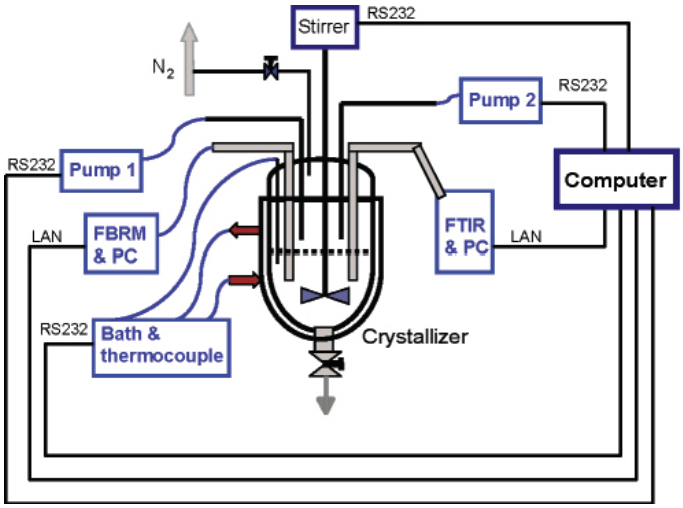
Advanced Control of Pharmaceutical Crystallization

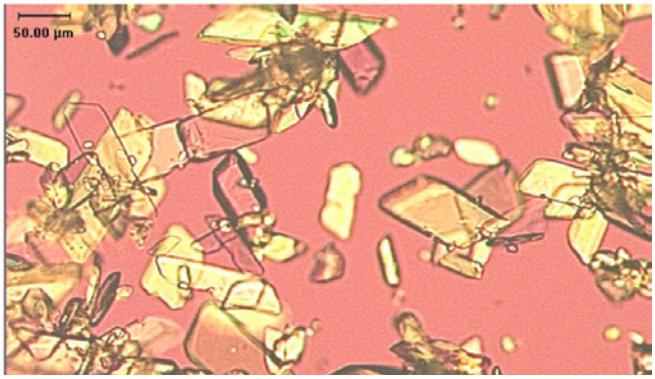
Nearly all pharmaceutical manufacturing processes use crystallization as the primary means for providing high purity, efficacy, and potency. Process modeling, monitoring, automation, and control systems are now widely used for the design and development of pharmaceutical crystallizers.

Modern control system technologies have reduced the time required to develop robust, scalable, and reliable crystallization processes; enabled the robust isolation of metastable and stable crystal forms of active pharmaceutical ingredients; and enabled the removal or simplification of post-crystallization processing—with associated increases in productivity, product quality, and product consistency.

The technologies have produced substantial technical and economic benefits.



Schematic of an apparatus and instrumentation setup for a pharmaceutical crystallizer



Microscope images of highly pure crystals produced by an automated process monitoring and control system (Source: G. Zhou et al., Evolution and application of an automated platform for the development of crystallization processes, Organic Process Research and Development, vol. 17, pp. 1320–1329, 2013; Copyright 2013 American Chemical Society, reprinted with permission)

Successful Applications Worldwide

Advanced process monitoring and control system technologies have been implemented in pharmaceutical crystallizations in many companies, including:

- AstraZeneca, United Kingdom
- AbbVie, United States
- Bristol Myers-Squibb, United States
- Merck & Co., United States and United Kingdom
- Novartis Pharma AG, Switzerland
- Sanofi-Aventis Deutschland GmbH, Germany
- Syngenta, Münchwillen, Switzerland

Implementations of Control

Control systems technologies that have been implemented in the pharmaceutical industry include:

- An automated procedure that designs nearly optimal batch control policies for crystallization processes. The states of the liquid solution and the crystal size distribution are monitored, and nonlinear state feedback control provides low sensitivity to disturbances.
- Monitoring techniques based on multivariate statistics that are applied to experimental data collected from attenuated total reflection – Fourier transform infrared (ATR-FTIR) spectroscopy to achieve highly accurate *in situ* solution concentration estimates in dense crystal slurries.
- A feedback control system that is provably robust to the large variations in the crystallization kinetics for cooling, solvent addition, and combined operations. Feedback control enables the production of large high-purity crystals, even with varying contaminants in the feed solutions and deviations in the seeding and temperature and solvent addition profiles.

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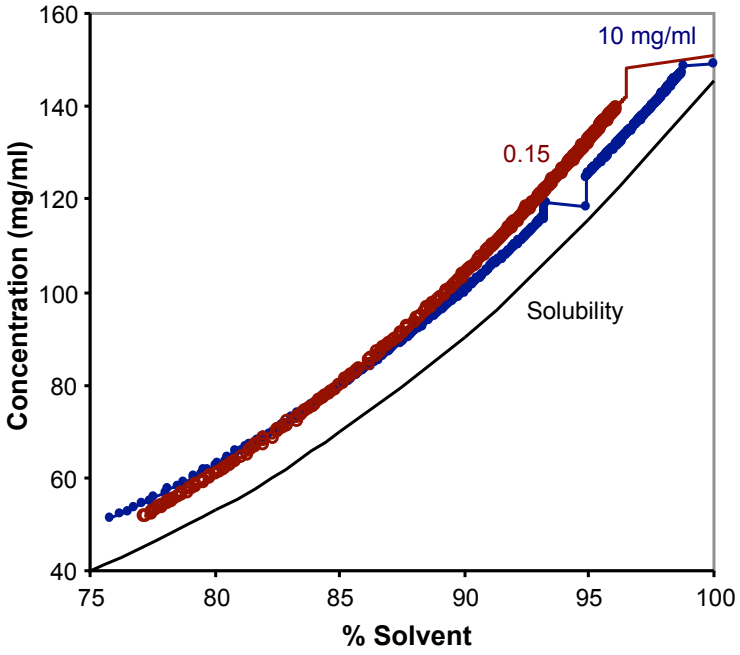
Innovations

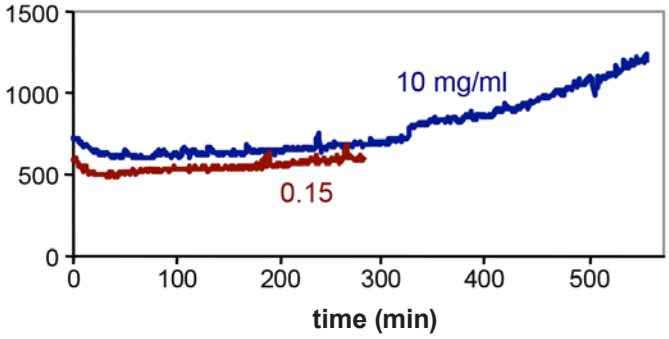
Advanced process monitoring and control systems have enabled many advances in productivity:

- The combination of multivariate statistical methods and ATR-FTIR spectroscopy provide *in situ* solution concentration estimates that are an order of magnitude more accurate than prior technologies.
- An automated software system that implemented advanced process monitoring and control was transferred from academia to Merck & Co., where it reduced process development times by more than an order of magnitude.
- A key challenge in pharmaceutical crystallization is to determine process operations that reliably produce the desired crystal structure, known as the polymorph. An undesired polymorph can have very different bioavailability and effects on the body than the desired polymorph. Automated process monitoring and control enables users to select which polymorph to produce in the crystallization. The specified polymorph, either stable or metastable, is reliably and repeatably produced for a wide variety of organic compounds and solvents.
- In a typical application at Merck & Co., the technology produced crystallizer operations that ensured the robust isolation of the thermodynamically most stable crystal form of an active pharmaceutical ingredient. The process was robust, scalable, and reliable and enabled the removal of post-crystallization product milling.



Two paths in the crystallization phase diagram followed by using an advanced process control system during a crystallization at Merck & Co. of a pharmaceutical compound from a mixture of solvents. The sharp deviation in the path with a setpoint of 10 mg/ml around 120 mg/ml was caused by an extremely large external disturbance in the pump flow rate that was introduced while temporarily turning off the control systems. When the pump was returned to automatic control mode, the robust nonlinear feedback control system quickly returned to the desired path in the phase diagram.

Advanced monitoring and control technologies in pharmaceutical crystallization have resulted in order-of-magnitude or greater improvements in chemical concentration estimates and process development times!



Measurement of number density in a crystallizer shows some crystal nucleation for controlled operations with a setpoint of 10 mg/ml, whereas a setpoint of 0.15 results in negligible nucleation. The minimal nucleation enables the production of large uniform crystals in a much shorter batch time of about 280 min.

For more information: G.X. Zhou et al., Direct design of pharmaceutical antisolvent crystallization through concentration control, Crystal Growth & Design, vol. 6, pp. 892–898, 2006; A. Cote, G. Zhou, and M. Stanik, A novel crystallization methodology to ensure isolation of the most stable crystal form, Org. Process Res. Dev., vol. 13, pp. 1276–1283, 2009.