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Crystal Engineering for Product and Process Design

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Abstract

Crystalline organic solids are ubiquitous as either final products or as intermediates in the specialty chemical, pharmaceutical, and home & personal care industries. Virtually all small molecular weight drugs are isolated as crystalline materials, and over 90% of all pharmaceutical products are formulated in particulate, generally crystalline form. Crystalline chemical intermediates, such as adipic acid, are produced in large amounts to make polymers and specialty products. Skin creams and other personal care product formulations contain crystalline solids. Solution crystallization is the most common operation in these industries for the separation and purification of products that are solids at room temperature and pressure. During crystallization, many physico-chemical characteristics of the substance are defined, including crystal polymorph, shape and size, chemical purity and stability, bioavailability, solubility and dissolution rate. In most cases the properties of the crystalline solid have a major impact on the functionality of the final product as well as the design and operation of the manufacturing process, and in most cases the two cannot be considered separately.

Selection and manipulation of crystal shape and size for organic materials has been a long term objective of many crystal growers in both industry and academia. In recent years, the additional objective of selecting and maintaining the crystal polymorph has joined this list of critically important attributes that need to be controlled, especially for pharmaceutical products. The ability of a compound with a distinct internal crystal structure to crystallize in various shapes and polymorphs is related to the underlying solid state physics

and chemistry and dependent upon external parameters such as the level of supersaturation, the type of solvent(s), impurities, surface active modifiers, and the design and operation of the crystallization equipment. Appropriate understanding of these factors, and their inter-relations allows the crystal designer to manipulate the crystal chemistry and technology in order to optimize the material performance characteristics. Such a capability is vital for reducing research and development times for new crystalline products. Crystal shape coupled with crystal size is associated with a range of properties of fundamental importance in many applications, e.g. rate of dissolution, solubility (which influences bioavailability), stability in storage and compressibility. In addition to these performance-related characteristics, shape can also influence processing properties such as particle flow, filtration rate, agglomeration, fragmentation and attrition.

Recently, progress has been made in developing techniques for predicting the morphology of solution-grown organic crystals. A model has been developed that can account for the solvent effect, and it has been used to successfully predict the shape of several industrially important solid products (e.g., adipic acid grown from water; ibuprofen from hexane and from methanol, and five other solute-solvent combinations). This new technique is based on detailed kinetic theories - especially the screw dislocation mechanism of Burton, Cabrera and Frank - in which relative face growth rates depend on two key concepts; the existence of periodic bond chains (PBC's) that run throughout the crystal lattice, and the kink energy associated with each PBC which corresponds to the energy required to remove a molecule from the individual PBC's. Kink sites correspond to docking sites for solute molecules on the crystal faces. The kink energy is an interfacial property that is estimated using the classical geometric mean approximation for the free energy of adhesion. To a first approximation, its calculation requires only known, pure component properties: the crystal's internal energy, which can be readily obtained from solid state molecular mechanics calculations, and the pure solvent surface tension, which is generally available in the literature.

Unlike absorption, distillation and other fluid phase separation technologies, crystallization takes much longer to develop and scale up successfully. This is mainly due to the lack of high fidelity engineering design models for crystallization technology. One of the key missing links is the integration of solid state and solution state chemistry coupled to engineering design models. The focus of this presentation is to describe models and methods that provide a strong coupling between crystal chemistry and crystal engineering for improved product and process design for the production of organic crystals of specified polymorph, shape and size, with particular emphasis on pharmaceutical products.

Keywords: Crystal engineering, crystal shape, crystal growth