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Towards crystal engineering: probing crystallization processes by computer simulation

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From a technological point of view the ability to control or engineer the crystal size, morphology, quality and the underlying structural form is highly desirable. For pharmaceuticals, an appropriate choice of crystal size, morphology and form of a drug can promote its bioavailability, ease manufacture of the dosage form, and enhance its stability.

In isolating crystalline particles the method of choice is crystallization from a solvent. In this process one can vary solvent, supersaturation, degree of agitation, temperature, pressure (as for supercritical fluids) and inclusion of auxiliary materials. Despite the considerable interest, our understanding of the fundamental principles of how these variables affect the final product is still rudimentary. Is such fundamental knowledge essential for engineering crystals? The answer here is a categorical 'yes'. Solving a particular technological problem solely on an empirical basis does not necessarily mean that one then has a general solution. The worst scenario is that one solves the same problem, but in a different guise, over and over again.

The obstacle to acquiring a molecular understanding of the processes taking place during crystallization is that crystallization, in particular the early stages, is in the main inaccessible to experimental methods. A viable alternative is to utilize computer simulations based on the atom-atom potential method. This method enables the interaction energy of atoms to be calculated, and extends to molecules and molecular systems. It forms the basis for calculating lattice energies, attachment energies for predicting crystal morphologies and the effects of auxiliary molecules during crystallization. Such calculations are static in nature since the atomic positions remain fixed, and thus do not lend themselves to investigating effects of solvent which would be in continuous motion. To include dynamic aspects one can utilize either Monte Carlo (MC) sampling or molecular dynamics (MD) simulation (Allen & Tildesley). Molecular dynamics is the more powerful of the two and involves calculating the forces (from the potential energy function) between the atoms and following the trajectories of the atoms as a function of time.

The potential of molecular dynamics is currently limited by the available computing power. Crystallization is a relatively slow process (nanoseconds scale). A simulation of crystallization on a large realistic molecular system is barely feasible on the fastest supercomputer. Consequently, one can either conside only realistic systems and simulate short selected snapshots of the process or simplify the atomic/molecular model in the simulation of the longer time scales. The situation is however changing rapidly with developments in computing power.

The current state of the art is illustrated below by reference to a few selected studies. Solvent is thought to modulate crystal morphology by adsorption, which may be selective, onto the growing surfaces, thus retarding the rate of attachment of the solute molecules. Calculations of the interfacial water-crystal face energies using Monte Carlo methods indicate that this indeed is the case for gluconamide crystals (Khoshkhoo Boateng 1998). Limited success has also been achieved for the solute acetic acid in carbon tetrachloride (Gavezzotti, personal communication). These simulations have given invaluable insights into the effects of supersaturation, clustering in supersaturated solutions, and the mechanism of action of nucleation inhibitors.

In summary, computer simulations are on the verge of making the molecular processes taking place during crystallisation transparent. The insights that these simulations promise will be invaluable for engineering crystals of technological importance.

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