Crystallization

Advanced crystallization development

Improving yield, throughput, and crystal purity

METTLER TOLEDO

Particle size matters in advanced crystallization development

METTLER TOLEDO Lasentec® technology is the ideal method for measuring crystals as they actually exist in-process.

Crystallization is often a critical processing step in the isolation of intermediates and final product. Advanced crystallization development, using in-process Process Analytical Technologies (PAT), enables you to:

- Maximize product yield
- Increase throughput
- Assure crystal quality and purity
- Design robust operating conditions
- Eliminate downstream processing bottlenecks
- Meet final crystal dimension specifications consistently
- Ensure a smooth scale-up from laboratory to production

Case studies demonstrating the use of Lasentec® FBRM® and PVM® in crystallization development and production have been presented by top pharmaceutical and fine chemical companies, including:

Abbott Laboratories	GlaxoSmithKline	Roche
AstraZeneca	Janssen Pharmaceuticals	Sanofi-Aventis
Akzo Nobel	Merck	Schering-Plough
Boehringer Ingelheim	Novartis	Sepracor
Bristol-Myers Squibb	Pfizer	Wyeth

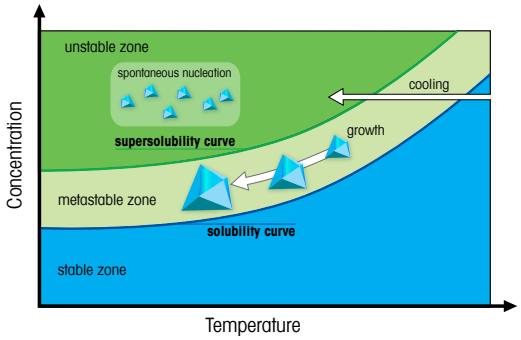
Visit our website at **www.mt.com\crystallization** for additional application information or to contact our global team of Technology and Application Consultants (TACs) who can help you achieve similar results.

METTLER TOLEDO provides integrated crystallization solutions for immediate, out-of-the-box results.

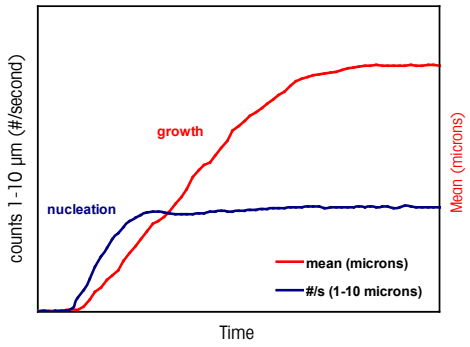
The system shown consists of the MultiMax system (2 x 250ml) and Lasentec® FBRM® S400 for in-process measurement of crystal dimension, number, and shape.

Maximize product yield

- Ensure maximum yield through an understanding of the solubility curve and metastable zone width
- Avoid yield losses due to over-washing by improving filterability and reducing solvent hold-up



The Metastable Zone Width often varies with changes in crystallizer operating and agitation conditions. Lasentec® FBRM® provides in-process characterization at any scale – to directly measure the impact of process changes on the crystallization kinetics.



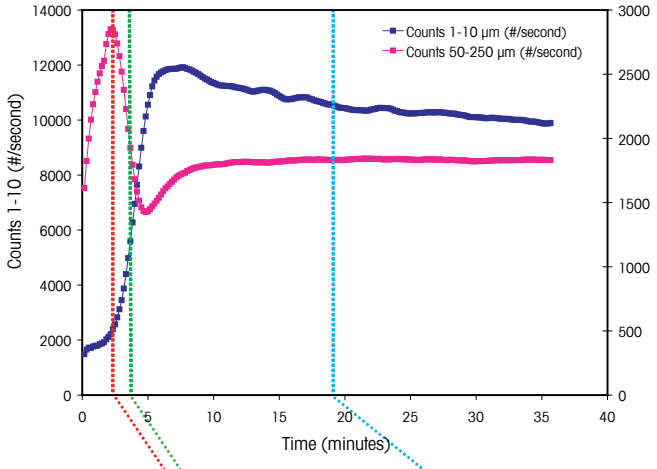
Lasentec® FBRM® can be used to identify and measure rates of spontaneous and secondary nucleation, growth, attrition and breakage. Thorough understanding of the solubility curve and crystallization kinetics can be used to maximize yield and purity and avoid downstream bottlenecks that can impact throughput.

Assure crystal quality

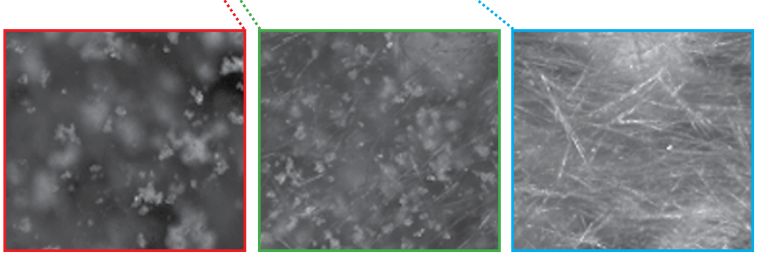
- Achieve desired crystal form, purity, and size through complete characterization and understanding of experimental design space
- Detect undesirable changes in the number, shape, and dimension of crystals, including the detection of breakage and attrition, secondary nucleation, agglomeration, and changes in crystal habit

Lasentec® FBRM® monitors changes in the crystal dimension and shape in-process and in real-time.

In this example, a habit shift due to a polymorph transformation is monitored to ensure complete conversion to the desired form.

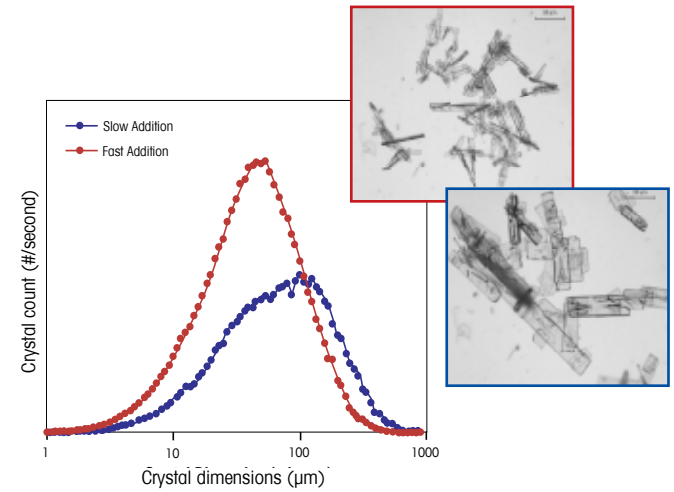


Lasentec® PVM® in-process imagining provides complementary information including a visual understanding of the changes measured with FBRM®.

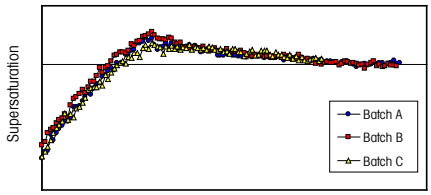


Increase productivity

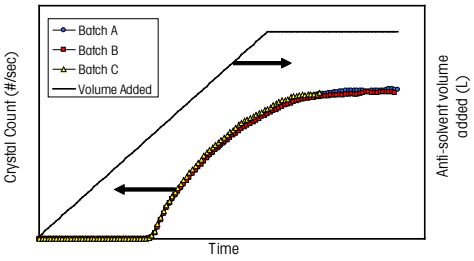
- Reduce the time and materials needed for development with data rich experiments using easy-to-implement technologies
- Identify critical operating parameters early by using PAT measurements throughout development
- Speed-up the optimization of complex processes involving seeding protocol and anti-solvent addition with direct monitoring of the crystals
- Predict downstream performance and avoid bottlenecks in filtration and drying, powder transport, milling and formulation processes



In-process measurements of the crystal product (with Lasentec® FBRM®) and the supersaturation (with METTLER TOLEDO ReactIR™ ATR-FTIR) can dramatically speed up the optimization of cooling, reactive, or anti-solvent (shown) crystallization.

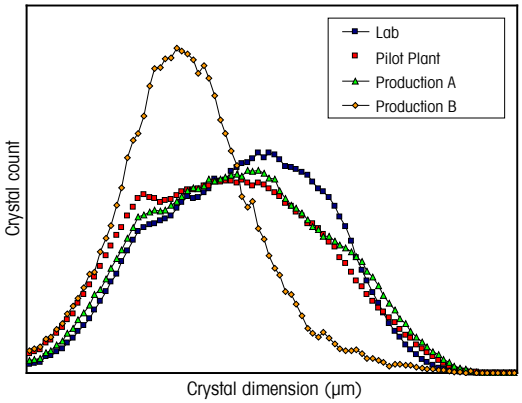


The resulting batch-to-batch repeatability of a robust process can also be clearly documented with continuous real-time monitoring. In this example, supersaturation is monitored and controlled throughout an isothermal anti-solvent crystallization to provide a consistent crystal product.



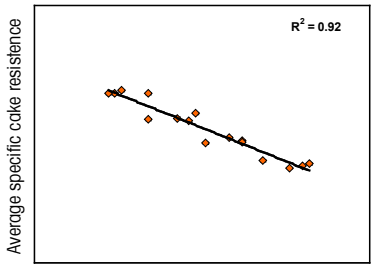
Streamline crystallization scale-up and transfer

- Facilitate team communication by using a consistent in-process measurement in laboratory, pilot, and production
- Characterize the impact of key scale-up parameters specific to product and equipment
- Identify and avoid unexpected conditions resulting in process upsets, product rework, and failed batches



Scale-up can be achieved efficiently by direct comparison of the entire crystallization process and final crystal product at all scales-laboratory, pilot, and production.

Failed batches can be identified in-process for immediate correction, and the source of deviation can often be identified to avoid future occurrences-reducing the number of reworked batches and improving overall throughput.



Direct correlation of the in-process FBRM® measurement with downstream process efficiency can be used to identify and remove potential bottlenecks in filtration, drying, or formulation before they occur.

In this example, the average crystal dimension measured in the crystallizer vessel is directly correlated to the downstream filterability of the crystal product.

Lasentec® FBRM®
for in-process crystal measurement

Focused Beam Reflectance Measurement (FBRM®) is the standard method for monitoring crystals as they actually exist in process.

FBRM® probe-based technology is used to track crystallization from laboratory to production-scale crystallizers.

The FBRM® chord length measurement provides a direct in-process method of characterizing crystal dimension, number, and shape in real time.

A laboratory FBRM® in a MultiMax 50ml crystallizer.

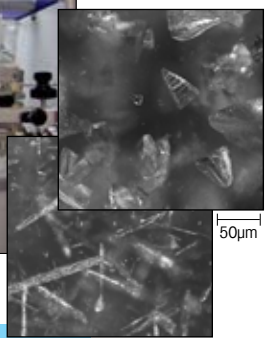
Dip-pipe installation is used for monitoring in a production scale crystallizer.

Lasentec® PVM®
for in-process crystal imaging

Particle Video Microscope (PVM®) provides high-resolution digital images of the crystals as they exist in the process.

PVM® probe-based technology provides an unparalleled understanding of how your crystals grow within the vessel-without the difficulty of sampling a dynamic system for offline measurement.

Lasentec® V700L in a LabMax® crystallizer



In-process images provide a clear understanding of the process.

ReactIR™ ATR-FTIR systems
for in-process supersaturation monitoring

The measurement of supersaturation provides a direct handle on the driving force of crystallization.

ReactIR™ uses mid-infrared ATR-FTIR technology with patented in-process probe technology to provide a highly sensitive measurement of supersaturation, without interference from the suspended crystals.

MonARC provides supersaturation monitoring in the production environment.

ReactIR™ iC10 provides in-process supersaturation monitoring in the laboratory.

Automated Lab Reactor systems
for optimal crystallization design

Precise control of temperature, mixing conditions, and anti-solvent addition rates are critical in fully understanding a crystallization process.

Integration of probe-based techniques, such as Lasentec® and ReactIR™ technologies, provide full capabilities for crystallization research and development.

Multiple reactor systems provide the ability to perform parallel experiments to efficiently map the crystallization operating space.

The LabMax® with Lasentec® FBRM® and ReactIR™ provides a complete toolkit for effective scale-up and scale-down crystallization experiments.

METTLER TOLEDO
Global services and support

METTLER TOLEDO is the world leader in the field of in-process crystallization monitoring and control.

Our technologies have been used extensively in the pharmaceutical and chemical industries for the past twenty years. With over 2000 installations in laboratory, process development and production environments worldwide, we have the experience and global support to assist you in the understanding and optimization of your crystallization process.

Our highly specialized team of Technology and Application Consultants (TACs) provide global training and support services to ensure our products perform optimally in the characterization, optimization, and control of crystallization and other reaction processes.

www.mt.com/crystallization

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