aragen

Case Study

Enhancing Crystallization Control with In-Line PAT for Scalable Manufacturing

In every molecule is the possibility for better health.

Overview

Crystallization is a critical unit operation in the pharmaceutical industry, essential for the purification and isolation of active pharmaceutical ingredients (APIs). However, the process is often complicated by phenomena such as "oiling out", also known as **liquid–liquid phase separation (LLPS)**. Oiling out occurs when the solution's supersaturation—the driving force for crystallization—is not properly controlled, resulting in the formation of a secondary, solute-rich liquid phase rather than direct nucleation of a solid crystalline phase. This secondary phase can entrap impurities, hinder crystal growth, and disrupt downstream operations like filtration and drying, ultimately impacting product purity, yield, and process scalability.

Challenge

At Aragen, the **Particle Science & Engineering** team encountered significant oiling out during the scale-up of an evaporative crystallization process. The process involved distillation of aqueous solution containing target compound, followed by co-distillation with isopropanol (IPA) to reduce water content and induce crystallization. However, rapid removal of water during co-distillation led to uncontrolled desupersaturation, triggering oiling out. This manifested as the appearance of a cloudy, heterogeneous suspension—a metastable emulsion of solute-rich droplets—rather than the desired crystalline solid. The oiling out phase caused:

- Formation of lumpy, sticky material
- Agglomeration and scaling on reactor walls
- Impurity entrapment within the oily phase
- Filtration and isolation challenges, compromising product quality and process efficiency

Aragen's Solution

To address the problem, the team employed Process Analytical Technology (PAT), specifically the Blaze Metrics probe, which enabled real-time, in-situ monitoring of the crystallization process via high dynamic range (HDR) imaging. This allowed for early detection and characterization of oiling out events, distinguishing between true solid–liquid suspensions and metastable liquid–liquid emulsions (Figure 1).

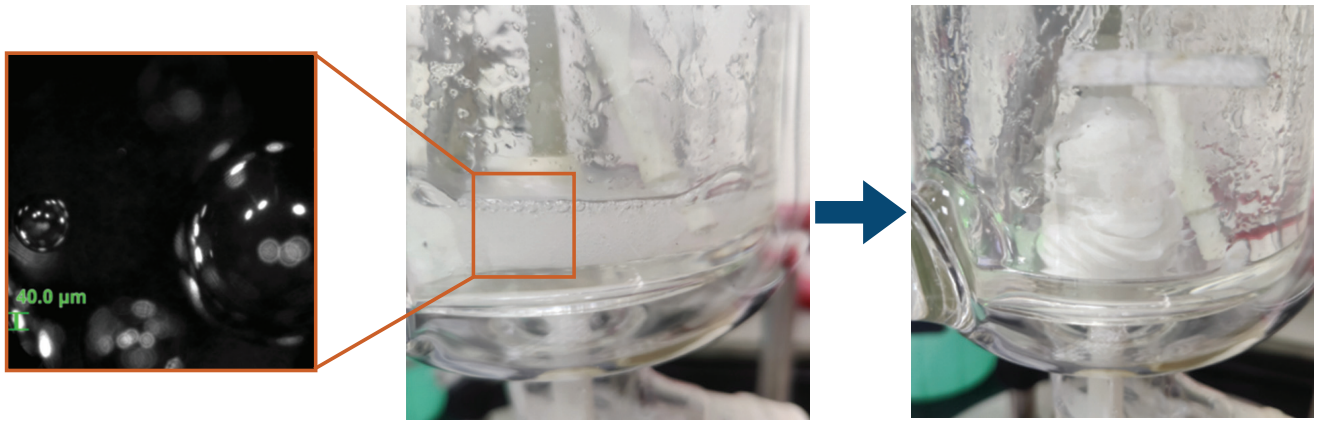

Figure 1: Blaze image of oil droplets.

Key process modifications included:

- **Controlled Evaporation Rate:** The rate of water removal during co-distillation was reduced, maintaining a higher water content for longer to moderate the rise in supersaturation.
- **Solvent Composition Management:** The volume of IPA was adjusted to fine-tune the solubility profile and prevent the system from entering the metastable oiling out region of the phase diagram.
- **Seeding Strategy:** Once a clear solution was achieved, seeding with pre-formed crystals was performed to induce nucleation at controlled supersaturation levels, promoting uniform crystal growth and minimizing spontaneous, uncontrolled precipitation (Figure 2).
- **Intermittent Solvent Addition:** IPA was added incrementally with intermittent holds, allowing for gradual supersaturation and steady crystal growth, rather than abrupt phase transitions.

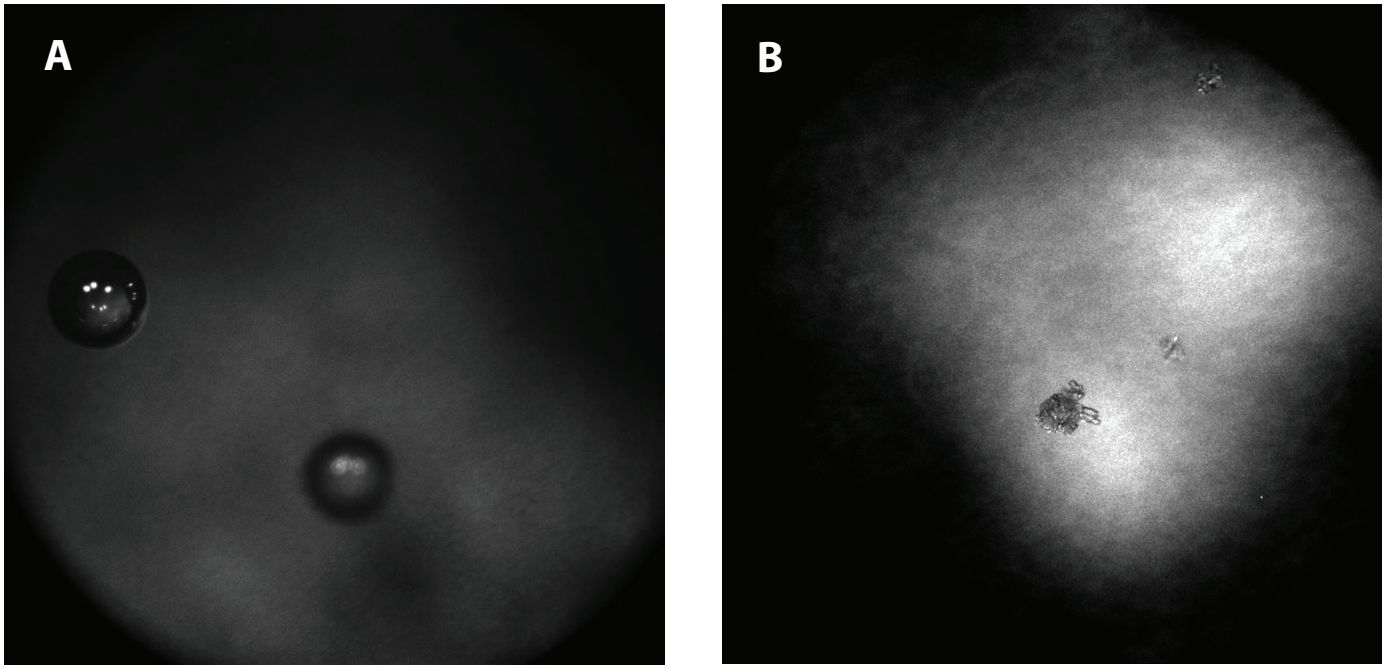

Figure 2: In situ Blaze image showing oil droplets prior to seeding **(A)** and onset of crystal formation post-seeding **(B)**.

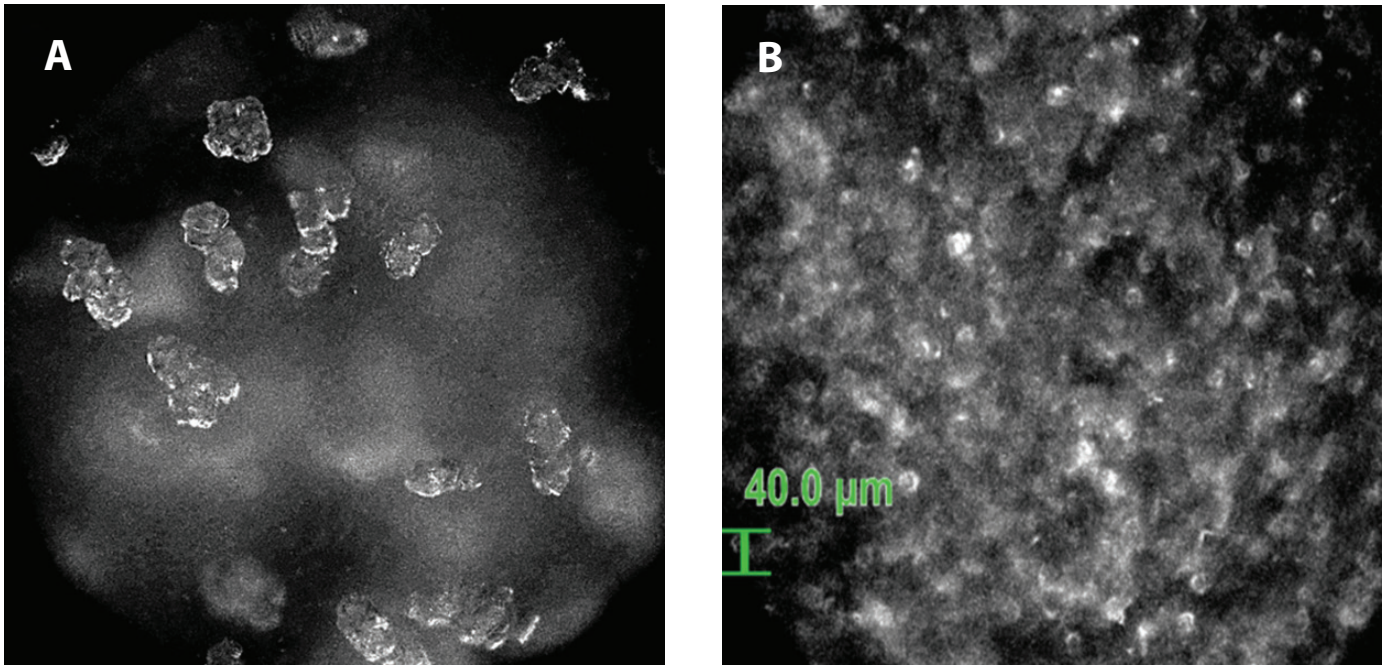

Figure 3: Image captured during ageing, showing well-formed crystals **(A)** and fully formed crystal at the end of crystallization **(B)**.

Outcomes

These interventions resulted in:

- **Elimination of Oiling Out:** Real-time imaging confirmed the absence of secondary liquid phases after process optimization.
- **Improved Crystal Quality:** The controlled process yielded crystals with uniform size distribution and reduced agglomeration (Figure 3).
- **Enhanced Purity and Yield:** By minimizing impurity entrapment in the oily phase, the final product met stringent pharmaceutical quality standards.
- **Scalable Process:** The optimized crystallization protocol was successfully implemented at manufacturing scale, demonstrating robust control over supersaturation and phase behavior.

This case study highlights the importance of thermodynamic and kinetic control in industrial crystallization, the utility of PAT tools for real-time process monitoring, and the value of tailored solvent and seeding strategies to prevent oiling out—a phenomenon increasingly recognized as a key challenge in pharmaceutical manufacturing.

Why Aragen?

At Aragen, we leverage particle science and advanced technologies to optimize your drug substance for stability, performance, and manufacturability—delivering tailored solutions from early research to commercial scale-up. We offer:

- **Customized Particle Engineering:** Optimize particle size, solubility, and polymorph stability to enhance drug performance.
- **End-to-End Support:** Guidance across all development stages, focusing on critical material attributes.
- **Cutting-Edge Technologies:** Real-time process monitoring and analytical tools for precise control.
- **Regulatory Alignment:** Compliance with global standards to streamline approvals and manufacturing.

Whether your goal is to optimize crystallization performance, solve complex scale-up issues, or reduce risk in manufacturing, Aragen brings the tools and expertise to get you there—faster and more reliably.

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Aragen is a trusted R&D and manufacturing partner to the global life sciences industry. From concept to commercial, we transform your ideas into solutions for better health. We have more than 20 years of experience providing a range of contract research, development and manufacturing services across the drug development continuum, with a focus on early-stage discovery and development of new molecular entities (NMEs). Whether large pharma or biotech, an agrochemical or animal health company, we provide you global resources and proven capabilities at every stage of the biopharma lifecycle, in small and large molecules. Our ability to offer end-to-end solutions or support standalone programs is underpinned by an innovation mindset, enabling technologies, and a partnership approach to every engagement.
At Aragen, we recognize your work is vital, urgent and impacts lives. Our purpose, 'In every molecule is the possibility for better health' motivates us to drive the success of your programs, so that we can together transform hope into health for millions of people around the world.

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