4cd Crystal Morphology Considerations in Processing of Pharmaceutical Drugs: a Computer Aided Molecular Design (Camd) Approach

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The broad objective of my research is to develop an efficient product design methodology, and apply it to important industrial product design problems such as pharmaceutical drug crystallization, solvents for separation processes, pharmaceutical product formulation etc.

A novel computer aided molecular design (CAMD) methodology , which can be used to solve a wide variety of product design problems has been developed [1]. The design algorithm involves formulating the CAMD problem as a mixed integer nonlinear programming (MINLP) optimization model and solving this combinatorially complex model using an efficient decomposition method, tailored specifically for CAMD type problems. OPT-CAMD+ a software implementation of this methodology was developed.

The effectiveness of this methodology was established by successfully identifying an extractant for liquid-liquid extraction process that had properties better than the ones being used in industry [1]. Further success was met when a real industrial problem from UNILEVER regarding design of pharmaceutical product formulation was provided to us. The implementation of this methodology on the industrial problem resulted in extremely good design results thereby making this approach an attractive method to solve complex practical industrial problems [4]. Other case studies on the design of solvents for cooling crystallization [2] and drowning out crystallization [5] were solved using this methodology. In the rest of the abstract I will present my work on a very interesting and important problem related to design of solvents, which produce crystals with specific desirable morphologies of pharmaceutical drugs [3].

Crystal morphology modification through solvent design: Crystal morphology of pharmaceutical drugs is an important phenomenon. By careful selection of solvents one can alter the morphology through recrystallization. The importance of morphological considerations stem from the fact that the problems of separating, washing, drying, packaging, handling and storage of crystals take their origin from undesirable crystal morphology. 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 the quest for identifying solvents, which can modify crystal morphology of drugs, a combined modeling and experimentation approach is taken. In the pre-design stage preliminary experimentation is used to identify, property constraints, which influence crystal morphology. In the design stage, promising solvents, which could alter crystal morphologies of the solute, are designed through the decomposition based CAMD algorithm. In the post design stage the morphology of the crystals formed from the designed solvent or solvents is verified experimentally. The experimental verification is done by conducting crystallization experiments and studying the morphology through scanning electron microscope (SEM). Powder 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.

Modification of crystal morphology of Ibuprofen, an important pain reliever, through solvent change, was achieved through this method. In the pre-design step property constraints on hydrogen bonding ability were developed. In the CAMD design stage 2-Ethoxy ethyl acetate was designed as the optimal solvent. The crystallization experiments in 2-Ethoxy ethyl acetate yielded crystals with higher aspect ratio as against crystals from other solvents such as n-hexane, thereby validating the model prediction.

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2] Karunanithi, A.T., Achenie, L.E.K., Gani, R., "A Computer aided molecular design framework for crystallization solvent design". *Submitted to Chemical Engineering Science.*

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4] Karunanithi, A.T., Achenie, L.E.K., Gani, R., "Decomposed CAMD strategy for solvent mixture design". *Proceedings of Foundation of Computer aided process design, 361-364, 2004.*

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