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Application Note

MultiMax

Crystallization Studies with Focused Beam Reflectance Measurement and MultiMax

1 Introduction

The Focused Beam Reflectance Measurement (FBRM) provides a real time measurement of dimension and number of crystals in the process.

In recent years there has been an increasing need to optimize particulate processes. The robust design of crystallizations as separation and purification unit operations for end products and intermediates is crucial. Examples like avoiding wrong polymorphs, obtaining a specified particle quality and size for formulation processing, and improving filtration, centrifugation or drying times in the downstream processing indicate the importance of the crystallization step in the manufacturing process [1, 2]. In the early research and process development, fast and effective optimization has to be obtained with small amounts of product available. Automation techniques at small scale are the most appropriate way to investigate process optimization in the early stage. Combining the automation with real time analytics provides a key insight in the dominate process mechanisms and a quick assessment of the impact of process variables on the process.

In a typical crystallization process, the liquid phase consists of a binary system of solvent and a compound to be crystallized. The thermodynamic properties such as the solubility of the compound in the solvent are defined by the system and vary with temperature and pressure. Hence, it is crucial to control these parameters in a defined way. The MultiMax system ensures such independent fast and accurate control of 4 reactors in parallel.

Moreover, the kinetics of the system under consideration determines the dynamics of the particulate process. The online monitoring of the solid phase to be optimized is therefore a prerequisite for successfully optimizing a crystallization process.

Aspects which can be answered with a combination of a MultiMax automated lab reactor and the Lasentec FBRM probe are:

- Determination of solubility and metastable zone width (MSZW) using dynamic measurements [3].
- To quickly access the dominant mechanism (e.g., nucleation, growth, agglomeration), and determination of the optimum operating conditions [4].
- The effect of changing the cooling rate on crystal growth and crystal formation in cooling crystallization [5].
- To study the effect of shear rate and mixing on the resulting particle dimension in antisolvent or reactive precipitation [6].

2 Apparatus

Technology that reduces the time required for screening, optimization, characterization, and scale-up of target compounds holds significant time-to-market value for chemical and pharmaceutical companies and contract manufacturing services. Automated laboratory reactors (ALR) are essential tools for these purposes. Companies are turning to this new technology to decrease time to market while increasing their knowledge base of the chemical processes at earlier stages of the development cycle. The information gained, directly impacts the areas of process research, organic synthesis, process development, and manufacturing. The combination of ALR with online monitoring allows you to understand rapidly the effect of key parameters of the process under consideration.



Fig. 1: Reaction setup with one reactor/FBRM probe in an RB02-250 Reactor Box, one Dispenser Box (for antisolvent addition) and the FBRM instrument with one S400 14/206 probe. Two PCs (one PC is possible as well) were linked to allow for data exchange between the two systems and their software packages

2.1 Materials

Paracetamol (4-Acetamidophenol), 98% and Ethanol pro analysi were obtained from Fluka AG, Buchs, Switzerland.

2.2 The Automated Lab Reactor

The ALR delivers precise and repeatable control of critical reaction variables (temperature, stirrer speed, etc.) and automation of routine experimental procedures (dosing, pH control, etc.), allowing the rapid optimization of critical reaction variables (catalyst, solvent, pressure, dosing rate, etc.). Experiments can be run on scales from as little as 25 mL (RB04-50 Reactor Box with four 50-mL reactors) during the characterization phase. In addition, calorimetric information can be obtained for use in scale-up and safety determinations.

The MultiMax Reactor Box 02-250, part of the MultiMax family is used here. MultiMax is an automated parallel reactor system designed for process screening and optimization. It allows increasing the productivity while taking benefit from precise, reproducible and documented experiments. MultiMax is very versatile so that a wide range of experiments can be performed. It features the temperature control of the reaction mixture and jacket simultaneously as well as multiple dosing, magnetic or mechanical stirring, pH and gravimetric dosing controls. Each reactor is independent from the other, offering enhanced flexibility. The high quality of the temperature control and measurement allows you to get valuable information such as reaction initiation, reaction end point and relative thermal data. The MultiMax intuitive software interface has been designed for easy experiment definitions, data visualization as well as data exchange and export.

2.3 Lasentec FBRM S 400

The measurement principle of the focused beam reflectance measurement is illustrated in figure 2. A focused laser beam rotates at high speed and propagates into the particle suspension to be monitored. When the focused laser beam crosses a particle in front of the probe, a signal is backscattered into the probe. The length of the scanned chord is determined in the electronics of the system and transferred into a chord length distribution histogram. Thus, the Chord Length Distribution (CLD) provides online particle count and particle dimension information. Every 2 seconds a new CLD can be measured to track the dynamics of the ongoing particulate process.

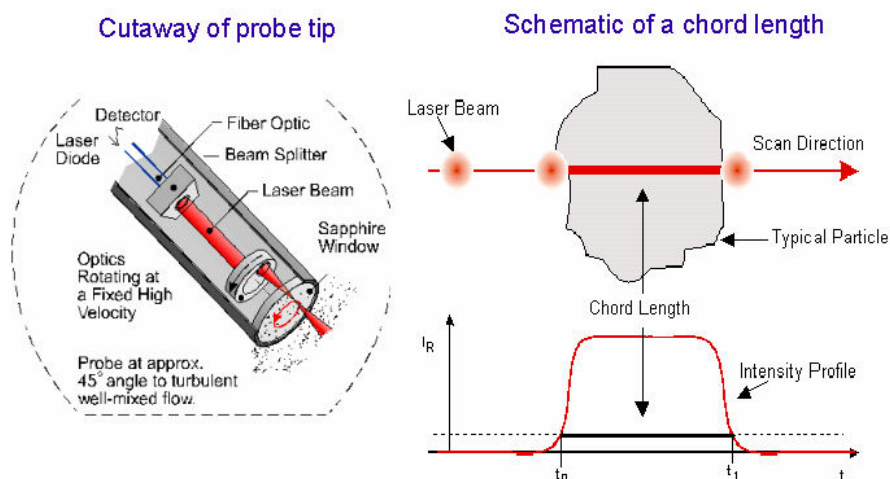


Fig. 2: FBRM measurement: FBRM probe tip (left), and chord measurement (right): the laser beam direction is perpendicular to the paper

The S 400 Q system allows you to connect up to four FBRM probes that can be placed in four MultiMax reactors in parallel. When purging the probes, operation temperatures in the range of $-20\text{ }^{\circ}\text{C}$ to $100\text{ }^{\circ}\text{C}$ are possible. Models are available for $-70\text{ }^{\circ}\text{C}$ up to $180\text{ }^{\circ}\text{C}$.



Fig. 3: Lasentec FBRM S 400 Q system with four independent probes.

2.4 Combination of MultiMax and FBRM: Software Data Exchange

When using real time analytical methods in an automated lab reactor system, it is essential that the data of both instruments can be exchanged. Additionally, actions in the lab reactor have to be related to conditions defined by measurement signals. The combination allows you to link the next step of the recipe automatically to any measured signal. An example of such procedure is given in figure 4. The end of the heating step is combined with the condition of complete dissolution that is given by an FBRM measurement condition. Here, the FBRM signal of all chords counted per second in a defined size range was used to define the complete dissolution (e.g., "Go to next phase if the FBRM signal is <50 counts per second in size range of 30 to 86 microns").

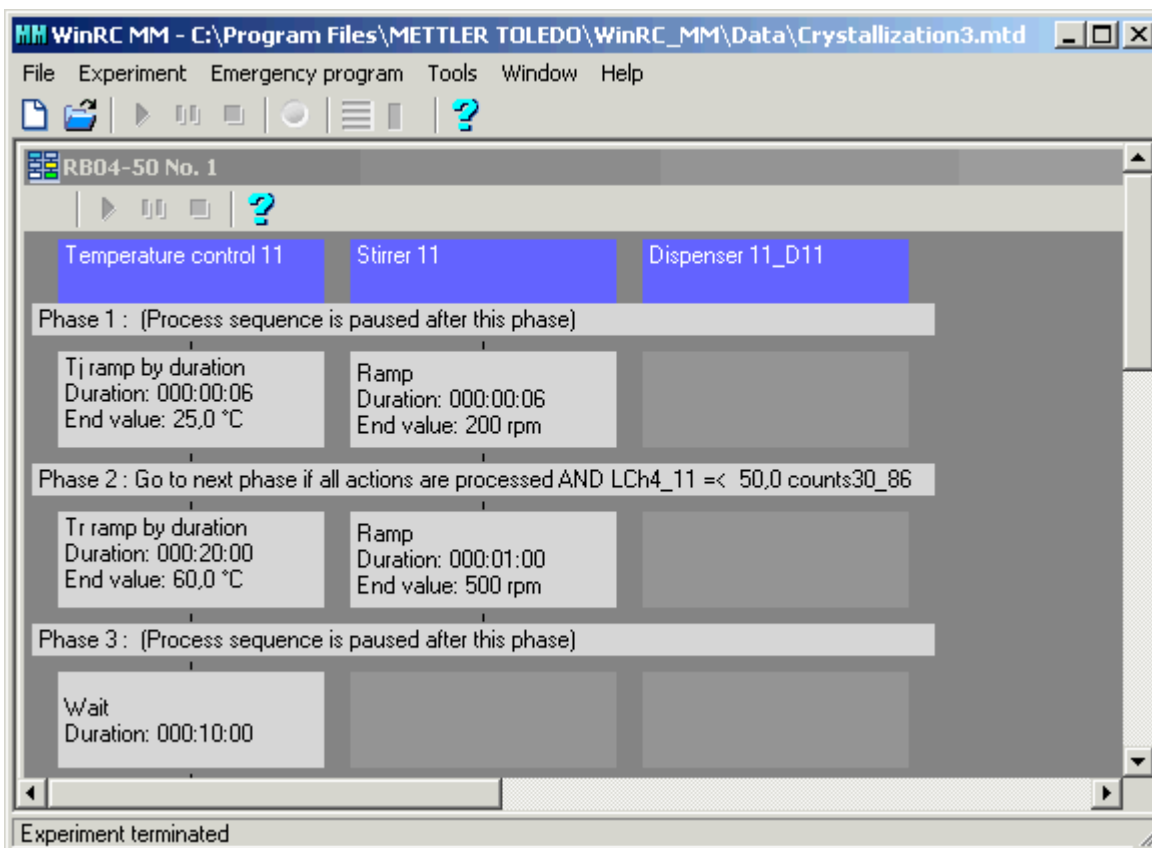


Fig. 4: Definition of a condition within the MultiMax process sequence: The data transferred from Lasentec FBRM channel 4 to MultiMax Reactor 1 of Reactor Box 1 (LCh4_11) is used to define when the process sequence must jump to the next action.

Up to 4 individual curves per FBRM probe can be read into the MM software (LCh1-4). These data are stored in the MultiMax experiment file. On the other hand, 7 values of the MultiMax are displayed in the FBRM software, so that information on temperature, stirrer speed, etc. are stored together with the FBRM measurement data.

2.5 Combination of MultiMax and FBRM: Hardware

A standard 250-mL glass reactor with round bottom and a 3-blade downward glass propeller was used together with an S 400 P14/206 probe and the standard eccentric adapter for such combination. The stirrer with a diameter of 40 mm is located 13 mm above the reactor bottom and the FBRM probe tip 3 mm off the reactor side wall and 5 mm above the upper stirrer blade level. The configuration allows you to use a minimum working volume of 50 mL (using an FEP-covered 3.2-mm Pt100 sensor) and a maximum working volume of 300 mL.

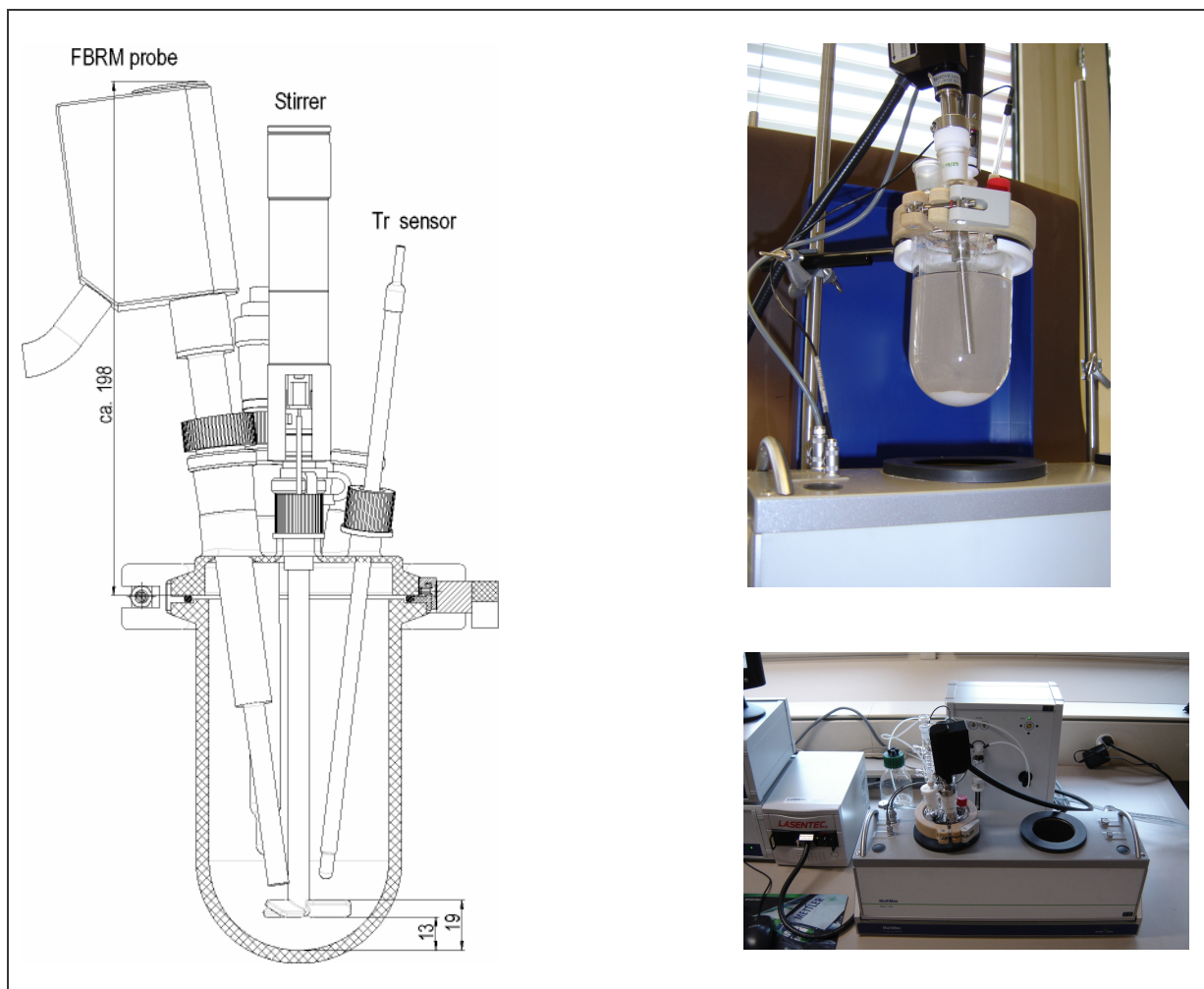


Fig. 5: Reactor setup: FBRM S 400 P14/206 probe in an RB02-250 reactor, a 3-blade downward glass stirrer with 40 mm in diameter and a 6-mm glass temperature sensor. The FBRM probe tip is located 3 mm off the reactor side wall and 5 mm above the upper stirrer blade level (in the drawing, the FBRM probe is heading to the front).

It is worth noting that the evaluation of the setup is based on a sound comparison of different reactor setups. Two reactor types (round bottom and elliptical bottom), two stirrer types (3-blade downward glass propeller with 40 mm in diameter and a 2-blade Hastelloy propeller with 40 mm in diameter), and different positions of stirrer and FBRM probe were considered for the evaluation.

3 Crystallization Experiment

3.1 Overview

A crystallization of paracetamol (4-Acetamino-phenol) in ethanol shows the benefits of a combination of an FBRM probe with an automatic lab reactor at small scale. The crystallization run consists of a heating step to 60 °C, where the initial suspension of solvent and solute is dissolved. The initial mixture is saturated at 55 °C and is kept at 60 °C to ensure complete dissolution. The solution is then cooled down below solubility level to 50 °C and 1 g of seed crystals is added. After holding the temperature constant, the solution is cooled down by a nonlinear cooling ramp. The cooling step is followed by a temperature cycling step. Finally, water is added as an antisolvent to further decrease the solubility and crystallize paracetamol from the solution. Profiles of temperature and total mass in the reactor are plotted in figure 6.

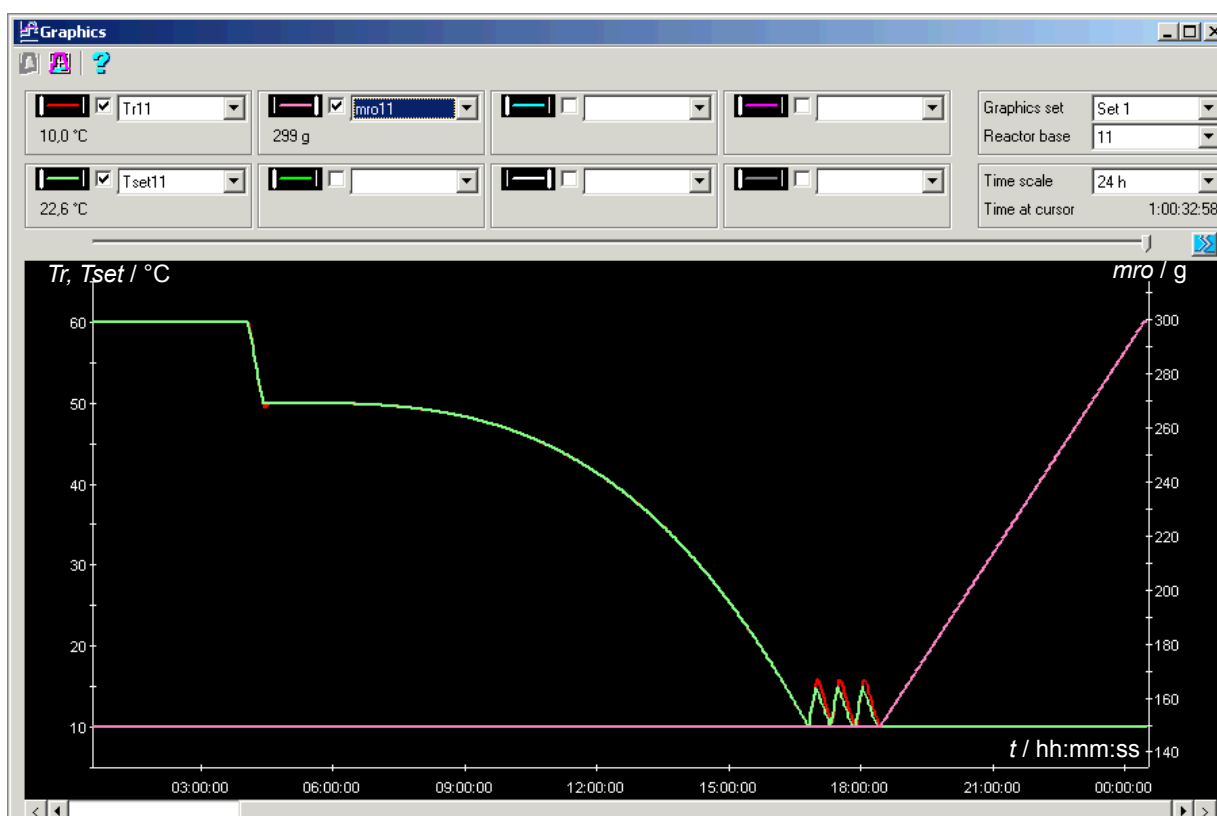


Fig. 6: Profiles of the reactor contents temperature Tr_{11} (red), its setpoint $Tset_{11}$ (green), and the total mass in the reactor mro_{11} (pink).

A comparison of the set temperature $Tset$ and the reactor contents temperature Tr indicates the high quality of the temperature control obtained by the MultiMax thermostat technology.

It is worth noting that this type of combination of cooling and antisolvent crystallization is applied rather frequently. While cooling, crystallization is easy to control by the reaction temperature, the antisolvent addition step increases the final yield of the overall process. Temperature cycling is a common way to decrease the amount of fine particles present in the system, which often lead to problems in the downstream processing like blocking filters, etc.

The results of the crystallization allow you to analyze the dissolution behavior, nucleation, growth, and agglomeration of the system and to optimize the following. As an example, figure 7 illustrates the evolution of the number of fines during the crystallization run, represented by the FBRM chords counted per second in the size range of 1 to 10 μm . The fines disappear at the beginning, when the system is heated up for dissolution. The seeds contain parts of fines and therefore fines are present after the seeding event. Without further examination, it is already obvious that no fines are created during the nonlinear cooling phase. Although fines are decreased during every heating step within temperature cycling, no significant decrease of fines is obtained by the temperature cycling step. A significant increase in fines can be observed during the addition of antisolvent.

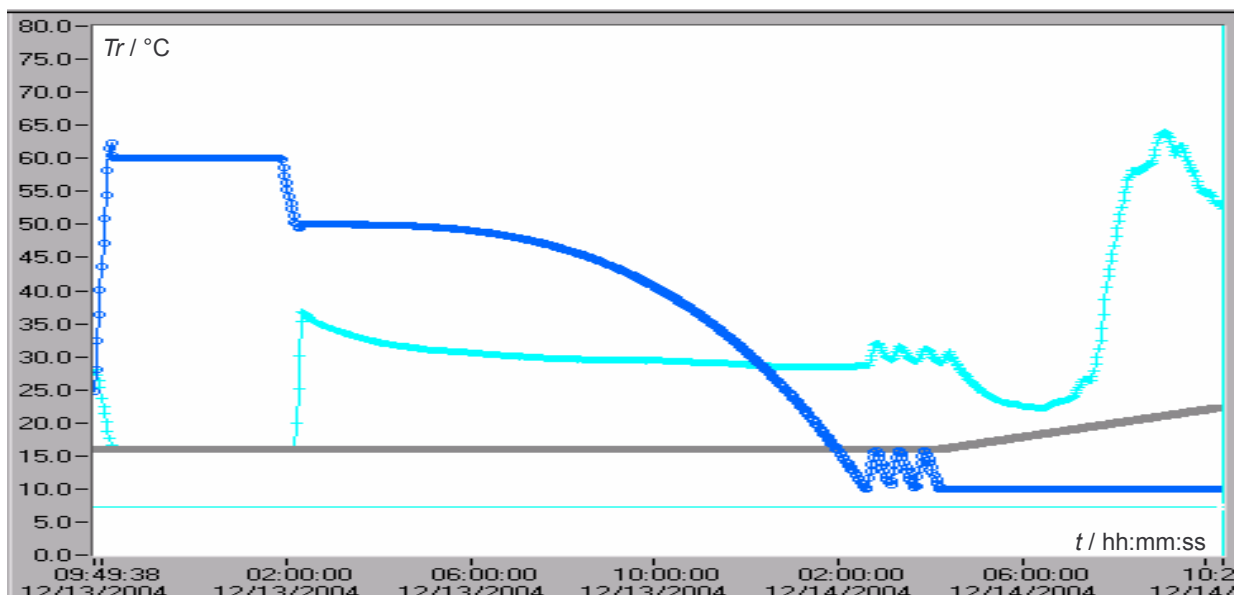


Fig. 7: Profile of FBRM fine chord counts per second between 1 and 10 microns over time together with profiles of the reactor contents temperature Tr11 (blue) and the total volume in reactor Vro11 (grey).

3.2 Heating and Dissolution

The first step consists of a fast linear heating to 60 °C leading to the dissolution of the solid phase. This is illustrated in figure 8, where the chord length distributions throughout the dissolution step are shown. The chord length distribution histogram is discriminated into 90 logarithmic channels between 1 and 1000 μm . The number of chords counted per second into a certain size channel is plotted in the histogram. The number of particles measured decreases with ongoing dissolution. It is worth noting that the dissolution follows a typical path, i.e., fines dissolve rather quickly while larger particles can still be observed to almost the very end of the dissolution step.

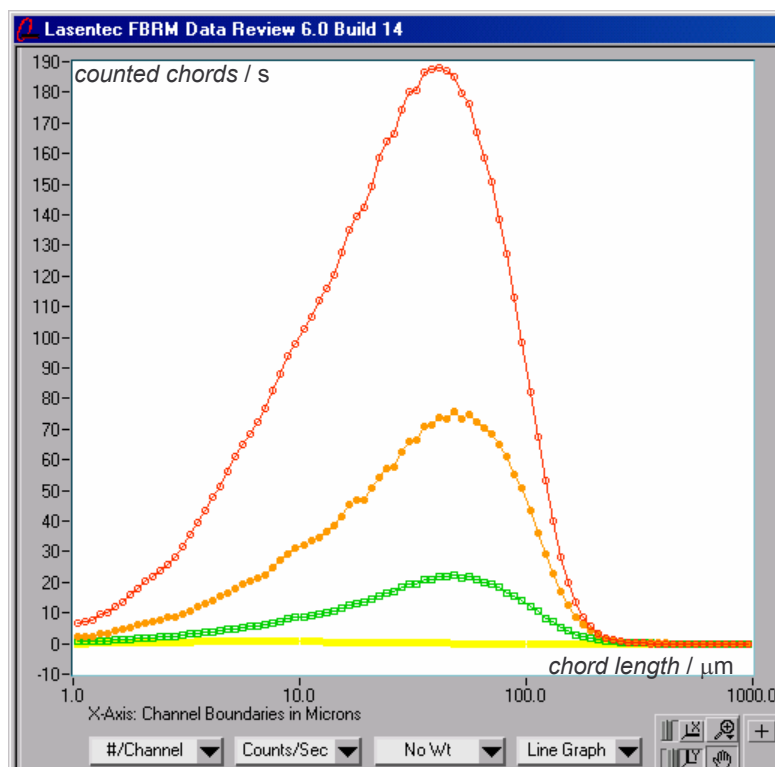


Fig. 8: Chord length distribution (CLD) histograms during the dissolution step, shown as chords counted per second into a certain size bin, with 90 logarithmic size bins between 1 and 1000 μm ; distributions from start of the dissolution (red) to partly disappearance of particles (orange and green) to complete dissolution with no particles present (yellow).

3.3 Nonlinear Cooling and Temperature Cycling

A typical concept for batch cooling crystallization is to apply a nonlinear cooling profile, i.e., to start with slow cooling at the beginning when the added seed crystals have a rather limited surface area for the further growth of the particles. With ongoing crystallization, the surface area of crystals present in the system increases and higher cooling rates can be used. Figure 9 shows the applied nonlinear cooling curve followed by a temperature cycling. During temperature cycling, typically fine particles present in the system are dissolved. The profile of the mean of the square weighted distribution (red curve in figure 9) nicely illustrates the increase of the mean, i.e., the growth of crystals throughout the cooling step.

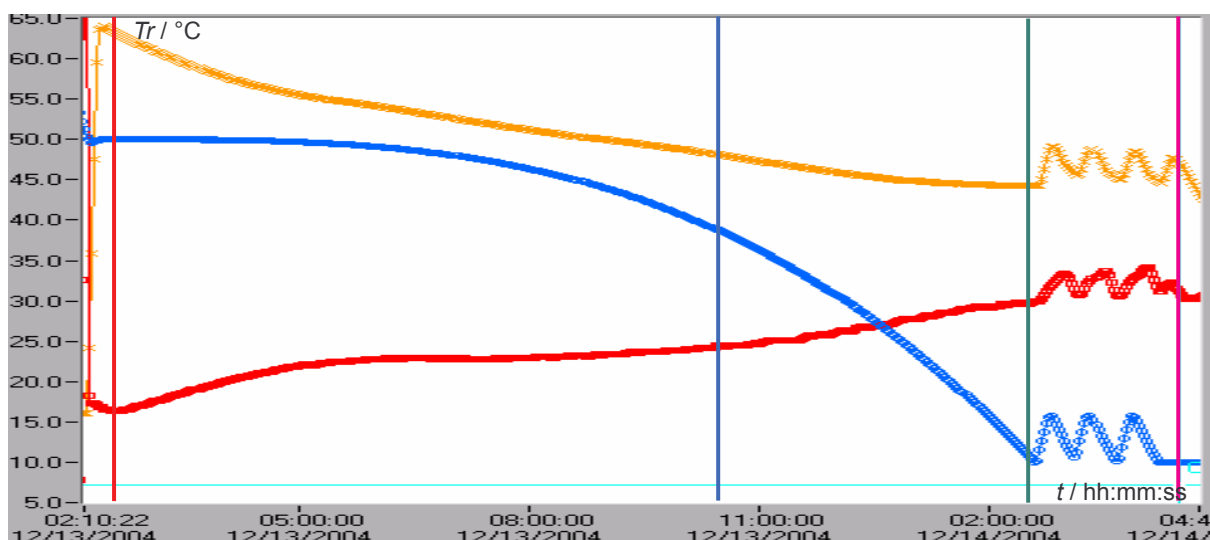


Fig. 9: Profiles of the FBRM chord counts per second between 10 and 100 microns (orange) over time, profile of the arithmetic mean of the square weighted CLD (red), and profile of the reactor contents temperature Tr11 (blue) during nonlinear cooling and temperature cycling. The vertical lines indicate points in time of distributions shown in figure 10.

The referring square weighted distributions shown in figure 10 highlight the shift of the distributions to the right. The square weighted mean increases in total from 66 to 82 microns at the end of temperature cycling. However, the effect of the temperature cycling is rather low in this case. The number of fines even increases from the beginning of temperature cycling (chord counts 1 to 10 microns at green point in time, i.e., 1671 counts per second) to the end of the process step (1841 counts per second).

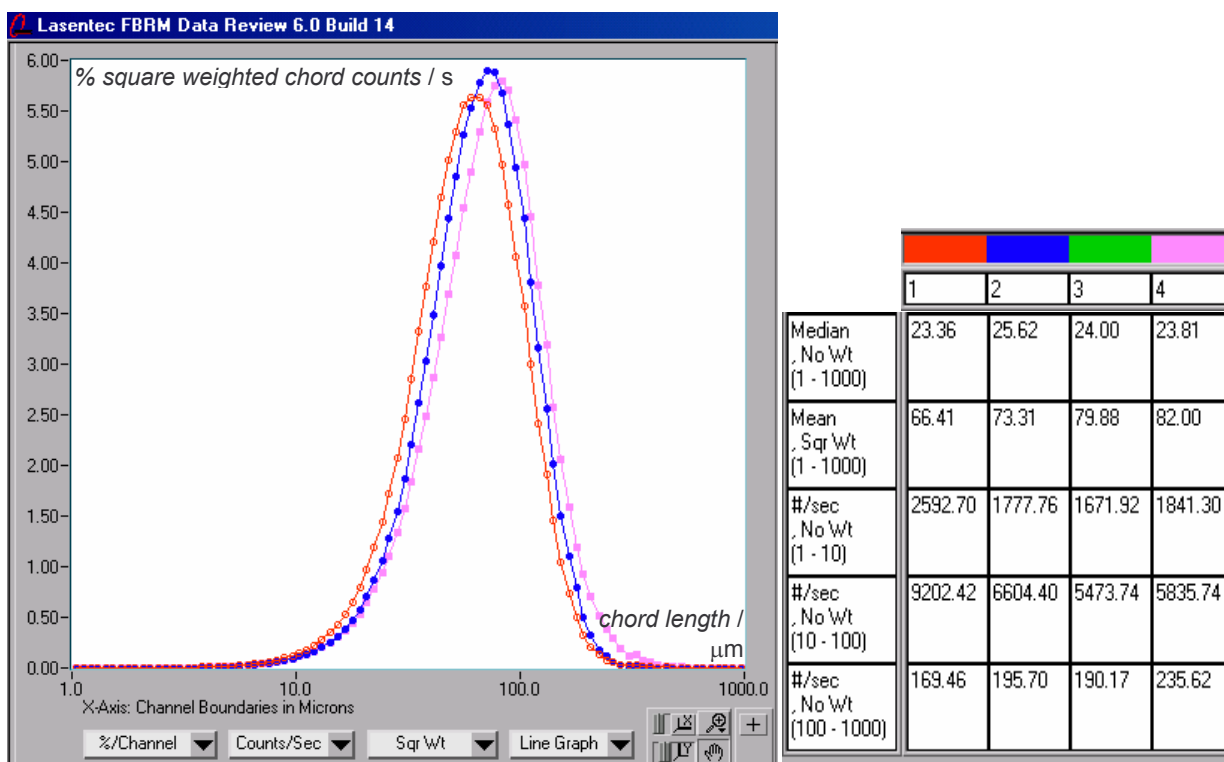


Fig. 10: Chord length distribution (CLD) histograms and referring statistics during nonlinear cooling and temperature cycling step: here shown as chords, square weighted with mean size of the referring size bin, counted per second. The square weighted distribution emphasizes the coarse end of the distribution, here highlighting the perfect growth of the seeds from the start of cooling (red), during cooling (blue), end of nonlinear cooling (green) and end of temperature cycling (pink). The referring points in time are shown in figure 9 as vertical lines with the corresponding colors.

3.4 Antisolvent Addition

In a final step, water is added as antisolvent to the system to further decrease solubility, i.e., to increase the yield of the crystallization. The addition of the antisolvent is linear as shown in figure 6. Figure 7 shows a significant increase of fines during the addition step. This can be further evaluated using the distributions shown in figure 11. With ongoing addition (green distribution), a second population of fine particles appears leading to a bimodal distribution of grown seeds and fines. The rather fast and linear antisolvent addition resulted in an increase of supersaturation and a secondary nucleation event. Towards the end of the addition, the significant fines peak disappeared, although a rather high number of fines is still present in the system. The disappearance of the peak suggests an agglomeration of the fines and seed crystals present. In fact, paracetamol is reported to tend to agglomerate.

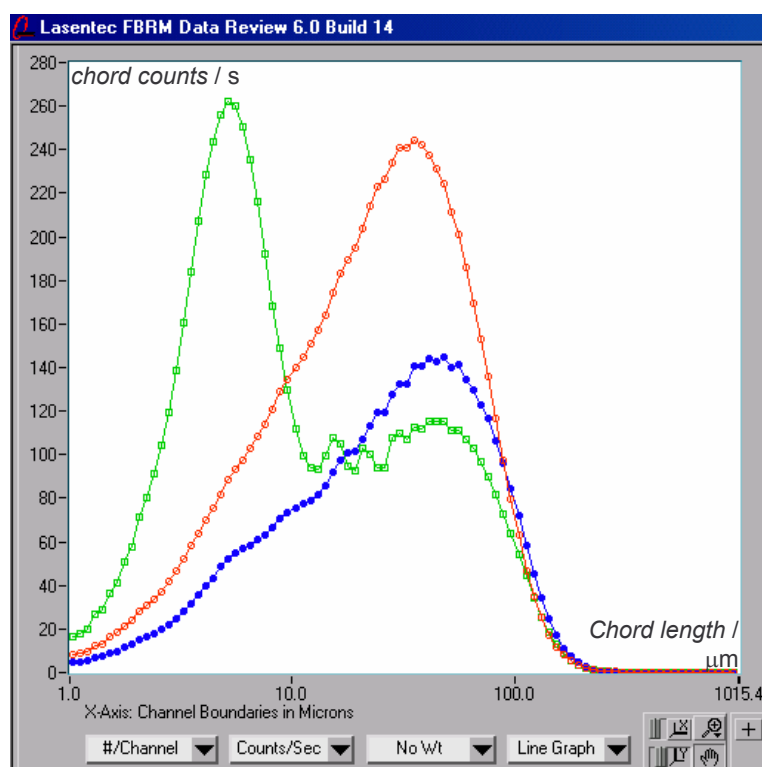


Fig. 11: Chord length distribution (CLD) histograms during antisolvent addition step: here shown as chords counted per second into a certain size bin, with 90 logarithmic size bins between 1 and 1000 μm ; distributions from start of addition (blue), during addition (green), and end of addition (red).

4 Conclusion

The MultiMax RB02-250 Reactor Box has been used in combination with a Lasentec FBRM probe to investigate a crystallization process. Even at this rather small scale accurate information on the effects of key parameters as a basis to optimize the crystallization process was obtained.

In particular, a rather typical crystallization procedure was followed, i.e., a cooling crystallization followed by an antisolvent addition. During the dissolution step, FBRM showed the disappearance of coarser particles at the end of the dissolution step. In fact, this information was used as a condition for the MultiMax to ensure a complete dissolution of the solute before performing the next step of the crystallization procedure. Seed addition followed by nonlinear cooling did lead to growth of the seed crystals without significant secondary nucleation. Therefore, the temperature cycling had almost no effect. During antisolvent addition, secondary nucleation occurred leading to a rather broad distribution at the end of the crystallization. This typically leads to high filtering, centrifugation, and drying times.

The presented crystallization highlights typical procedures applied in crystallization processes. While the cooling step is often well designed with cooling rates that are slow enough for the dynamics of the system under investigation, the effect of antisolvent addition is often underestimated. As seen in the example, the antisolvent addition step leads to a significant increase of fines and thus decreasing the quality of the final product. Antisolvent addition can change the solubility drastically. Therefore, slow and nonlinear addition with low addition rate at the beginning might be necessary.

Please note that within this study, thermodynamic aspects, i.e., the solubility and supersaturation levels throughout the crystallization have not been discussed at all. The data nicely illustrates that an optimization and improvement is possible even if thermodynamic data is lacking. This is for sure not an optimal case, but often realistic enough when fast optimization of a crystallization process is required. As a result of one experiment, clear conclusions on the relevant mechanisms within the crystallization could be drawn. As a consequence, the process sequence might directly be optimized and improved by skipping the temperature cycling step and changing the antisolvent addition procedure. Additionally, an investigation of the effect of shorter cooling times can be considered.

To summarize, the main benefits of the combined system of the MultiMax automated reactor system and the Lasentec FBRM probe are:

- Very accurate temperature control
- Accurate dosing of small volumes
- Optimized suspension mixing
- Excellent ratio minimum / maximum working volume: 50 mL / 300 mL
- Perfect process data analysis possibilities
- Sound understanding of particulate processes
- Optimized crystallization functions
 - Nonlinear cooling
 - Automated antisolvent addition
- Modular expendable reactor system
- Online monitoring of particle count and particle dimension throughout crystallization
- Accurate analysis of crystallization mechanisms, e.g. agglomeration, growth, nucleation

- Automated study of parameter effects
 - Parallel variations of parameters
 - High sensitivity to changes in particulate system
- Quantification of changes in particulate system, e.g. magnitude of attrition
- Highest reproducibility of on-line measurement and process sequence

5 Literature

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