# API Crystallization

Batch-to-batch variability during the crystallization of active pharmaceutical ingredients (API) can have a profound impact on both safety and efficacy of the final drug formulation, and direct business and cost implications for both the API manufacturer and downstream drug-formulation partners.

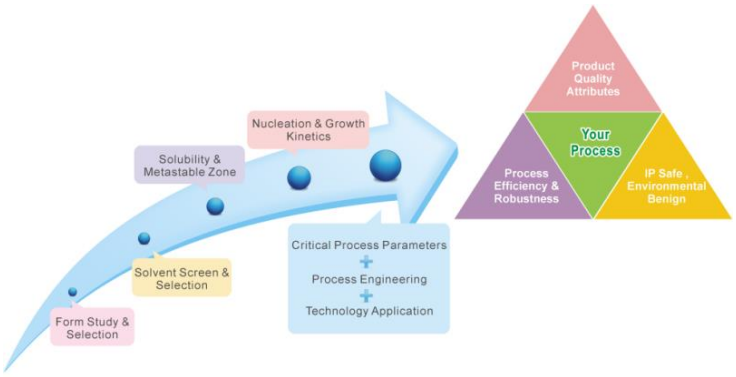
The ability to design, engineer and operate an appropriate crystallization system and maintain tight control is essential, yet challenging. Even small changes in crystallization processes can quickly lead to a wide range of undesirable events, which have costly implications. For instance, poor crystallization can negatively impact crystal shape and particle-size distribution, and lead to unwanted events such as polymorphic conversion, agglomeration, and solvent inclusion. Failure to achieve target purity and quality specifications can lead to batch failure, which has serious cost implications for both the API producer and the downstream pharmaceutical partners who depend on that API. And issues that are not reconciled at the small scale will be amplified as scaleup efforts proceed.

When crystallization efforts during the production of API (and their intermediates) are successful, operators are able to obtain the desired product attributes (such as specified API purity, crystal shape, bulk density and size distribution of the individual crystals), and maintain greater control on performance attributes such as flowability, hydrogscopicity, color stability, solubility and dissolution rate of overall final crystalline product.

The ability to minimize batch-to-batch variation reduces the need to rework or discard costly batches of API and intermediates. This has a direct impact on product yield, volume efficiency and cycle time. Savings come from the ability to reduce both the overuse of costly ingredients and the production of unwanted byproducts or off-specification product batches. Off-spec production not only leads to the misuse of costly raw materials, but also engender costly disposal requirements. In competitive markets, the ability of API manufacturers to produce reliable, on-specification API — and to get it right the first time in accordance with Quality by Design (QbD) principles — is essential for supporting drugmakers' efforts to meet their own tight timelines related to clinical trial work, regulatory-approval milestones and time-to-market goals.

Crystal Pharmatech's approach to a robust crystallization is based on our extensive innovator pharmaceutical experience and can generally be outlined in Figure 1 below:

Figure 1: Approach to a robust crystallization of Crystal Pharmatech




This approach includes best practice principles including:

- Process design and optimization strategies — The ability to study and characterize the crystallization behavior at the small scale and gather the analytical information needed to understand the behavior of the solid chemical products inside the crystallizer will help operators to predict process performance at larger scale and design the necessary chemical process systems accordingly.

- Understanding of temperature and mixing effects — During crystallization, polymorphic transformations are directly impacted by changes in temperature and mixing phenomena inside the reactor. It is essential to identify solubility and metastable zones (that is, to identify the kinetic limits between the nucleation point and the solubility curve), as these will impact crystal formation. Poor mixing can result in variation in supersaturation zones (which impacts nucleation and agglomeration), while excessive agitation can lead to particle breakage and secondary nucleation.
- Selection and use of solvents and growth inhibitors — A crucial part of any crystallization effort is to study and screen different solvent options. The goal is to determine which will produce the desired API polymorphs, whether the desired API can be produced via the chosen process conditions, or whether it must be obtained by the desolvation of an intermediate solvate or hydrate formation while drying, and so on. In some cases, growth inhibitors can be added to direct and control crystal growth and modify crystal shape.
- Knowledge of supersaturation principles — For both seeded and unseeded crystallizations, the level of supersaturation has direct control over the ultimate particle-size distribution (and whether the final batch will dominated by larger-sized crystals or by fines). Knowledge of the various techniques that are available to control supersaturation — for instance, through cooling, antisolvent addition, evaporation or chemical reaction — is also important.
- Understanding of principles of polymorph isolation — Too often a system will create and trap the metastable form of a desired crystal that has no chance of converting reliably to a more stable form. Several techniques can be used to avoid generation (or nucleation) of metastable forms that are kinetically hindered from conversion to the desired stable form. This will ensure increased polymorphic purity upon scaleup. Controlling polymorph isolation requires a strong understanding of the thermodynamic relationships of all relevant crystal forms in the system.

## Summary

A robust crystallization should involve:

- Complete understanding of the crystal forms in the system including solvates and hydrates.
- Accurate solubility measurements include understanding of form in equilibration with solvent and equilibration time.
- Knowledge of metastable zone widths and growth kinetics.
- Understanding of scale factors that can impact nucleation and growth including vessel material, mixing, and humidity.

## References

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