Crystallization development in a CDMO environment

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Crystallization plays a crucial role in the pharmaceutical industry, particularly in the manufacturing and purification of small-molecule active pharmaceutical ingredients (APIs). Over 90 % of APIs are synthesized as crystalline products [1]. By controlling the crystallization process, manufacturers can ensure the purity and quality of the API. Solid state properties directly and indirectly influence the quality of the final drug product.

Crystallization development refers to the design and optimization of crystallization techniques to produce high-quality crystals. Consistently producing crystals with specific physical properties is essential for downstream processes such as filtration, drying, dissolution testing, and formulation. These properties include crystal size distribution, habit, and polymorphic form.

The United States Food and Drug Administration's (FDA) framework for process analytical technology (PAT) emphasizes efficient pharmaceutical development, manufacturing, and quality assurance. PAT plays a pivotal role in developing robust crystallization processes as it facilitates real-time monitoring of critical process parameters (CPPs). Figure 1 shows how PAT can support the early-stage development of crystallization processes and subsequent scale up. PAT enables a clear understanding of crystal nucleation and growth kinetics, solubility, breakage, and agglomeration data. By assessing key process variables like temperature, concentration, and supersaturation, crystallization scientists can gain further insights into the process which lead to a designed and controlled robust crystallization.

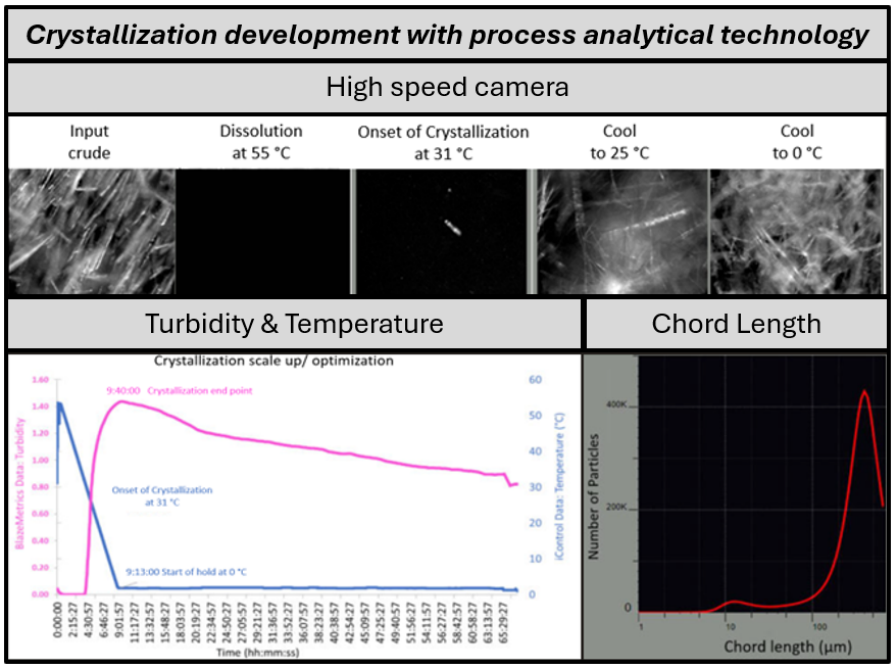

Figure 1: Crystal engineering utilising process analytical technology (PAT) to aid crystallization development.

[1] J. Orehek, D. Teslić and B. Likozar, *Org. Process Res. Dev.*, **2021**, *25*, 16-42.