522b Morphological Considerations in Solvent Design for Ibuprofen

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Computer Aided Molecular Design (CAMD) technique has been extensively used for the design of solvents for various separation processes such as liquid-liquid extraction, gas absorption, crystallization etc. Usually the properties under consideration are quantitative in nature and can be evaluated to a certain degree of accuracy through group-contribution models. In the case of design of solvents for pharmaceuticals (e.g. crystallization solvents) morphology of crystals formed from the solvents, which has to be assessed qualitatively, is of great importance, since the problems of separating, washing, drying, packaging, handling and storage of crystals take their origin from undesirable crystal morphology. The crystal morphology can also influence properties such as packing density, agglomeration and re-dissolution characteristics. It can also affect the ease with which the crystals are compressed into tablets and also play a role in the quality and efficacy of solid dose pharmaceuticals, where crystals of different shapes have different bioavailabilities. Usually, for pharmaceutical products plate shaped crystals are preferred to needle shaped crystals. The type of crystals formed depends on the hydrogen bonding interaction between the solute and the solvent. In this paper we present an approach where, through pre-design steps such as preliminary experimentation or data from literature, property constraints for crystal morphology of Ibuprofen are identified, then the solvent design CAMD problem for Ibuprofen is formulated as a mixed integer nonlinear programming (MINLP) model and solved to identify optimal solvent molecules and finally in the post design step the morphology of Ibuprofen crystals formed from the designed solvent is verified experimentally. The primary properties that we are interested in the preliminary experiments are properties related to hydrogen bonding. In the CAMD design stage in addition to the properties related to morphology, other considerations such as potential recovery, solute solubility, safety and toxicity related properties are considered. The experimental verification is done by conducting crystallization experiments and studying the morphology through scanning electron microscope (SEM). X-ray diffraction (P-XRD) experiments on the crystals as well as original solute are conducted to make sure that only the crystal morphology has been modified and the basic crystal structure remains the same. The optimal solvent designed was 2-Ethoxy ethyl acetate. The crystallization experiments in the designed solvent yield crystals with higher aspect ratio thereby validating the model prediction. For comparison purposes crystallization was also carried out in n-hexane and then the morphologies were compared.