**Ternary solvent system for crystallizing the desired solid form of indomethacin with increased productivity**

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**Highlights**

* Novel antisolvent crystallization process for Indomethacin
* Increased productivity obtained from ternary solvent system
* Desired polymorph obtained via seeding

**1. Introduction**

Development of crystallization processes for manufacturing of active pharmaceutical ingredients (APIs) with the desired purity, solid form, particulate properties, as well as sufficiently high process yield is very crucial for pharmaceutical industry. Polymorphism, particle size distribution and crystal shape of APIs are a complex function of crystallization process parameters, whereas the productivity of a batch crystallization process strongly depends on the difference between the API concentration at the initial operating conditions and the final condition of the batch. A high process yield requires a solvent system that provides high API solubility at the initial batch conditions and a remarkable change of the API solubility with the changing operation parameter, i.e., decreasing of temperature and/or addition of antisolvent [1]. In this work, we show that the use of binary solvent mixture compared to the pure solvent can provide increased solubility leading to the increased productivity of APIs during crystallization. We also show that the altered solute-solvent interactions favoring the formation of desired polymorph can be obtained by using solvent mixtures instead of pure solvents. Indomethacin (IMC), a nonsteroidal anti-inflammatory drug, is used as the model compound. It has been reported that IMC can form five polymorphs and several solvates [2]. However, metastable α-IMC having needle like crystal shape and thermodynamically most stable γ-IMC having plate like crystal shape are most commonly observed. In this work, antisolvent crystallization of IMC from acetone-methanol-water system has been carried out with acetone-methanol (66.5-33.5 Wt%) as solvent and water as an antisolvent.

**2. Methods**

Binary solvent mixture acetone-methanol was selected based on the solubility of γ-IMC in single and binary solvent mixtures (Fig. 1) reported earlier [3,4]. Firstly, the solubility of γ-IMC in acetone-methanol-water with varying composition of water was measured at 25 °C. Based on the determined solubility data, seeded and unseeded antisolvent crystallization experiments of IMC from acetone-methanol-water were performed at 25 °C. The procedure included dissolution of IMC in 30 g of acetone-methanol solvent contained in a 100 ml reactor followed by stepwise addition of water as an antisolvent. Each experiment was performed at two different initial concentrations of IMC as shown in Fig. 2. In experiments with high (*C*i1) and low (*C*i2) initial concentrations, 9 and 12 g water was added, respectively to obtain the respective solvent composition of 23 and 28.5 wt% water as shown in Fig. 2. In case of seeded experiments, seed load (γ-IMC, 71-125 µm) of 0.75, 1.5, 3, and 4% of Δ*C* were used. The experiments were monitored with ATR-FTIR probe and characterization of IMC crystals was carried out with XRPD, SEM and particle size analyzer.

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**Figure 1.** Solubility of γ-IMC in pure organic solvents (left) [4] and in binary solvent mixtures at 25 °C (right) [3].

**3. Results and discussion**

In comparison to the seeded cooling crystallization of IMC from ethanol reported earlier [4], significantly high productivity was obtained during antisolvent crystallization of IMC from acetone-methanol-water (Table 1). Increased crystal yield was obtained mainly due to the extended thermodynamic boundaries allowing much higher initial concentration of IMC in acetone-methanol binary mixture [5].

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| **Figure 2.** Measured solubility of γ-IMC in acetone-methanol-water at 25 °C. | **Table 1.** Results from antisolvent crystallization of IMC from acetone-methanol-water at 25 °C. |
| Properties | Unseeded | Seeded |
| *C*i1 | *C*i2 | *C*i1 | *C*i2 |
| Solid form | Solvate | Solvate | γ-IMC | γ-IMC |
| Productivity(mg/g/min) | - | - | 0.75 | 0.38 |
| 0.015\* |
| \*Maximum productivity of IMC obtained during cooling crystallization from ethanol [4]. Productivity values for current work are for highest seed load. |

**4. Conclusions**

In this work, we have shown that the desired γ-IMC can be produced consistently through seeded antisolvent crystallization from acetone-methanol-water with improved productivity.

**References**

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