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Linear models for prediction of ibuprofen crystal morphology based on hydrogen bonding propensities

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ABSTRACT

Solvents have a significant impact on the final crystal form of organic solids during solution crystallization. The use of polarity scales such as Hildebrand solubility parameter and dielectric constant for solvent selection often proves too generalized and do not provide enough insights into the solvent–solute intermolecular interactions directly affecting crystal growth and morphology. This paper addresses the challenging task of selecting an appropriate single component solvent property index that most accurately and sufficiently characterizes crystal morphology. Cooling crystallization experiments were carried out in a wide range of solvents using ibuprofen as a model pharmaceutical compound. Subsequently, optical microscope images were used for quantitative characterization of morphology. Linear models that correlate ibuprofen crystal morphology with pure solvent properties were developed. Our results show that, in general, there is a negative linear correlation between crystal aspect ratio (morphology) and a given solvent index. Some correlations revealed significant deviations which were explained with the help of infrared spectroscopic measurements. The "*acceptance number*" was identified as an index that significantly captures the ibuprofen–solvent hydrogen bonding intermolecular interactions. Predictions, using model based on *acceptance number*, were found to compare very well with experimentally determined aspect ratio data from the open literature. Finally, based on insights gained from this work, a flowchart which serves as a useful solvent selection guideline for crystallization of ibuprofen is proposed.

1. Introduction

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) marketed under trademarks such as Advil, Nurofen, Act-3, Brufen, Dorival, Herron Blue, Panafen, Motrin, Nuprin and Ipren. In view of its importance as a pain reliever, several research efforts have focused on improving the physical, chemical and mechanical properties of ibuprofen [1–3]. The physicomechanical properties (bulk density, mechanical strength, wettability, flowability, dispersibility, stability, and bioavailability) of solute crystals depend to a great extent on the crystal morphology which can be controlled by manipulating the crystallization conditions such as solvent type, growth temperature, supersaturation, addition of tailor-made auxiliaries and additives [4–10]. The crystal morphology also has significant impact on downstream processing such as ease of separating, washing and drying. Solvents tend to have a strong influence on the final crystal form and the morphology of certain compounds can be modified by changing the solvent used in the crystallization process.

Aspect ratio, which is the quotient of the two major dimensions of a given crystal in two-dimensional plane, is an often used index to quantify crystal morphology. High aspect ratio crystals were observed when ibuprofen was grown from non-polar hexane whereas low aspect ratios were observed from polar solvents such as ethanol and methanol [11]. Typically, these high and low aspect ratio crystals were of one of the following forms: (a) isometric crystals when ibuprofen was grown from methanol or ethanol; (b) elongated crystals from isopropanol; (c) needle-like crystals from n-hexane [12] and thin elongated platelets from ethyl acetate [13]. Plate-shaped crystals were observed when ibuprofen was recrystallized from polar organic solvents while needle-like crystals were obtained from non-polar solvents such as hexane or diethyl ether [2]. An experimental verification study [14] of the morphology of ibuprofen grown from 2-ethoxyethyl acetate, a sol-

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vent designed through computer-aided molecular design (CAMD) technique, yielded low aspect ratio crystals compared to ibuprofen crystals grown from n-hexane. From the foregoing, it can be observed that low aspect ratio ibuprofen crystals are often associated with highly polar solvents whereas high aspect ratio needles are linked with crystallization from non-polar solvents.

Few models exist for predicting the morphology of crystals grown from solution [15–17]. Molecular level simulations of solvent–crystal interface have been successfully used to predict the shapes of several organic crystal systems [18]. A similar approach based on detailed kinetic principles was developed for predicting crystal shape [19,20]. This method makes use of pure solvent properties and does not require molecular level fluid-phase simulations. A CAMD approach [21] for designing solvents for crystallization processes used the relationship between hydrogen bonding solubility parameter of solvents and crystal morphology to design solvents giving desired ibuprofen crystal morphology. Generally, ibuprofen crystal aspect ratio was shown to be negatively and inversely correlated to the hydrogen bonding solubility parameter [11,22].

The application of models based on physical laws requires kinetic and transport coefficients which are determined from experiments that measure face-specific growth rates [23]. The major drawback here is that these experiments are very costly. Morphology prediction models based on molecular level simulations often find less practical use since these simulations are computationally burdensome and results may not be available in a timely fashion. With regards to experimentation on ibuprofen crystal morphology, most work has employed no more than a few solvents. The use of such small populations in analysis limits the ability of the data to represent any significant window of the solvent spectrum and thus the general applicability of such models for predicting the crystal morphology of ibuprofen remains questionable.

This paper addresses three main issues: (a) validity of the assertion that low aspect ratio ibuprofen crystals are always obtained from polar solvents and high aspect ratio crystals obtained from relatively non-polar solvents was examined through a series of cooling crystallization experiments. The hydrogen bonding intermolecular interactions between solvent and ibuprofen was studied using infrared spectroscopy to gain molecular level understanding of observed macroscopic crystal morphology. (b) Aspect ratio data derived from experiments were used to build linear models that correlate aspect ratio with pure solvent properties such as: (i) Hansen's dispersion parameter, δ_D; (ii) Hansen's polar parameter, δ_P; (iii) Hansen's hydrogen bonding solubility parameter, δ_H; (iv) Hildebrand's total solubility parameter, δ; (v) dielectric constant, ε; (vi) Kamlet–Taft parameter, α; (vii) beta parameter, β; (viii) Kosower's parameter, Z; (ix) acceptor number, AN. The aim was to identify an overall best solvent property index for the selection of solvents for crystallization of ibuprofen having desired morphology. The solvent AN is derived from spectroscopic measurements and it characterizes the ability of a solvent to hydrogen bond with a solute by accepting an electron pair from the solute. (c) Finally, based on the selected solvent index, a general flowchart is proposed to serve as a guideline for solvent selection for crystallization of ibuprofen.

2. Materials and methods

2.1. Solute and solvents

High grade ibuprofen (Sigma–Aldrich) meeting USP specification was used as solute in all experiments. Solvents used in this study were n-hexane (n-HXNE), carbon tetrachloride (CCl_4), acetonitrile (ACNT), ethyl acetate (ETAC), sulfolane (SFLN), methylene dichloride (CH_2Cl_2), isopropanol (ISOP), ethanol (EtOH), methanol (MeOH), propylene glycol (PGCL), ethylene glycol (EGCL), cyclohexane (c-HXNE), acetone (ACTN), t-amyl alcohol (TAA), benzyl alcohol (BzOH) and toluene (TOLN). Not all of these solvents are industrially important or pharmaceutically recommended; solvents were selected solely for the purposes of generating morphological data for modeling. These solvents obtained from Sigma–Aldrich had purities of at least 98.0%.

2.2. Cooling crystallization

Small amounts of ibuprofen were dissolved in 5 ml of solvent at 25 °C and agitated in an American Optical model 406015 heated water bath shaker until saturation. A constant supersaturation of 1.1 was effected. The temperature of supersaturated solution was then raised to 65 °C and cooled to 25 °C over a 4-h period. All experiments were repeated for repeatability and consistency of crystal morphologies.

2.3. Optical microscopy

Optical microscope (OM) images were obtained using a computer-assisted CCD camera at 120 times magnification. The OM images were used to quantitatively (calculation of aspect ratio) study the ibuprofen crystal morphology.

2.4. X-ray diffractometry

Powder X-ray diffraction (PXRD) patterns of the original and recrystallized ibuprofen samples were recorded using an X-ray diffractometer (Scintag XDS 2000 X-ray diffractometer equipped with a Cu Kα X-ray source, λ = 1.54 Å) with radiations generated at 30 mA and 40 kV. These patterns were used to confirm the internal structure of both the original and recrystallized ibuprofen.

2.5. Fourier transform infrared (FT-IR) spectroscopy

The ability of infrared spectroscopy to examine the degree of hydrogen bonding as well as the ability of two species to form these relatively weak but important bonds have been reported [24,25]. In this work, hydrogen bonding interactions between ibuprofen and solvent were investigated using Fourier transform infrared (FT-IR) spectroscopy. For instance, the infrared spectra of alcohols show a readily recognizable, intense and broad absorption over a range of 3200–3650 cm^{-1}. The breadth of this band is due to hydrogen bonding to other alcohol and solute molecules [24]. IR spectra of all samples were taken using a Nicolet Magna IR 750 spectrometer with 4 cm^{-1} resolution linked to an IBM 350-P133 model PC and raw data analyzed using OMNIC™, and Microsoft Excel. A background spectrum was taken with clean ZnSe plates washed with isopropanol, washed again with the solvent, and dried in air. A small drop of solution was then placed between the plates and the IR spectrum taken for each sample. In between spectrum recordings, the ZnSe plates were cleaned with isopropanol and then again with solvent. All measurements were made at ambient conditions with no less than 25 scans.

The infrared band stretching of the various solvent functional groups was quantified using a scaled parameter, B^{40}_{scl} defined by:

$$B^{40}_{scl} = \frac{w_{solution} - w_{solvent}}{w_{solvent}} \times 100 \quad (1)$$

Here "w" corresponds to the breadth of the solvent functional group responsible for hydrogen bonding between the solvent and the solute. For instance, in the case of alcohols the –OH band is analyzed. The B^{40}_{scl} was calculated at 40% transmittance for practical reasons, as all spectra obtained displayed a continuous and easily readable tendency at that intensity. This scaled parameter was used as a measure of hydrogen bonding intermolecular interactions.