Application-oriented Crystallization of Pharmaceutical Products

As the technology for drug research expand two trends are becoming apparent. One is the increase in the molecular complexity of the new drugs, and the second is a much higher number of drug candidates. A downside to the increase in complex molecules, is that they tend to exhibit poor water solubility which in turn lead to lower bioavailability of the drug. This often disqualifies drugs from further investigation although the biological effects might be beneficial if only the human body were able to absorb the medicine correctly. One of the main problems related to these studies are the various polymorph forms that dugs can exhibit. However with the great increase in the number of suggested drugs from methods like high throughput screening, a similar revamp of determining crystal landscape and employ polymorphic control is needed. On several occasions the sudden appearance of a new polymorph have had devastating effects on a drug, but with the lack of computer models to predict polymorphism, and the fairly large amount of time as well as the amount of Active Pharmaceutical Ingredient (API) needed for normal studies of polymorphism, some new technologies are starting to emerge.

UV, Raman and IR probes have been used to measure concentrations and determine polymorphic behavior during various crystallization processes. This helps to avoid unwanted polymorphs from growing or at least determine when an unwanted form is produced. More robust methods of forcing a specific polymorph to form are also being developed. The old method of seeding is still employed and are often quite effective, however the use of other compounds as seeds are slowly emerging. These range from additives either in solution or suspension, over different solvent compositions to induce solvate formation, to various other crystalline compounds that may help form co-crystals. The use of cooling systems at sub-zero temperatures were found to create forms that were previously reported only to crystallize from very specific solvents, and the option of lower operating temperature also allows for the use of solvents that would otherwise be disqualified due to a low boiling point.

Other than the polymorphic behavior, the particle size and structure is also often of great importance, especially in industry where a change in flow characteristics or dissolution rates can wreck havock in a production line. Although polymorphic behavior will often also impact size and structure of the particles, several compounds show vast differences in crystal shape while not changing the polymorphic form. Options for controlling these parameters have in the past been limited to offline sampling and tuning the production to fit requirements. The issue with such an approach is the lack of flexibility. Ideas for new excipients or wanting to change the product features would require re-tuning the system, and a lot of effort have recently been put into feedback control options for crystallization processes.

Using FBRM to determine particle counts in suspension along with control software have been employed to cooling crystallization and the increase in particle size where found to be on a scale obvious even to the naked eye. Super Saturation control (SSC) also help increase

particle size by trying to keep supersaturation fairly low, favoring crystal growth instead of new nucleation.

These methods are slowly making their way from laboratory settings into production lines the world over, and the areas where crystallization and polymorphism crops up is steadily climbing. Most often this is done to increase product performance, but to this day, appearing or disappearing polymorphs are keeping scientists on their toes but in the laboratory and in large scale production.