolvent addition cycles. In this work, we have performed one cycle of the solvent-antisolvent addition for an antisolvent crystallization of IMC carried at low initial concentration. However, due to the lack of real time data from FBRM, the solvent-antisolvent addition cycle was applied when enough crystals were present in the
crystallizer. Having enough crystals formed in the crystallizer after 150 min into the crystallization, 10 g solvent i.e., a binary mixture of acetone-methanol (66.5-33.5 wt%) was added to the suspension. After stabilization of IR signal, 4 g antisolvent i.e., water was added to the suspension. After 30 min of antisolvent addition, the experiment was stopped and IMC crystals were collected, dried and analyzed by XRPD as well as a particle size analyzer.

3. Results and Discussion

3.1 Solubility of Indomethacin in Binary and Ternary Solvent Mixtures

Selection of a suitable solvent or solvent mixture for crystallization of APIs is very crucial as it can have direct role in deciding the outcome of crystallization such as yield, polymorphism, particle size, shape, and purity. As far as yield is concerned, high solubility of solute in the solvent is a prerequisite. In case of polymorphism, particle size, shape, and purity, the solute-solvent interactions can be important to the outcome, especially in the kinetically driven crystallization processes. Therefore, the solubility measurement of APIs in different solvents or solvent mixtures is indispensable in development of crystallization processes. Previously measured solubilities of γ-IMC in pure organic solvents at different temperatures and in the binary solvent mixtures at 25 °C is shown in Figure 2a and b, respectively. It is obvious from Figure 2b that the solubility of γ-IMC reaches a maximum at a certain composition of binary solvent mixture, which is significantly higher than the solubility in pure solvents. This kind of solubility behavior, where a maximum solubility is observed at a certain composition of binary mixture, is very often observed for many APIs. Therefore, the use of binary solvent mixtures with high solubility of APIs can allow a higher initial concentration of APIs, thereby increasing the batch yield as well as lowering the crystallizer volume. In addition, it also offers the opportunity to alter the solute-solvent interactions where pure solvents favor the crystallization of undesired polymorphs or solvates.
Figure 2. Solubility of γ-IMC in (a) pure organic solvents, modified from Malwade et al.\textsuperscript{23} and (b) binary solvent mixtures at 25 °C, modified from Hellstén et al.\textsuperscript{24} Solid and dashed lines are drawn for visual guidance.

As shown in Figure 2b, the highest solubility of IMC was observed in dichloromethane-methanol and dichloromethane-ethanol followed by acetone-methanol binary mixtures. In order to obtain a high yield from antisolvent crystallizations, preliminary experiments have been performed using dichloromethane-alcohol binary mixture as a solvent and water as an antisolvent. However, as water is immiscible with dichloromethane, a two-liquid phase system was formed after the addition of water. Crystallization of needle-shaped particles took place in the dichloromethane phase, which was characterized as the dichloromethane solvate of IMC. Therefore, dichloromethane-alcohol binary mixtures were not used as solvent in this work, and acetone–methanol (66.5-33.5 wt%) binary mixture was selected as the solvent for antisolvent crystallization of IMC. The solubilities of γ-IMC measured in acetone-methanol-water mixtures at 25 °C are shown in Figure 3. It is evident from Figure 3 that the solubility of γ-IMC decreases significantly with increasing water content, clearly indicating the potential of water as an antisolvent for crystallization of IMC. It is also evident from the solubility data that the crystallization experiments can be started with IMC.
concentration as high as 22 g/100 g solvent, thereby allowing to harvest higher yield of IMC. The planned antisolvent crystallization experiments with high \((C_{0,1})\) and low \((C_{0,2})\) initial concentrations of IMC have been marked with solubility data in Figure 3. It has been reported earlier that the IMC form solvates when in contact with pure acetone or methanol, which was also confirmed in the present investigation.\(^{30}\) However, analysis of the solid recovered from the equilibrated suspension at the end of the solubility measurement by XRPD (Supporting Information, Figure S2) indicated no solid phase transformation of \(\gamma\)-IMC to any of the solvates during the measurements. This observation suggested that the solid phase transformation from the \(\gamma\)-IMC to the acetone or methanol solvates can be retarded by the presence of water in the solvent, which could be attributed to the altered solute-solvent interactions. A trajectory of IMC concentration due to dilution after addition of antisolvent, calculated based on mass balance, is also shown in Figure 3. It is obvious from the trajectory that the dilution factor is relatively small compared to a sharp decrease in the solubility of IMC. It means that a relatively small amount of antisolvent is needed to harvest a significant crystal yield. Thus, the solubility data clearly suggests

![Figure 3](image-url)

**Figure 3.** Measured solubility of \(\gamma\)-IMC in acetone-methanol-water mixtures at 25 °C. Solid and dashed lines are drawn for visual guidance.
requirement of a small volume of solvent and antisolvent due to high solubility and a sharp decrease in solubility of IMC, respectively. However, the use of small volume of solvent and antisolvent may lead to the dense slurries that are difficult to stir.

3.2 Antisolvent Crystallization of Indomethacin

3.2.1 Unseeded Antisolvent Crystallization of Indomethacin

The results from unseeded antisolvent crystallization of IMC from acetone-methanol-water for high \(C_{0,1}\) and low \(C_{0,2}\) initial concentrations are shown in Figure 4. The blue line in the figure represents the concentration of IMC in the form of infrared absorption monitored with an ATR-FTIR probe and the brown line indicates the temperature during antisolvent crystallization of IMC. Two antisolvent (water) addition steps of 6 g each are evident from a small increase in the temperature and a corresponding reduction in the infrared absorbance due to the dilution effect. As expected, the nucleation of IMC commenced earlier in the experiment with high initial

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Unseeded antisolvent crystallization of IMC from acetone-methanol-water with (a) low initial concentration and (b) high initial concentration of IMC at 25 °C. Peak height is determined from the second derivative of IR spectrum.
concentration (Figure 4b) than in experiment with lower initial concentration (Figure 4a). In both the cases, IMC concentration continued to decrease rapidly after the nucleation and a dense slurry of crystals formed, which was difficult to stir and to filter. The solid phase analysis by XRPD (Supporting Information, Figure S3) revealed the crystals obtained as the acetone solvate of IMC in both the cases. Figure 5a shows an SEM image of the fine needle shaped crystals of IMC acetone solvate forming a cotton like structure. The difficulty in stirring the slurry was mainly due to the ability of the needlelike crystals to form a cotton like structure.

![SEM images of crystals obtained during antisolvent crystallization of IMC with low initial concentration. a) Unseeded; b) seeded with 4% γ-IMC.](image)

**Figure 5.** SEM images of crystals obtained during antisolvent crystallization of IMC with low initial concentration. a) Unseeded; b) seeded with 4% γ-IMC.

### 3.2.2 Seeded Antisolvent Crystallization of Indomethacin

As shown in the previous section, the crystallization of undesired acetone solvate of IMC occurs during the unseeded antisolvent crystallization from acetone–methanol solution. Seeding with the desired polymorph is a widely used strategy to control the polymorphism, even though it is not always guaranteed to obtain the seeded polymorph as product.23 In this case, the degree of supersaturation and the amount of seed load can affect the outcome. Therefore, seeded antisolvent crystallization of IMC from acetone–methanol solution was performed for two initial concentrations ($C_{0,1}$ and $C_{0,2}$) as shown in Figure 3 and four different seed loads of γ-IMC at 25
°C. The results from antisolvent crystallization of IMC for low initial concentration ($C_0,1$) and all seed loads are shown in Figure 6. Two antisolvent addition steps of 6 g each during the antisolvent crystallization experiments are evident from a small increase in the temperature and a corresponding reduction in the infrared absorbance due to the dilution effect in Figure 6a. The dry

![Figure 6](image)

**Figure 6.** Seeded antisolvent crystallization of IMC from acetone-methanol-water with low initial concentration at 25 °C. a) IMC concentration as peak height at 1322 cm$^{-1}$ derived from second derivative of IR spectrum; b) particle size distribution of IMC crystals.

seed crystals of γ-IMC were added to the solution immediately after first addition of antisolvent at 20 min. It is clear from Figure 6a that the IMC concentration starts decreasing gradually after second addition of antisolvent and eventually reaches equilibrium in 300 min. It is also evident from the figure that the crystallization kinetics is slightly faster with the increasing seed load as shown by a red arrow. Analysis of IMC crystals collected at the end of the experiments by XRPD confirmed crystallization of the most stable γ-IMC form for all seed loads. Comparison of these results with the unseeded antisolvent crystallization experiments clearly show that the seeding has effectively altered the outcome of the crystallization. The results from particle size distribution (PSD) with laser diffraction method for all seed loads are shown in Figure 6b along with the γ-
IMC seed crystals. A bimodal distribution of γ-IMC crystals is obvious from the figure for all seed loads. Other than a slight increase in the volume fraction of larger particles with increasing seed load, there is no pronounced effect of seed load on the PSD of γ-IMC. A bimodal distribution of γ-IMC product might suggest presence of other crystallization mechanisms such as secondary nucleation, breakage, attrition, agglomeration along with growth of the seed crystals. An SEM image of crystals obtained from antisolvent crystallization of IMC with 4% seed load at low initial concentration is shown in Figure 5b, which show the agglomeration as well as breakage, some of the small crystals seen in the image might suggest the occurrence of secondary nucleation at later stage of the batch.

Figure 7. Seeded antisolvent crystallization of IMC from acetone-methanol-water with high initial concentration at 25 °C. a) IMC concentration as peak height at 1322 cm\(^{-1}\) derived from second derivative of IR spectrum; b) particle size distribution of IMC crystals.

The results from antisolvent crystallization of IMC for high initial concentration (\(C_{0,2}\)) and all seed loads are shown in Figure 7. Three antisolvent addition steps of 3 g each are obvious from a slight increase in the temperature and a corresponding decrease in the infrared absorbance in Figure
7a. In this case, the dry seed crystals of γ-IMC were added to the solution immediately after the first addition of antisolvent at 24 min. It is also evident from the figure that the IMC concentration starts decreasing immediately after the first addition of antisolvent due to high supersaturation at the beginning. The decrease in IMC concentration becomes more pronounced with successive antisolvent addition steps. In case of 0.75% seed load, IMC concentration as indicated by a red curve in Figure 7a starts decreasing rapidly after 100 min because of massive secondary nucleation and reaches a plateau for a brief period at 150 min as indicated by an arrow. Microscopic images of the crystals taken at 120 min, 180 min and at the end of the experiment shown in Figure 8 confirms the occurrence of several mechanisms involved in the process. Secondary nucleation of

![Microscopic images of crystals](image)

**Figure 8.** Microscopic images of crystals taken during antisolvent crystallization at high initial concentration of IMC and 0.75% seed load. a) 120 min; b) 180 min; c) at the end of the experiment.
needle shaped α-IMC took place when seeds were added to the system, at a later stage the α-IMC was transformed into the platelike crystals of γ-IMC. For better understanding and visualization of the events during this experiment, a short video is provided in the Supporting Information. The results for 0.75% seed load clearly indicates the obedience of Ostwald’s rule of stages, where secondary nucleation of a metastable α-IMC form occurred in presence of γ-IMC seed crystals followed by solvent mediated transformation into stable γ-IMC. The XRPD analysis of the crystals obtained at the end of the experiments confirmed the product as γ-IMC for all seed loads. The results from PSD measurement of the product crystals are shown in Figure 7b. It is obvious from the results that a bimodal distribution of γ-IMC is obtained for all seed loads, again suggesting the presence of other crystallization mechanisms along with seed crystal growth.

Productivity, a measure of the crystal yield as well as crystallization kinetics as defined below, is used to evaluate the process in this work.

$$\text{Productivity} = \frac{C_0 - C_{eq}}{\Delta t}$$

Where $C_0$ is initial IMC concentration, $C_{eq}$ is equilibrium IMC concentration at the end of crystallization and $\Delta t$ is the time elapsed to reach equilibrium after seeding the crystallizer. So far, very few studies have reported the crystallization processes for the production of stable γ-IMC polymorph and most of the studies do not discuss the crystal yield or productivity of process and report very long batch times. In our previous work, we have reported seeded cooling crystallization of IMC from ethanol at different temperatures, initial IMC concentrations and seed loads. While it was shown to produce γ-IMC consistently with high initial IMC concentration (5.5 g/100 g solvent) at 15 °C, the yield was very low due to low solubility of IMC in ethanol and a
very long batch times up to 20 h were observed leading to the poor productivity. A comparison of the results from present work to the cooling crystallization of IMC from ethanol is summarized in Table 2. Results of antisolvent crystallization of IMC from acetone-methanol-water at 25 °C and cooling crystallization from ethanol reported earlier.

<table>
<thead>
<tr>
<th>Properties</th>
<th>Unseeded</th>
<th>Seeded</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>$C_{0,1}$</td>
<td>$C_{0,2}$</td>
</tr>
<tr>
<td>Solid form†</td>
<td>Solvate</td>
<td>Solvate</td>
</tr>
<tr>
<td>Solid form*</td>
<td>α-IMC</td>
<td>α-IMC</td>
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<tr>
<td>Productivity (mg/g/min)</td>
<td>-</td>
<td>-</td>
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†Present work, *Previous work (high initial IMC concentration at 5 °C).

in Table 2. It is evident from the table that the productivity of the process developed in present work for low ($C_{0,1}$) and high ($C_{0,2}$) initial concentration of IMC is 16 and 26 times higher, respectively, compared to the maximum achievable productivity during cooling crystallization from ethanol. The possibility of employing high initial concentration of IMC due to its higher solubility in acetone-methanol (66.5-33.5 wt%) mixture and faster crystallization kinetics in acetone-methanol-water are the major reasons for increased productivity observed in this work. The results from present work clearly highlight the advantages of using solvent mixtures to improve the productivity of the crystallization processes for APIs. In addition, the use of solvent mixtures can lead to altered solute-solvent interactions compared to pure solvents, which may help in avoiding undesired polymorphs or solvates formed in pure solvents. In this work, use of a ternary solvent mixture could not avoid formation of IMC solvate as observed during unseeded antisolvent crystallization; however, the problem was solved by seeding the experiments with desired γ-IMC.
3.3 Antisolvent Crystallization of Indomethacin with Dissolution-Growth Cycle

The results from seeded antisolvent crystallization of IMC from acetone-methanol-water with an addition of solvent-antisolvent cycle are shown in Figure 9. It is evident from the infrared absorbance of IMC shown by blue line in Figure 9a that the absorbance increases at 150 min after addition of 10 g solvent i.e., acetone-methanol (66.5-33.5 wt%) due to dissolution of IMC and subsequently decreases gradually after addition of 4 g antisolvent. The PSD of IMC crystals from antisolvent experiment with solvent-antisolvent addition cycle (blue) and without cycle (red) along with γ-IMC seed crystals are shown in Figure 9b. The effect of solvent-antisolvent addition cycle on PSD of IMC is obvious from a slight increase in the volume fraction of larger particles and a decrease in the volume fraction of small particles as indicated by arrows in Figure 9b. This suggests the potential of solvent-antisolvent addition strategy for particle size tuning of APIs in order to obtain a narrow unimodal size distribution. However, the addition of solvent-antisolvent to the suspension leads to the dilution of solution, thereby reducing the productivity of process. Therefore, this strategy could be suitable for the solvents having high solubility of a solute and an antisolvent reducing the solubility sharply so that the small amounts of each are required to effect dissolution-growth cycles. In order to limit the number of cycles to avoid dilution, the strategic addition of solvent-antisolvent based on a real time information such as particle count, chord length distribution from FBRM and solute concentration from inline probes is required. Furthermore, this strategy can be used in combination with other techniques such as temperature cycling or in process comminution with ultrasound and wet milling. Moreover, it is also possible to use hot solvent and cold antisolvent in order to limit the amount used. Nonetheless, the strategy of solvent-antisolvent addition offers an alternative to implement the dissolution-growth cycles in order to engineer the particle size of APIs. We aim to implement this strategy to engineer particle size of
IMC and investigate various related aspects such as the amount of solvent-antisolvent per cycle, timing of cycle, number of cycles etc. in our future work.

Figure 9. Results from antisolvent crystallization of IMC with solvent-antisolvent addition cycle.
(a) IMC concentration as peak height at 1322 cm\(^{-1}\) derived from second derivative of IR spectrum;
(b) particle size distribution of IMC crystals.

4. Conclusion

A novel rigorous procedure for the selection of solvent and antisolvent has been developed for the crystallization of IMC. A mixture of acetone and methanol was selected as a solvent due to the high solubility of IMC in this mixture as well as the miscibility of the solvents with water, which has been selected as the antisolvent. The operation condition of the antisolvent crystallization process was designed based on the solubility of IMC in mixed solvents of acetone-methanol at 25 °C. The developed antisolvent crystallization process showed manifold increase in the productivity as compared to the crystallization processes reported earlier for the production of γ-IMC. This increased productivity was due to a high initial concentration of IMC owing to its high solubility in acetone-methanol (66.5-33.5 wt%) and faster crystallization kinetics. The acetone solvate of IMC was produced from unseeded antisolvent crystallization while stable γ-IMC was obtained in
the experiments seeded with γ-IMC. Secondary nucleation of metastable α-IMC and subsequent transformation into stable γ-IMC was observed in an experiment with 0.75% seed load and high initial concentration of IMC. Faster crystallization kinetics was observed with increased seed load at both initial concentrations of IMC. In terms of PSD, a bimodal distribution was observed in all seeded experiments indicating occurrence of other crystallization mechanisms along with the seed crystal growth. In the end, the feasibility of implementing dissolution-growth cycles for particle size engineering through solvent-antisolvent addition was tested successfully. The results obtained in this work show that the solvent mixtures showing higher solubility of a solute than pure solvents could be used for the following:

1) to increase the product yield and to fasten the crystallization kinetics, thereby the increased productivity

2) to alter the solute-solvent interactions in favor of a desired polymorph formation or avoiding solvate formation, if it does form in pure solvents. However, it was not observed during this study as the acetone solvate of IMC formed during unseeded crystallization as it does form in pure acetone

3) to implement dissolution-growth cycles for particle size engineering, either in a standalone fashion or in combination with temperature cycling.

ASSOCIATED CONTENT

Supporting Information. FTIR spectra of IMC in acetone-methanol-water and its second derivative, XRPD patterns of the excess solid phase from solubility measurements and the acetone solvate of IMC from unseeded antisolvent crystallization experiments.

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**Funding Sources**

Danish Council for Independent Research (DFF) financed this work with grant ID: DFF-6111-00077B.

**ACKNOWLEDGMENT**

Authors would like to thank Danish Council for Independent Research (DFF) for financing this work with grant ID: DFF-6111-00077B.

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