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CRYSTAL GROWTH & DESIGN

Novel Design Integrating a Microwave Applicator into a Crystallizer for Rapid Temperature Cycling. A Direct Nucleation Control Study

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ABSTRACT: The control of nucleation in crystallization processes is a challenging task due to the often lacking knowledge on the process kinetics. Inflexible (predetermined) control strategies fail to grow the nucleated crystals to the desired quality because of the variability in the process conditions, disturbances, and the stochastic nature of crystal nucleation. Previously, the concept of microwave assisted direct nucleation control (DNC) was demonstrated in a laboratory setup to control the crystal size distribution in a batch crystallization process by manipulating the number of particles in the system. Rapid temperature cycling was used to manipulate the super(under)saturation and hence the number of crystals. The rapid heating response achieved with the microwave heating improved the DNC control efficiency, resulting in halving of the batch time. As an extension, this work presents a novel design in which the microwave applicator is integrated in the crystallizer, hence avoiding the external loop though the microwaves oven. DNC implemented in the 4 L unseeded crystallizer, at various count set points, resulted in strong efficiency enhancement of DNC, when compared to the performance with a slow responding system. The demonstrated crystallizer design is a basis for extending the enhanced process control opportunity to other applications.
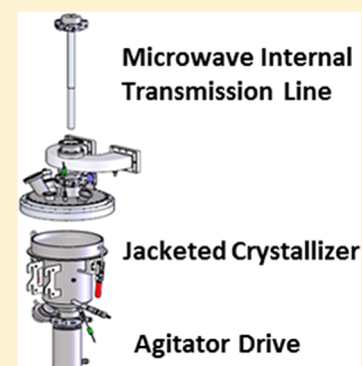
1. INTRODUCTION

Specialty chemicals and high value molecules such as active pharmaceutical ingredients (APIs) usually pose high demands on product quality attributes and require also that the product quality is stringently met.[1] The desired quality attributes can often be difficult to achieve, and hence the complexity of the production process and the production costs increase. Crystallization is one of the key unit operations involved in production of solid products by separating the solute from the solution.[2] Traditionally in the industry the crystallization is carried out in stirred tank reactors operating in batches with a predetermined recipe.[3] The batch approach, with fixed operation recipe, often leads to variability in product quality. Additional downstream processes are required in order to treat the product after the crystallization step in order to achieve desired product quality.[4]

During crystallization, one of the typical quality attributes of concern is to be able to produce a desirable and repeatable particle size distribution (PSD). To achieve this, tight control over the nucleation rate is required to generate a sufficient number of nuclei initially in the batch. Under tight control, the nucleated nuclei grow out uniformly to the desired size by consuming the large part of the generated supersaturation in the remainder of the batch. Many control strategies have been employed to gain control over the crystal size distribution either based on models which require *a priori* knowledge of the crystallization kinetics to predict an optimum process trajectory or more popularly seeding based strategies to suppress primary

nucleation have been employed.[5−11] Unfortunately many of these strategies are often unsuccessful due to model uncertainties resulting from poor estimation of the complex nonlinear crystallization process and due to the unexpected process disturbances which often offset the process.[12] Direct nucleation control (DNC) is a model free feedback control strategy based on using PAT tools for process monitoring.[13,14] Real time control over the process, based on *in situ* measurements of the state variables, is implemented in the DNC framework to recover the process from the deviations from the desired set point. The DNC approach fits well in the QbD approach, as not only strict control over the product quality can be ensured but also through process monitoring mapping of the operating conditions and the resulting product quality can be obtained.

Temperature cycling (heating and cooling) is yet another control strategy usually used for the crystal shape and size control and for the removal of fines during crystallization where the fine particles are expected to dissolve sooner compared to the larger particles, when the system temperature is increased.[15−17] Upon cooling, the generated supersaturation is ideally expected to be consumed by the larger particles remaining after the dissolution step. Since temperature cycles are in principle dissolution and growth/nucleation cycles, the

application of temperature cycling to serve various control objectives exists. Application of temperature cycling within the DNC framework is, thus, not limited to size control of the crystalline product only. DNC has been applied or has potential to be applied to areas such as crystal shape manipulation, polymorphism control, or chiral resolution, to name a few.[18,19] However, the issue of limited heat transfer capacity can be a limiting factor for the application of process control based on the temperature cycling approach. Especially at large scales, the heat transfer limitation worsens as the ratio of the cooling surface area to the crystallizer volume decreases at increasing crystallizer capacity. As an alternative for increasing the heat transfer surface area (which can be undesirable in the context of controlling nucleation), the application of microwave heating can be one of the solutions to attain an enhanced heat transfer.[20] However, the limited penetration depth of the microwaves presents a challenge for large scale implementation. Careful design, probably utilizing multiple sources of microwaves in combination with efficient stirring, is needed to ensure uniform bulk heating. The improved process control opportunity achieved by implementation of microwave heating is not particularly restricted to high heating rates but also a faster switch to cooling can be made, saving time otherwise spent in changing the process stream from hot to cold and vice versa in the case of conventional heat transfer via the same jacket.

In a previous study, the concept of a microwave assisted DNC approach was demonstrated.[21] Manipulation of the crystal size distribution in a batch crystallization process was achieved by manipulating the number of particles in the system. The DNC approach was implemented via the feedback control based on the *in situ* measurement of the number of particles by focused beam reflectance measurement (FBRM). Temperature cycling was triggered upon the deviation of the particle count from the set point, resulting in heating for dissolving the excess particles and cooling for generating new particles via nucleation or to grow the particle for achieving the desired yield. The study concluded that the use of rapid heating, achieved by applying microwaves in comparison to the slower heating response (limited by jacket heat transfer), leads to the improvement in the efficiency of the control by reducing the number of temperature cycles required to reach the desired set point. Overall, a reduction of the batch time by a factor of 2 was achieved. At the same time, the size distribution of the end product obtained when microwave was used was narrower as better control over fines removal was achieved. The significant improvement in the control efficiency was due to the rapid response after the detection of a nucleation event. Due to the strong nonlinear dependence of the nucleation rate on the supersaturation, a fast response on a nucleation burst is essential to prevent a large overshoot in the number of particles, which can only be counteracted by dissolution. The direct heating property of microwaves allowed the rapid response in terms of heating and eliminated the delay usually involved with switching between heating and cooling phases. Our study showed the need to have fast response to nucleation for controlling the number of particles during crystallization, which require special design consideration in order to not get limited by the heating rates usually restricted by the limited heat transfer surface in conventionally heated crystallizers.

The proof of concept study published earlier showing the enhanced DNC control, by combining microwave heating during crystallization, was carried out at a laboratory scale using an external loop which circulated the slurry from the crystallizer through a microwave cavity to introduce the microwave heating in the system. Such an external loop is not desired as the influence of circulating the crystals through the loop on the process is not clear and difficult to scale up. Therefore, in this work we present the microwave assisted DNC in a novel crystallizer designed to apply the microwaves directly into the crystallizer, thus avoiding the implementation of an external loop. Also, the scale of the crystallization process has been enhanced. The integrated microwave assisted crystallizer has been developed by Siarem SAS, based on internal transmission line technology, which directly integrates microwave heating in a jacketed crystallizer made of steel (Labrotron 4000, 4 L in capacity). Through the implementation of the DNC approach for controlling the size of paracetamol crystals in isopropyl alcohol (IPA) in the Labrotron 4000 unit, we intend to further the novel crystallizer design and demonstrate the concept crystallizer which can serve as a base for industrial applications.

2. MATERIALS AND METHODS

2.1. Materials. Acetaminophen (Paracetamol, BioXtra, ≥99%, Sigma-Aldrich) and isopropyl alcohol (IPA; technical grade (99%), VWR) has been used in this study.

2.2. Methods. 2.3. Particle Count Measurement: Focused Beam Reflectance Measurement. The FBRM probe (model G600) from Mettler Toledo was used to measure *in situ* the particle count and the chord length distributions (CLD). The iC FBRM software (version 4.4) was used for the data acquisition and analysis. The scan speed of the unit was set to 4 m/s with measurement interval of 5 s in all experiments. Both primary mode and macromode are available to analyze the FBRM data. The count data reported here are based on primary mode which means that the count data have high sensitivity for the edges detected. Mean squared chord length data from FBRM is used for reporting the mean particle size as measured by the FBRM.

2.4. Particle Size Distribution: Laser Diffraction. A laser diffractometer (Mircotrac S3500) was used for particle size measurement using dry mode sample measurement. Samples for particle size distribution analysis were prepared by filtering the slurry. The residue containing the product crystals was washed with a small amount of IPA and left overnight for drying in an oven maintained at 30 °C. The samples have also been pictured under a microscope.

2.5. *In Situ* Concentration Measurement. An ATR probe, model K1 Katana 6 mm supplied by Hellma, connected to a deuterium light source (model DH-2000-BAL) and to a spectrometer (HR2000+CG), both supplied by Ocean Optics, has been used to measure the absorption spectra of paracetamol in IPA. The concentration of paracetamol in IPA is estimated from the spectra collected by Spectrasuite software (Ocean Optics), by calculating the absorbance between the wavelengths of 255 up to 270 nm. Calibration was performed by measuring the absorbance spectrum of known concentration samples at temperatures ranging from 50 to 10 °C. The measurements always started at the highest temperature and were stopped when nucleation was detected or when the temperature reached the lower end. A model was then fit to relate the absorbance spectra to the concentration, in the form of eq 1.

$$c = a_1 \text{Abs} + a_2 (\text{Abs})^2 + a_3 T + a_4 (\text{Abs})T + a_5 \qquad (1)$$

where c is the concentration (g of paracetamol/(g of isopropanol)), a_i are the coefficients to be adjusted, T is the temperature (°C), and Abs is the absorbance. In order to correct for the baseline fluctuations of the spectra, the derivative of the absorption spectra from 255 to 270 nm is estimated. The derivate is then integrated between the desired wavelengths to retrieve the absorbance. The parameter estimation was done by a least-squares optimization. The model parameters obtained are $a_1 = -0.398$, $a_2 = 0.214$, $a_3 = 1.55e - 5$, $a_4 = -2.89e - 3$ and $a_5 = 2.26e - 3$. The concentration measurement and the calibration

procedure adopted here are as reported in the literature in a previous study.[22] Figure 1 shows the measured concentration of sample with
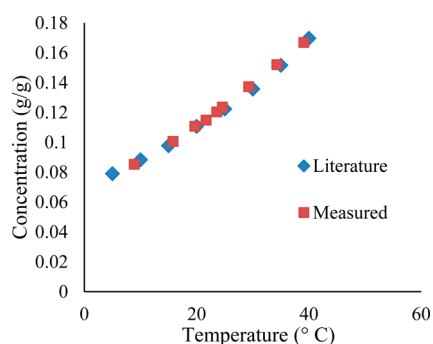

Figure 1. Concentration measurement using the model described by eq 1 vs saturation concentration as per literature: (blue diamonds) saturation concentration data from literature,[23] (red squares) measured data.

known concentration of paracetamol in IPA against the saturation data reported in the literature.[23] The measured values are in line with literature values. The error between the measured and the estimated concentration was ascertained using a validation set prepared separately. Validation experiments were performed to test the calibration by heating a slurry of paracetamol IPA in steps in a temperature range similar to the calibration curve. As the slurry was heated, a part of the excess particles in the slurry dissolved to reach the new equilibrium concentration at the end of each step and the error in predicted concentration was estimated to be in the range of ±2%

3. EXPERIMENTAL SECTION

3.1. Setup. The unit, Labotron 4000, designed and manufactured by Siarem SAS, allows integration of the microwave heating within a jacketed reactor. It uses internal transmission line technology for transfer of microwave directly into the slurry for direct heating of the contents inside the reactor. Thus, the unit consists of a microwave generator (2 kW, 2.4 GHz) connected via the internal transmission line to a 4 L jacketed stainless steel reactor. The system is detailed in Figure 2.
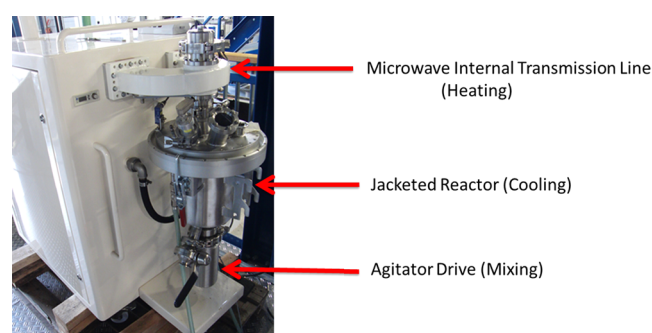

Figure 2. Labotron 4000, along with schematic of the essential constituents.

An agitation drive connected to a pitched blade propeller provides sufficient mixing in the crystallizer to keep the crystals in the crystallizer suspended. The FBRM has been introduced at the bottom of the reactor through the drain at the bottom of the crystallizer. Sufficient mixing is achieved in the system for FBRM to give a reliable indication of the change in particle count in the crystallizer.

Cooling crystallization was carried out in the jacketed reactor (as described above) which was connected to a Lauda RE-310 (Ecoline Star edition) thermostat unit for regulating the temperature of the jacket. A Pt 100 temperature probe connected to the thermostat unit

was used to measure the temperature inside the reactor and the measured temperature was conveyed to the main controller as feedback for the control. In the case of experiments with microwave heating, the input power of the system was set to a maximum of 2 kW, which was regulated internally by the PID controller in the Labotron unit to achieve the desired set temperature based on the difference from the current crystallizer temperature. The heating rates realized in the crystallizer depend on the dielectric properties of the liquid which dictate the amount of the microwave energy absorbed by the liquid solvent. Figure 3 provides the overview of the implementation of process monitoring and control.
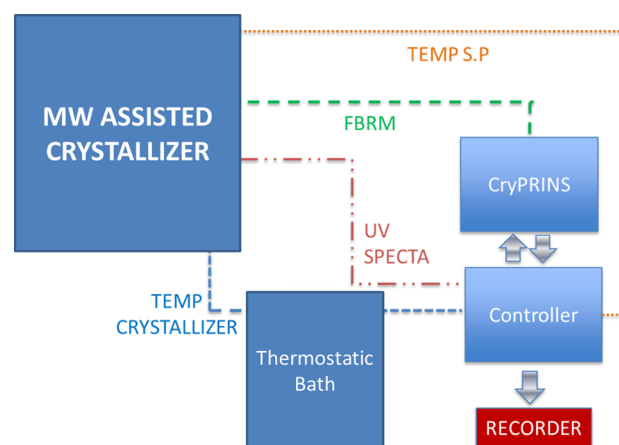

Figure 3. Control overview of the setup, with CryPrins giving the temperature set point based on the particle count (FBRM) feedback and the Labview based controller communicates the temperature set point to the thermostat bath and the microwave unit. TEMP has been used in short for temperature.

3.2. Microwave Assisted Direct Nucleation Control Structure. Figure 3 provides the overview of the implementation of process monitoring and control. CryPRINS (crystallization process informatics system) software which has the DNC approach implemented has been used to obtain the feedback of the particle count via the FBRM. For information about DNC using CryPRINS, literature can be referred to.[24] The temperature set point output by CryPRINS is linked to a Labview program (developed in-house) which controls and communicates the temperature set point of the thermostat and the microwave unit. Based on the temperature set point received by the microwave unit, an internal PID controller on the Labotron unit itself switches the microwave on or off and regulates the power level (maximum 2 kW)

Primarily due to nucleation or dissolution events, the particle count deviates, which (detected via the FBRM) triggers a heating or cooling response in the form of a new temperature set point for the crystallizer. In the case of no microwave heating, the controller simply regulates the thermostatic bath to achieve heating and cooling via the jacket in the crystallizer. When the microwave is used, only cooling is then carried out by the thermostatic bath. The use of microwave heating allows us to maintain the jacket at a lower temperature (approximately 6 °C less than the crystallizer temperature) during the microwave heating cycles, thereby obtaining a quicker switch to cooling. An overview on the microwave assisted DNC control structure implemented in this study can be found in our previous proof of concept work.

3.3. Experimental Design. Experiments have been performed with and without microwave heating to demonstrate the enhancement in efficiency of DNC using rapid temperature cycling. In both cases, the experimental configuration was kept the same. Saturated solution at 40 °C was prepared by dissolving 0.18 g of paracetamol/(g of the solvent (IPA)). Then the solution was heated to 50 °C and left for 1 h to ensure complete dissolution. Direct nucleation control was switched on (count set point activated).

The rate of change in temperature set point in the crystallizer with microwave heating was set to 2 °C/min, while in the experiments with jacket/conventional heating (when no microwave heating is used) a value of 0.7 °C/min is used. The lower heating rate in the case of conventional heating is due to the heat transfer limitations of the jacket. In the case of IPA as solvent, heating rates of up to 5−6 °C/min could be achieved at a full microwave output power of 2 kW. In the case of conventional heating the heat transfer via the jacket was limiting. The maximum and minimum temperatures in the system were limited to 50 and 5 °C, respectively. This was done to avoid excessive dissolution of the particles, which could lead to a total loss of nucleated particles and hence would require new nucleation events repeatedly in order to generate the required number of particles. A cooling rate of 0.5 °C/min was used in all experiments for gentle supersaturation generation to avoid excessive secondary nucleation during the cooling cycles. Experiments at different set points for the particle count were performed in order to analyze the effect of the set point values on the process dynamics and the product quality. In essence, by maintaining a lower number of crystals in the system, larger crystals can be obtained, whereas a high number of crystals will lead not only to relatively smaller crystals but will also possibly have a lot more fine particles. On the other hand a batch process without any feedback control with a simple linear cooling profile (cooling a saturated solution at 40 to 5 °C at 0.5 °C/min) results in a counts value on the order of 20,000 and a broad particle size distribution (data not shown in this work for brevity). The count set point chosen here, with a tight control bound of ±250 counts, set a challenge for the controller to maintain the crystal count in the crystallizer at much lower values when compared to the count achieved by primary nucleation with the same linear cooling rate but no control. The DNC control at various count set points should lead to a different final size of the crystal product. Table 1 summarizes the experiments carried out at the various counts set point.

Table 1. Summary of Experiments and Associated Experimental Conditions

expt	heating type	rate of change in SP (°C/min)	count SP
Conv 1	jacket/conventional	0.7/−0.5	4500
Conv 2	jacket/conventional	0.7/−0.5	3500
Conv 3	jacket/conventional	0.7/−0.5	2250
MW 1	microwave	2/−0.5	4500
MW 2	microwave	2/−0.5	3500
MW 2	microwave	2/−0.5	2250

4. RESULTS AND DISCUSSIONS

4.1. Microwave Assisted DNC. Experiments have been carried out at different count set points with and without rapid temperature cycling (summarized in Table 1). These experiments evaluate the performance of DNC in the current crystallizer. Different count set points for the DNC impose the growth of a different number of crystals in the process and thus a different product size. As shown before in our previous study, the low count values are the most demanding for the control especially when nucleation is dominating, requiring a large number of temperature cycles to reduce the count after nucleation and to maintain the desired set point value. Figure 4 shows the results of the DNC with conventional heating for a set point of 3500 (Conv 2). The figure shows the trends in the particle count, the temperature, the concentration, and the mean particle size. The first peak in the count profile is due to the primary nucleation which occurs when the clear saturated solution is cooled. The primary nucleation peak is the largest compared to the subsequent peaks which are due to the

secondary nucleation. Upon deviation from the count set point, the controller switches to the heating/cooling cycles. Excess nuclei are dissolved when sufficient undersaturation is created during the heating phase of the temperature cycles. Subsequently nuclei are generated by triggering nucleation during the cooling phase of the temperature cycles creating supersaturation in the system. The process control continues to cycle between heating and cooling phases until the end temperature is reached and the count set point is within the set bounds. Overall, about six to seven cycles were required at this count set point value of 3500 before the target temperature (close to 5 °C) and the desired count set point were reached. Figure 4 also shows (in the plot inset) the trend of the solute concentration which also varies with the process changes before reaching a constant value close to the saturation shortly after the temperature reached the target value. The plot inset in Figure 4 also shows the evolution of the mean particle size which varies with the nucleation and the dissolution events and reaches a steady value at the end of the control process.

Figure 5 shows the particle count and the temperature profile from the experiment with the microwave heating at the same count set point of 3500 (MW 2). Concentration and the mean size are shown in the plot inset in Figure 5. The striking difference compared to experiment CONV 2 in Figure 4 is the reduction in the number of cycles needed before the control reaches the target temperature and the count set point value. In addition, the value of the first count peak due to primary nucleation is strongly reduced (approximately by 50%) in the experiment MW 2 due to the rapid heating and the reduced lag time between switching of temperature cycles. By avoiding the number of particles to drop far below the set point value during dissolution, the subsequent need of supersaturation generation for generation of new nuclei to recover the particle count is also lowered. Hence, gentle secondary nucleation cycles are observed. The consecutive dissolution and growth cycles continue until the set point is achieved. The count reaches approximately a value of 3000, in both experiments with conventional heating and with microwave heating, close to the lower bound of the set point. At the end of the cycles, the concentration data (plot inset in Figure 5) confirm that constant concentration close to saturation is achieved, signifying the end of the process and a steady particle size. The batch time is dependent on the number of cycles before the control objective is achieved. Hence by the implementation of rapid heating a reduction in the number of temperature cycles and therefore a reduction in batch time is obtained. Overall the batch time is approximately lowered by a factor of 2 in the case of experiment MW 2 due to the lower numbers of temperature cycles.

Experiments have also been performed at other count set points. Figure 6 shows the temperature and counts profile for experiments at the counts set point of 2250 (experiments Conv 3 and MW 3). A larger number of temperature cycles are needed before the count set point is reached. Due to the low count set point and due to slow response in the conventionally heated/cooled system, a large undersaturation is created after the primary nucleation event which almost completely dissolves the nucleated crystals. Thus, subsequent nucleation cycles are required for generating new nuclei to regain the count set point. Figure 7 (left) shows the concentration profiles for experiments Conv 3 and MW 3. A large drop in the concentration is seen during the crystallization phase (*i.e.*, during nucleation events) followed by excess dissolution
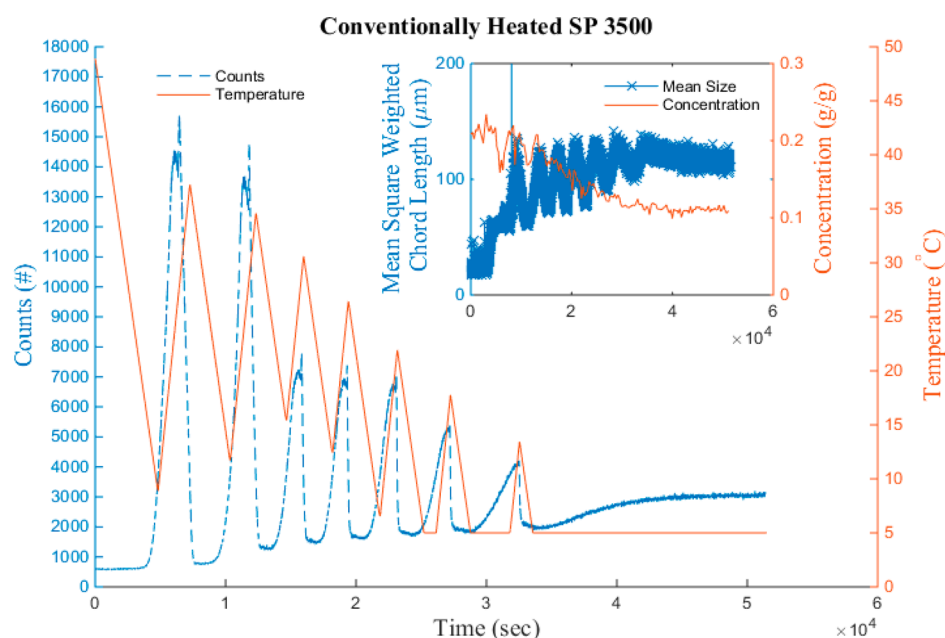
Figure 4. Count and temperature profile measured during DNC with conventional heated crystallizer, experiment Conv 2. The plot inset shows the evolution of the mean square weighted chord length of the crystals and the concentration of paracetamol in the crystallizer. Main graph, (blue --) count and (orange −) temperature; inset graph, (blue −×−) mean size and (orange −) concentration.
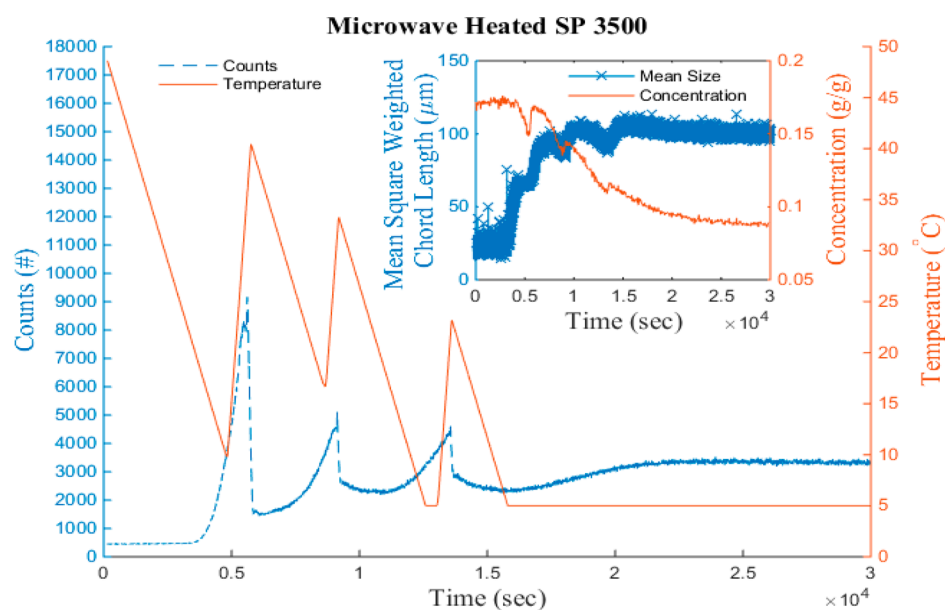

Figure 5. Count and temperature profile measured during DNC with microwave heated crystallizer, experiment MW 2. The plot inset shows the evolution of the mean square weighted chord length of the crystals and the concentration of paracetamol in the crystallizer. Main graph, (blue --) count and (orange −) temperature; inset, (blue −×−) mean size and (orange −) concentration.

reinstating the starting concentration throughout the experiment Conv 3. Poor control due to the slow response in the experiment (Conv 3) results in the temperature cycles being stuck between dissolution and nucleation events and in no convergence to the desired set point. The almost complete dissolution of the nucleated crystals at the end of each temperature cycle results in the temperature of the system to be high, far from the desired end temperature, and hence the solution concentration remains high

In experiment MW 3, the fast response significantly lowers the number of excess crystals after the cooling phases and the shortage in number of crystals after the heating phase, making

the convergence to the set point value much easier. The smaller drops in the concentration during nucleation seen in the concentration profile for experiment MW 3 (Figure 7 (left)) is because of the tight control achieved by rapid heating. As a result, the batch in experiment MW 3 reaches the targeted end temperature at the desired count set point. Overall the process with microwave heating converges toward the set point in a total of five to six cycles. Samples of crystals were taken at the end of experiment MW 3 only as the experiment Conv 3 did not converge to the set point and had to be stopped.

The temperature and count profile for both experiments MW 1 and Conv 1, with the higher count set point of 4500, are
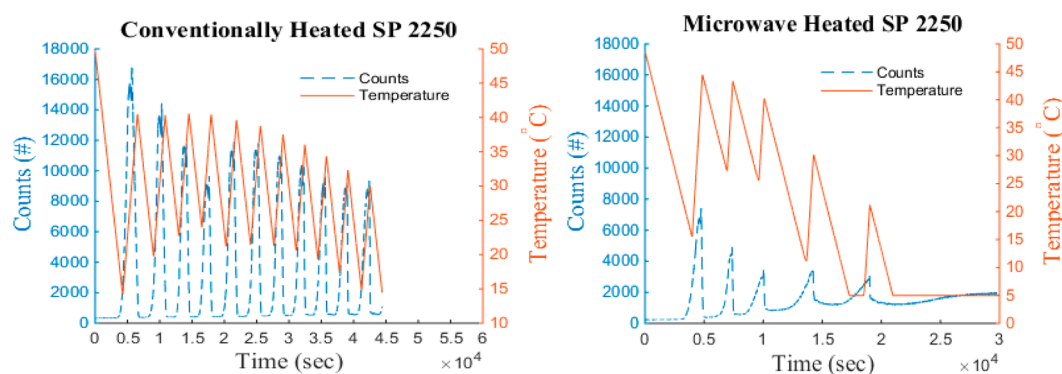
Figure 6. Count and temperature profile measured during experiments Conv 3 (left) and MW 3 (right) at count set point of 2250: (blue --) count and (orange −) temperature.
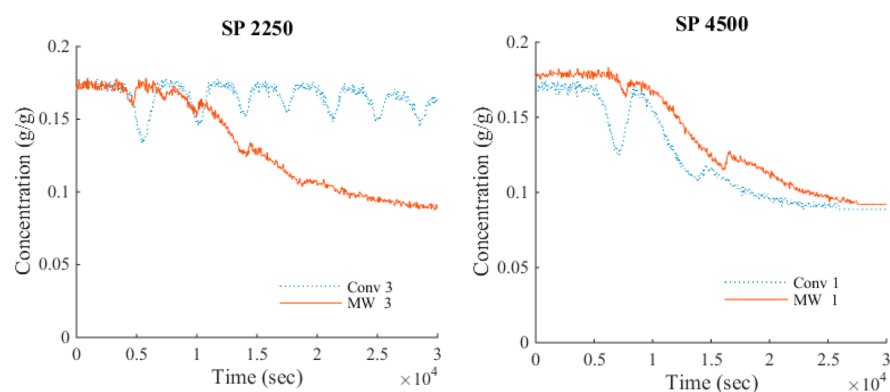

Figure 7. Concentration profile measured during DNC with conventional and microwave heated crystallizer at count set point of 2250 (left) and at count set point of 4500 (right): left panel, (blue ⋯) Conv 3 and (orange −) MW 3; right panel, (blue ⋯) Cov 1 and (orange −) MW 1.
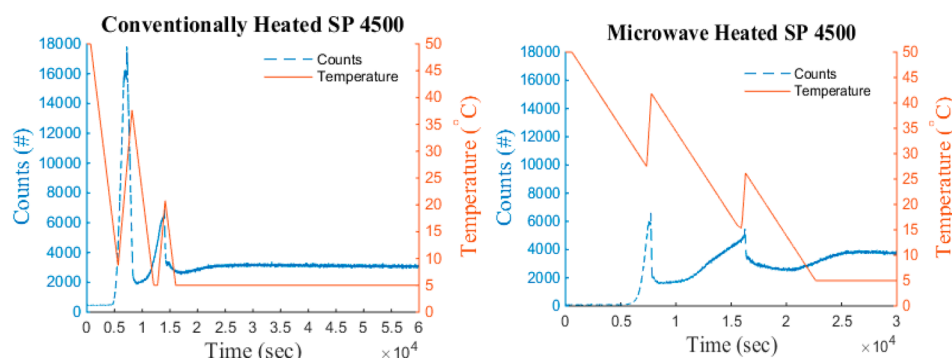

Figure 8. Count and temperature profile measured during experiments Conv 1 (left) and during experiment MW 1 (right) at count set point of 4500: (blue --) count and (orange −) temperature.

shown in Figure 8. At this count set point of 4500, approximately the same number of cycles and comparable batch time are observed in both experiments MW 1 and Conv 1. The low number of cycles observed is due to the high number of particles being maintained in the system which rapidly consumes the supersaturation. Figure 7 (right) shows the concentration profile for both experiments Conv 1 and MW 1, respectively. Both concentration profiles approach saturation values expected at the end of the experiment. However, in experiment MW 1 the count set point reached is closer to the set point value of 4500 ± 250, whereas the final count value in experiment Conv 1 is much lower and the set point is not achieved. Even though the paracetamol IPA system exhibits dominant secondary nucleation, the high particle count allows rapid consumption of the supersaturation for the growth of the

particles and hence helps to avoid secondary nucleation. Process dominated by growth rather than nucleation events makes it difficult for the control process to reach the count set point by triggering nucleation even as the supersaturation is generated during the cooling to the end temperature. In experiment MW 1, the tight control over the number of particles during nucleation and dissolution allows for the batch to approach the desired count set point closely.

4.2. Particle Size Distribution with Rapid Temperature Cycling. To assess the final product crystals, the size distribution of crystals at the end of each experiment has been determined, by measuring the dried sample in a forward laser diffraction instrument. In addition, samples have been imaged under the microscope and the chord length distribution data measured by the FBRM are also available.
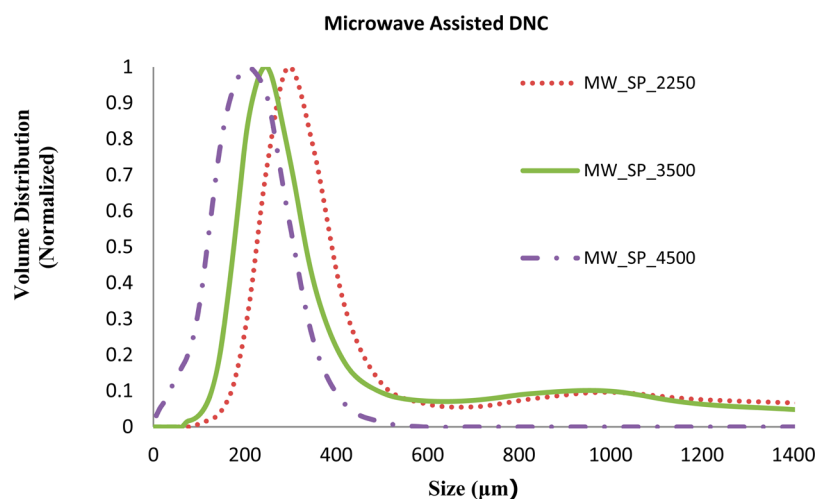
Figure 9. Volume particle size distribution obtained at various count set points with microwave assisted heating: (red ⋯) MW_SP_2250, (green —) MW_SP_3500, and (blue —·—) MW_SP_4500.
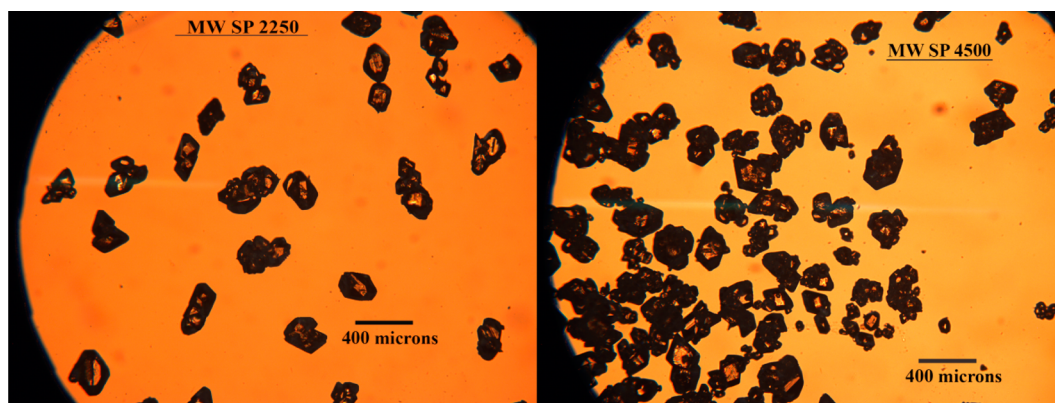

Figure 10. Images of samples taken at the end of the experiment with count set points of 2250 (left) and 4500 (right). (All pictures are at 5× magnification.)

Figure 9 shows the normalized volume distribution for microwave assisted DNC experiments carried out at various count set points. Unimodal distribution is observed, with a small shoulder at large sizes. The shoulder could be due to agglomerated crystals resulting during the sampling process which involves filtration and drying. The effect of the different count set points on crystal size is seen from the peaks in the size distribution (Figure 9). The enhanced control with microwave assisted DNC allowed the three count set points in our experimental design to be realized through strict regulation of the number of particles. As a result, increased particle size is observed as the count set point is decreased. However, at high count set point of 4500, a lot of fine particles still remain in the system and that is visible in the size distribution at small sizes around 50 μm.

Images of the product crystals from the above experiments were also taken under microscope. Figure 10 shows the product crystals obtained from the experiments at count set points of 2250 and 4500, respectively. Larger crystals with fewer fines are seen in the case of count set point of 2250 in accordance with the measured particle size distribution. The large number of temperature cycles experienced at the low count set point ensures that fine particles dissolve and hence larger crystals are obtained. In the case of the count set point of 4500, a large number of fines are visible. The large crystals are surrounded by many smaller fine particles, and agglomeration is also noticeable. The large count set point allows a large number of particles to be sustained in the process, and due to the fewer temperature cycles a lot more fines are present.

4.3. Effect of Design and Scale on Microwave Assisted DNC. In comparison with our earlier study in which a 1 L scale glass reactor with external loop for microwave heating was used, the 4 L stainless steel design presented here integrates the microwave heating into the crystallizer vessel. With this design the use of an external loop though the microwave oven is avoided which is known to cause problems, such as attrition of crystals due to pumping, poor temperature control, and scaling. In the previous design, high temperature of slurry in the loop was reached in order to achieve the required heating rate to respond to the nucleation event. The new integrated setup is an alternative design for rapid and flexible bulk heating of the crystallizer, utilizing microwave heating in combination with the already present convective dispersion due to the stirring. The Labotron unit allows high heating rates directly in the crystallizer without the need of an increased heat transfer surface area or the use of external heat exchangers. Our design allowed rapid response against the onset of nucleation by creating undersaturation to tightly control the number of particles in the crystallizer, essential for efficient DNC control strategy.

At large scales, the limited penetration depth of the microwaves warrants the use of multiple power sources in combination with efficient stirring to ensure proper heat distribution. The integration of microwave fields with the crystallizer however also restricts the use of PAT tools in the vicinity of the microwaves. Careful design based on the knowledge of attenuation of the microwave field allowed the PAT tools to be placed near the bottom of our crystallizer, where the microwave fields, if present, are very weak. Positioning the FBRM probe at the bottom near the impeller is not the optimum positioning for efficient performance of the FBRM. Analogously for industrial implementations a draft tube crystallizer design could ensure safe introduction of the microwaves in the central annular region with the outer region isolated from microwaves for implementation of PAT tools.

The results obtained with the novel crystallizer presented in this study are in line with our previously reported proof of concept study. The process control response achieved with rapid heating in both these studies resulted in a significant enhancement in the direct nucleation control efficiency. In both setups the low count set points required a larger number of cycles when compared to higher set points. Most importantly the tight control achieved with rapid heating resulted in the control process to converge for the low count set points in both studies, which was more challenging for the control process. A direct comparison between the experiments done with the laboratory unit with external circulation loop and the Labotron unit is difficult due to the differences in the impeller design (mixing) and the PAT tool (FBRM) positioning which influence the detected particle count. In a separate experiment the control performance was also tested with higher heating rates (4−6 °C/min) with the Labotron unit. The result showed that the temperature cycle time was reduced, but excessive dissolution occurred as the system was heated too fast to temperatures above the saturation level. The resulting excessive dissolution resulted in additional cycles to achieve the count set point. Additional tuning of the control is required to optimize the use of the higher heating rates, and hence experiments with high heating rates were not reported here. A simple solution is to limit the maximum temperature and thus limit the undersaturation which can be created by the controller.

5. CONCLUSIONS

In this study a novel microwave integrated crystallization unit is presented and successfully applied to demonstrate the enhancement in the efficiency of DNC using rapid heating. The Labotron 4000 unit (4 L in capacity) from Sairem with its internal transmission line technology was re-designed to enable integration of microwave heating directly into a crystallizer, avoiding the use of an external dissolution loop.

By performing a DNC study on the paracetamol−isopropanol system, it has been demonstrated that the application of rapid heating to counter the bulk nucleation directly in the crystallizer offers a much higher efficiency, resulting in significant reduction in batch time. The integration of microwave heating along with the PAT tools for process monitoring in a single crystallizer offers an alternative for designing and implementing advanced process control. Fast response to the deviations in the process resulted in a significant reduction in the number of control cycles, and the best result was obtained for the experiments at the count set point of 3500, where the batch time with microwave heating was halved in comparison to slower response to nucleation.

With rapid nucleation control, all the tested count set points were achieved and the particles size could be manipulated to different sizes accordingly. The results obtained with the microwave assisted DNC in the new crystallizer design were in line with our previous proof of concept study.

The novel crystallizer design with integrated microwave heating promises to be a convenient tool for optimizing processes based on temperature cycling. At laboratory/pilot scale, the microwave assisted crystallizer can be used for screening and for mapping the process space for gaining better control over nucleation and growth events. Such knowledge is valuable for rapid process development and design of crystallization processes. Our design, thus, serves as a basis for advanced control opportunity to be realized in similar equipment or applications to meet stringent product quality standards.

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■ ABBREVIATIONS

DNC, direct nucleation control; FBRM, focused beam reflectance measurement; TEMP, temperature

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