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An experimental verification of morphology of ibuprofen crystals from CAMD designed solvent

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Abstract

In our previous work [Karunanithi et al., 2006. A computer-aided molecular design framework for crystallization solvent design. Chemical Engineering Science 61, 1247–1260] we proposed a computer-aided molecular design (CAMD) framework to design solvents for crystallization processes. One of the important aspects of that work was the consideration of a qualitative property, namely crystal morphology, along with other physico-chemical properties (quantitative) of the solvents within the modeling framework. However, it is our view that consideration of any qualitative property, such as morphology of crystals formed from solvents, necessitates additional experimental verification steps. In this work we report the experimental verification of crystal morphology for the case study, solvent design for ibuprofen crystallization, presented in Karunanithi et al. [2006. A computer-aided molecular design framework for crystallization solvent design. Chemical Engineering Science 61, 1247–1260]. This we believe is an important step for the validation of the proposed solvent design model.

Keywords: CAMD; Morphology; Ibuprofen; Crystallization; Solvent

1. Introduction

In a recent publication (Karunanithi et al., 2006) we proposed a computer-aided molecular design (CAMD) framework to design solvents for crystallization processes. This mathematical programming framework involves formulating the solvent design problem as a mixed-integer non-linear programming (MINLP) model. The MINLP model is constructed in such a way that potential recovery is the objective function (which needs to be maximized) and various property requirements are posed as constraints. The integer variables represent the solvent structure while the continuous variables represent composition of the solution. We used a decomposition methodology (Karunanithi et al., 2005) to solve the CAMD-MINLP mathematical programming model, whose solution is the structure of the designed solvent. The proposed framework was applied to a solvent design problem for crystallization of ibuprofen, an important pharmaceutical compound (Karunanithi et al., 2006). We identified the following as the key properties that need to be considered for the design of crystallization solvents: solubility of solute, potential recovery of solute crystals, morphology of solute crystals, flash point of the solvent, toxicity of the solvent, viscosity of the solvent, boiling and melting point of the solvent. All the above properties, except crystal morphology, are quantitative in nature and hence can be modeled (represented through structure–property relationships) and their values estimated. Solute solubility in the solvent is the key factor which determines the potential recovery. A good solvent for crystallization should not only have high initial solubility for the solute at high starting temperature but also relatively low solubility at low final temperature, so that maximum amount of crystals can be recovered. The critical role played by solubility

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of the solute in the solvent at two different temperatures can be seen from Eq. (1) which was used to calculate potential recovery

$$\mathrm{PR}\% = \frac{100}{1 - X_1} * \left(1 - \frac{X_1}{X_2}\right). \quad (1)$$

Here, X_1 and X_2 are weight fraction solubilities at high and low temperatures, respectively. Since crystal morphology is essentially qualitative in nature its consideration in the solvent design framework necessitated in us using a constraint on solubility parameter of solvent as an approximate representation for crystal morphology. Solubility parameter is defined as the square root of the cohesive energy density and it can be calculated using Eq. (2). Solubility parameter is a quantitative measure of the polarity of a compound

$$\mathrm{Sol.Par.} = \left[\frac{1000 * H_{298}^{\mathrm{Vap}} - R * T}{V_{298}^{m}}\right]^{1/2}. \quad (2)$$

Here, H_{298}^{vap} and V_{298}^{m} are heat of vaporization and molar volume, respectively. Karunanithi et al. (2006) provide evidence on relationship between solubility parameter of solvents and morphology of crystals obtained from them and also discuss the theoretical explanation on how the polarity of solvents influences the morphology. It should be noted that solvent selection is not the only approach to design crystallization processes yielding desired crystal morphology. Other approaches such as the ones described in Kwon et al. (2006), Jones et al. (2005) and Ma et al. (2002) can also be used to tailor the processes to obtain desired crystal morphology. It is our view that consideration of any qualitative property (such as morphology of crystals formed from solvents) within the solvent design modeling framework necessitates additional experimental verification steps. In this work we report the experimental verification of crystal size and morphology for the case study, solvent design for ibuprofen crystallization, presented in Karunanithi et al. (2006).

The paper is organized as follows: Section 2 touches briefly on ibuprofen and its significance. In Section 3, we summarize the CAMD results. Section 4 describes the actual experimental verification. In this section, the cooling crystallization procedure is outlined in sub-section 4.1. This is followed by a qualitative and quantitative morphological analysis in sub-sections 4.2 and 4.3, respectively. Sub-section 4.4 presents P-XRD patterns for analyzing the ibuprofen internal structure. Finally, the conclusions of this experimental verification work is presented in Section 5.

2. Ibuprofen morphology and its significance

In pharmaceutical industrial crystallization processes the control of crystal size and shape is very important since such control affects the ease of separating, washing, drying, packaging, handling and storage of crystals. The crystal morphology can influence properties such as packing density, agglomeration and re-dissolution characteristics (Cano et al., 2001). Crystal morphology also affects the ease with which crystals are compressed into tablets. Size and shape seem to play a role in ibuprofen's tendency to stick to the faces of the tablet punches and dies during compressing and its tendency to laminate during decompression (Gordon and Amin, 1984). Hence, it is imperative to address morphological considerations during solvent selection for ibuprofen crystallization. In summary, for pharmaceutical products, crystals which are larger in size and lower in aspect ratio (ratio between the two major dimensions of the crystal) are preferred to crystals which are smaller in size and higher in aspect ratio because of reasons related to efficient downstream processing.

Ibuprofen, an important pharmaceutical compound, is used to relieve pain, stiffness, inflammation caused by arthritis and grout. It is also used to reduce fever and relieve headaches, muscle aches, backache and aches from cold. Ibuprofen exhibits different morphologies when grown from different solvents (Gordon and Amin, 1984; Rasenack and Muller, 2002; Garekani et al., 2001; Cano et al., 2001). For starters, Rasenack and Muller (2002) show that plate shaped crystals were obtained from alcohol while needle-shaped crystals were obtained from non-polar solvents like diethyl ether. Cano et al. (2001) also report that an isometric form is obtained when ibuprofen is grown from methanol whereas a thin platelet elongated along one axis is obtained from non-polar ethyl acetate. Garekani et al. (2001) show the difference in morphologies of ibuprofen crystallized from various alcohols and non-polar hexane. They obtained plate-like or grain-like crystals from methanol and ethanol, while in the case of hexane needle-like crystals were observed. The overall results of the above three works were consistent. In all of the above cases the different morphologies of ibuprofen were not attributed to different polymorphs but only due to the changes in the relative growth rates of specific faces. Winn and Doherty (2000) predict that ibuprofen crystallized from methanol is plate-like, while ibuprofen crystallized from non-polar hexane is needle-like. Their method allows for predicting the shapes of organic crystals, where solvent effect is accounted through the knowledge of pure component properties. Specifically, solvent surface free energies are used to take into account the solvent effects. These free energies have been either experimentally measured or they are correlated with their bulk solubility parameters. These solvent surface free energies along with crystal surface free energies are used to calculate kink free energies. Thus, from both experimental observations and modeling predictions, it is evident that the morphology of ibuprofen is dependent on the solvent being used. It has been proposed that preferential absorption of the solvent at specific faces will inhibit their growth as removal of bound solvent poses an additional barrier for continued growth (Lahav and Leiserowitz, 2001). The crystal structure of ibuprofen is an arrangement of hydrogen-bonded dimers interacting with dispersive forces (Winn and Doherty, 2000). Cano et al. (2001) show an illustration of the molecular arrangement of ibuprofen crystal structure which clearly shows the polar and non-polar entities of the compound. Like most monocarboxylic acids, it is thought that this packing stems from dimer formation in