

Post-breakage Crystal Regeneration: Multiple Breakage Sites, Growth Kinetics, and Effects on Mass Production

Published as part of *Crystal Growth & Design* special issue "Design of Crystals via Crystallization Processes".

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Cite This: *Cryst. Growth Des.* 2025, 25, 8073–8080



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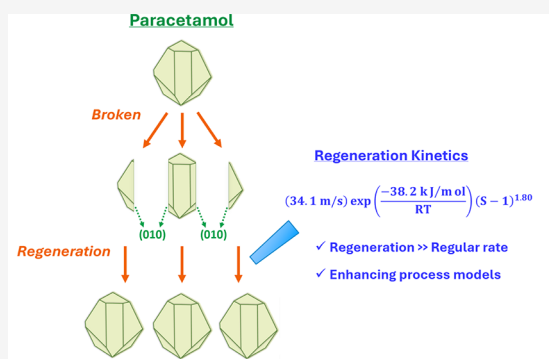
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ABSTRACT: Post-breakage crystal growth is obscure. Recently, form I paracetamol (PCM) crystals, broken to expose their internal cleavage plane (010), grew back into their original shapes through "regeneration." This work reports on regeneration in crystals with multiple breakage sites, regeneration growth kinetics, and regeneration's process optimization potential. Single PCM crystals with two breakage sites grew into their original shapes in ethanol, with a rate twice that of crystals with one breakage site. In a surface integration-limited regime, PCM regeneration in ethanol followed the kinetic equation $G = (34.1 \text{ ms}^{-1}) \exp(-38.2 \text{ kJmol}^{-1}/RT)(S - 1)^{1.80}$. With a higher pre-exponential factor and lower activation energy, regeneration is indicated to proceed significantly faster than regular growth across different temperatures and concentrations. A modified "two-crystal" setup enabled the comparison of mass growth rates between regenerating and unbroken crystals during PCM evaporative crystallization in acetone, evaporative crystallization in ethanol, and isothermal crystallization in ethanol. In these cases, regenerating crystals grew faster by $36 \pm 8 \text{ wt } \%$, $75 \pm 19 \text{ wt } \%$, and $94 \pm 34 \text{ wt } \%$, respectively. Projections to multi-crystal systems indicated that crystallization processing times could be lowered by up to 42%, 60%, and 65% for the respective cases. These findings offer improvements for crystallization process modeling and optimization.



1. INTRODUCTION

Regarded as one of the earliest chemical engineering processes,¹ crystallization is today used in a wide range of applications, including pharmaceuticals, food, fine chemicals, and agrochemical production.^{1–3} The applications of crystallization are expected to widen further, particularly in replacing chromatography operations, which tend to be economically and environmentally very costly for overall processes.^{4,5}

Crystallization is considered a two-stage process: nucleation and crystal growth. The former refers to the formation of stable clusters (i.e., nuclei) in a supersaturated solution. The latter describes the growth of the formed crystals. Crystal growth is composed of two steps: the mass transfer step, which describes the transport of solutes from the bulk solution to the crystal surface and the surface integration step, which follows the mass transfer and describes the integration of solutes onto the crystal surface by stable intermolecular interactions. Rates of both mass transfer and surface integration contribute to the overall crystal growth rate. Most industrial processes are initiated with crystal seeds and operate within the metastable zone to allow crystal growth without nucleation, in order to obtain ultimate crystal products with a narrow distribution of attributes (e.g., size).^{6,7}

Crystal breakage is another phenomenon occurring in real crystallization processes. Accordingly, the growth of crystals

post-breakage is not well explored, and broken crystals are usually modeled to grow indifferently from unbroken crystals.^{8,9} Regarding breakage mechanisms, crystal–agitator collisions are the most prevalent, whereas crystal–crystal and crystal–wall collisions are relatively negligible.¹⁰ Regarding its extent, breakage incidences have been reported to increase with higher agitation rates,^{11,12} larger crystal sizes,^{11,13} higher supersaturation,¹¹ and higher magma density.¹² From a thermodynamic perspective, upon a breakage impact, the directional preference of crystals is to be cleaved to expose their internal cleavage planes, that is, the set of parallel planes within the crystal featuring the weakest interplanar interaction energy.^{14,15}

Recently, a novel phenomenon named “crystal regeneration” was reported for the post-breakage growth of form I paracetamol (PCM) crystals in ethanol. When cleaved along their (001) surface, resulting in the exposure of the (010)

Received: May 31, 2025

Revised: August 22, 2025

Accepted: August 25, 2025

Published: September 12, 2025



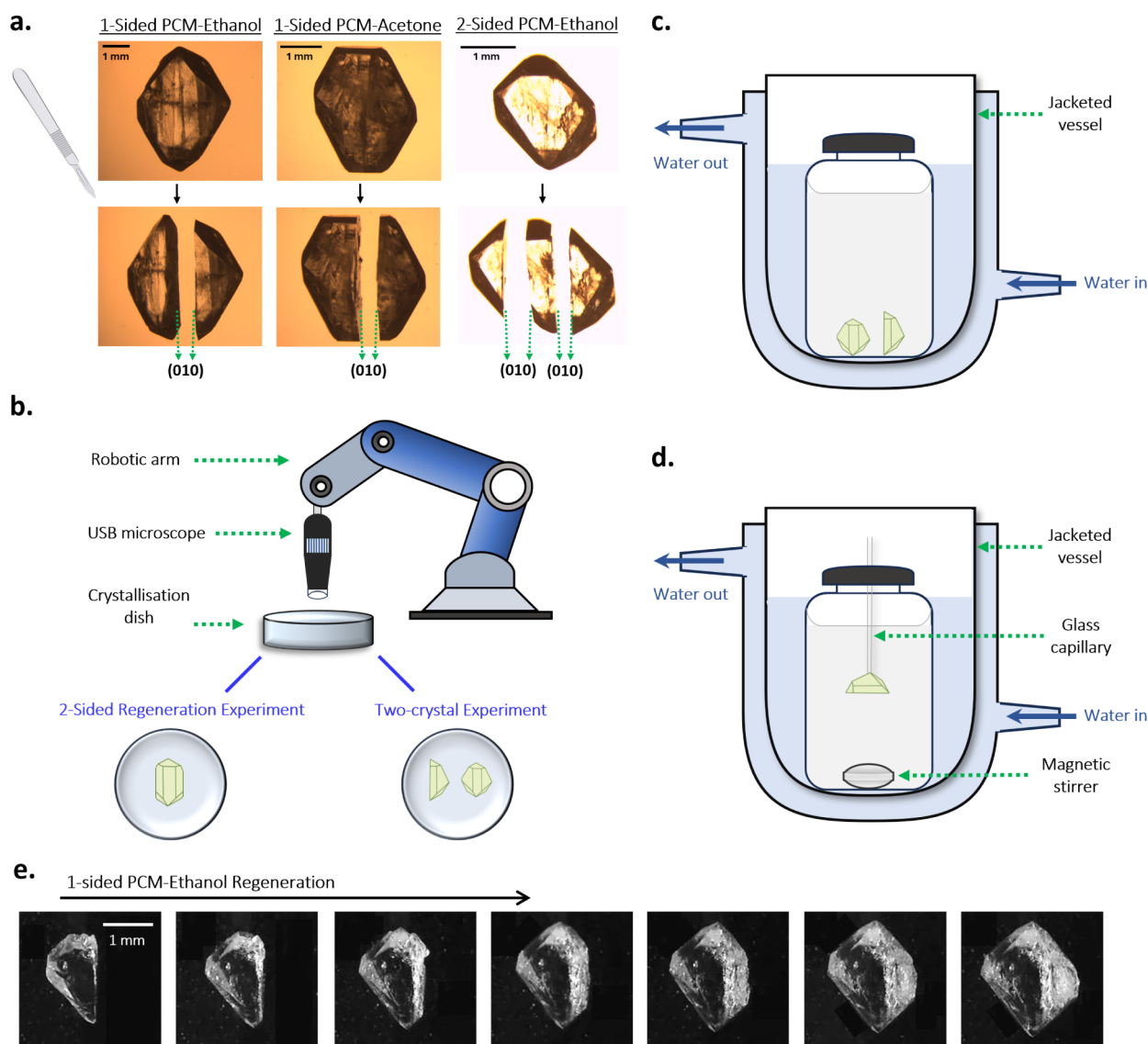


Figure 1. (a) Pre- and post-breakage pictures of paracetamol crystals for one-sided regeneration experiments in ethanol, one-sided regeneration experiments in acetone, and two-sided regeneration experiments in ethanol. (b) Schematic diagram of the evaporative crystallization experimental setup utilized for single-crystal and two-crystal experiments. (c) Schematic diagram of the isothermal crystallization experimental setup utilized for two-crystal experiments. (d) Schematic diagram of the isothermal crystallization experimental setup utilized for single-crystal experiments in the kinetic studies. (e) Visual developments of one-sided paracetamol regeneration in ethanol.

internal cleavage plane, the broken PCM crystals rapidly grew from their exposed (010) surface into their original shape. Regeneration was demonstrated for PCM crystals of different sizes. It was also reported to be independent of the extent of cleavage, i.e., both of the resulting broken crystals regenerated as long as the cleavage exposed a surface constituting planes with a (010) Miller index. Moreover, regeneration was reported to be unique for breakages exposing the (010) surfaces—upon cleavages in other directions, the crystals showed growth trends similar to unbroken crystals and did not rapidly grow into their original shape.⁹ It was subsequently reported that crystal regeneration is not exclusive to the PCM–ethanol system. Regarding different solvents, regeneration of PCM was later reported for acetone and tetrahydrofuran solvents.¹⁶ Considering different solutes, regeneration of aceclofenac crystals was also reported, for acetone and methyl acetate solvents.¹⁷ Therefore, crystal regeneration is a recently explored phenomenon, and its

further elucidation and integration into process models would enhance the prediction and optimization of crystallization processes.

Kinetics of crystal growth can be formulated to describe dependencies on supersaturation and temperature for a given crystal–solvent combination. Kinetic formulations are established for individual crystal surfaces and therefore have [distance/time] units. The general form of crystal growth kinetics is provided in eq 1. The terms G , A_0 , E_a , R , T , and S , respectively, denote the surface growth rate, pre-exponential factor, activation energy, ideal gas constant, temperature, and supersaturation. The exponent g , describing the growth's dependency on supersaturation, takes a value between 1 and 2.⁷ Importantly, considering the two steps of crystal growth, kinetic measurements should be conducted in a surface integration-limited regime to avoid being influenced by bulk mass transfer rates.^{7,18,19} Kinetic formulations are useful for

predicting crystal growth rates under process conditions, as well as for modeling and optimize processes.^{20,21}

$$G = A_0 \exp\left(-\frac{E_a}{RT}\right)(S - 1)^g, \quad 1 \leq g \leq 2 \quad (1)$$

Experimental techniques for crystal growth are mainly categorized into direct and indirect methods. Direct methods refer to single-crystal experiments and involve monitoring the growth of individual crystals by using laboratory-scale setups. Indirect methods utilize suspensions of crystal seeds in agitated crystallizers, where growth trends are inferred from concentration measurements. Thus, direct methods are beneficial for gathering detailed and accurate information about growth rates and mechanisms, although their small sample size could be a limitation. Indirect methods are advantageous due to their larger sample size and better mimicking industrial-scale hydrodynamics, although it is difficult to explore detailed growth mechanisms of particular crystal surfaces.^{22,23}

To advance the knowledge on post-breakage growth, exploring the feasibility and growth trends of regeneration for particles with multiple breakage sites would be a timely contribution to the field. Moreover, crystallization process models are increasingly used and developed, with kinetic growth equations being utilized in computational softwares, including gPROMS,²⁰ Python,²¹ and MATLAB,²⁴ as well as within machine learning frameworks that employ neural networks.^{21,25} Therefore, formulating the growth kinetics of regeneration and comparing it with regular crystal growth would enhance the accuracy and capability of crystallization process models. From an industrial perspective, as most industrial processes start with a certain mass of seeds to reach a target final mass,^{1,6,7} and regeneration is reported to be faster than regular growth while resulting in the same particle shape,⁹ studying the effect of regeneration on crystal mass growth would elucidate its potential to improve the productivity of crystallization processes.

In this study, the possibility of simultaneous regeneration for particles with multiple breakage sites was first investigated using PCM–ethanol system via single-crystal experiments. Then, via controlled isothermal crystallization experiments with the PCM–ethanol system, surface growth kinetics of crystal regeneration was formulated. In addition, via a modified two-crystal setup, the advantages of regenerative crystal growth compared to regular growth are translated into mass production rates. In these tests, two crystals with similar initial masses were selected to grow together, one being broken with an exposed internal cleavage plane (i.e., to follow regenerative growth) and the other being unbroken (i.e., to follow regular growth). Two-crystal tests were conducted for PCM–acetone regeneration with evaporative crystallization, PCM–ethanol regeneration with evaporative crystallization, and PCM–ethanol regeneration with isothermal crystallization cases. Finally, based on these outcomes, the potential of crystal regeneration to reduce processing times was estimated, highlighting improvements in the productivity and efficiency of crystallization processes.

2. EXPERIMENTAL SECTION

2.1. Materials. Paracetamol ($\geq 98.0\%$) was procured from Sigma-Aldrich. Ethanol ($\geq 99.8\%$) and acetone ($\geq 99.8\%$) were procured from VWR Chemicals.

2.2. Preparation and Cleavage of Crystals. PCM crystals of millimeter scale were grown for use in the experiments. For that, initially, saturated solutions were prepared via mixing excess PCM with solvents overnight. Then, small seeds were obtained through slow evaporation of 30 mL of saturated PCM solutions in 50 mL of borosilicate glass beakers at room temperature. The seeds were collected using tweezers and gently dried with a tissue. Subsequently, the seeds were grown individually in 10 mL borosilicate glass vials via slow evaporation of saturated solutions at room temperature until they reached the desired size. Finally, the crystals were collected and gently dried with a tissue. For both seed production and growth procedures, slow evaporation was enabled via covering the beaker or vial with parafilm, followed by piercing the covered parafilm with tweezers to open 3 holes of around 1 mm each.

For regrowth experiments, prepared crystals were cleaved via applying point pressure to their (001) external surface using a scalpel. This resulted in a self-propagating clean fracture, with both resulting fragmented crystals exposing a flat (010) surface on a microscopic level. The crystals were cleaved around their midpoint for one-sided regeneration experiments, whereas they were cleaved parallelly from both sides for two-sided regeneration experiments. Images of crystals before and after cleavage are shown in Figure 1a for a one-sided cleaved PCM crystal from ethanol, one-sided cleaved PCM crystal from acetone, and two-sided cleaved PCM crystal from ethanol, respectively.

2.3. Crystal Regrowth via Evaporative Crystallization. Borosilicate glass crystallization dishes with a 6 cm diameter and 3.5 cm height were filled with 60 mL of saturated PCM–ethanol or PCM–acetone saturated solutions. For single-crystal experiments used in the studies on crystal regeneration with multiple breakage sites, cleaved single crystals were placed inside the dishes. Borosilicate glass plates were placed on the dishes, allowing slow evaporation at room temperature. For two-crystal experiments, utilized to study the effect of regeneration on mass growth, the setup was modified so that it was initiated with a broken and an unbroken crystal with a similar initial mass ($\pm 15\%$) (Figure 1b). Details of the evaporative crystallization setup are provided in Figure S1.

2.4. Crystal Regrowth via Isothermal Crystallization. Two types of isothermal crystallization setups were utilized in this study. For two-crystal experiments, borosilicate glass crystallization dishes with a 3.8 cm diameter and 5.8 cm height were filled with 60 mL of PCM–ethanol solution saturated at room temperature. A pair of broken and unbroken crystals of similar initial mass ($\pm 15\%$) were placed inside the dishes, and the dishes were enclosed with lids. The dishes were inserted into a water bath of 15 °C, corresponding to a supersaturation (S) of 1.1 (Figure 1c). Details of the isothermal crystallization setup are provided in Figure S2.

The kinetics study involved single-crystal experiments with the same crystallization dishes with a diameter of 3.8 cm and a height of 5.8 cm. To prepare solutions with specific supersaturation and temperature, a bulk solution was initially prepared at a higher temperature (T_i) based on PCM's solubility curve (Figure S3). Then, 60 mL of the bulk solution was filtered into the crystallization dish and kept for 2 h at the experimental temperature (T_e) for equilibration. The list of T_i and T_e values for tested cases can be found in Table S4. The high solution volume relative to the growth of a single crystal ensured negligible changes in supersaturation throughout the

experiments, which was confirmed via gravimetric analysis. Cleaved PCM crystals were glued to the tips of glass capillaries with a 1-mm diameter and 10-cm length. To note, the glue was minimally applied to the adhesion point of the crystal to ensure that crystal growth was not affected. A 1 mm hole was opened on the lid of the dishes to allow the capillaries to pass through so that the cleaved crystals were submerged in supersaturated PCM–ethanol solutions. For cases involving stirring, a 1.5 cm magnetic stirrer was placed at the bottom of the dish. Once the crystal was submerged, the setup was allowed 10.5 min for crystal growth (Figure 1d).

2.5. Crystal Regrowth Monitoring and Analysis. For the evaporative crystallization setups, crystallization dishes were monitored with a USB microscope (RS Pro, SM) throughout the crystal growth. The USB microscope was connected to a robotic arm (DOBOT, Magician), enabling simultaneous monitoring of multiple crystallization dishes (Figure 1b). In addition, pictures of the crystals were taken with a stereomicroscope (Leica Microsystems, M60) before and after the experiments, also allowing the measurement of crystal dimensions. Using the calibrated stereomicroscopic measurements, growth rates of crystal surfaces and dimensions were estimated via ImageJ software from the recordings of the USB microscope. As an example case, visual developments for the regeneration of one-sided broken PCM crystal in ethanol are illustrated in Figure 1e. For the two-crystal experiments, additionally, crystals were also gently dried with soft tissue, and their mass measurements were taken with a microbalance (OHAUS, Pioneer PA214C).

For the isothermal crystallization experiments, pictures of the crystals were taken with the stereomicroscope before and after the experiments. In the kinetic studies, the growth distance of the regenerating (010) surface was calculated by the difference in measurements between the pictures, and the result was divided by 10.5 min to estimate the growth rate. In the two-crystal experiments, mass measurements were also taken as described for the evaporative crystallization case. Reported experimental errors were calculated based on repetitions of the same experiment with different crystals for both isothermal and evaporative crystallization setups.

3. RESULTS AND DISCUSSION

3.1. Crystal Regeneration with Multiple Breakage Sites. The possibility of simultaneous regeneration from multiple surfaces was tested with PCM crystals with 2 breakage sites. Growth trends, in terms of visual developments and quantified dimensional growth rates, are provided in Figure 2. The regenerating crystal dimension and the normal dimension are also marked in the first image ($t:0$). As seen, PCM crystals cleaved from two sides were successfully regenerated in ethanol, demonstrating the capability of crystals to simultaneously regenerate from multiple surfaces, returning to their original shape. A video showing the growth developments of this case is also provided in Movie S1. Regarding the growth rates, during the first half of the regeneration (0–16 h), the regenerating dimension grew at a rate of 0.068 mm/h. In the second half of the regeneration (16–32 h), the regenerating dimension gradually transitioned with an average rate of 0.032 mm/h. After regeneration (32–48 h), the regenerating dimension proceeded at a rate of 0.009 mm/h. The rate of normal dimension varied insignificantly and proceeded at 0.015 mm/h throughout the overall process (0–48 h). For comparison, during one-sided PCM regeneration in ethanol

2-Sided PCM-Ethanol Regeneration

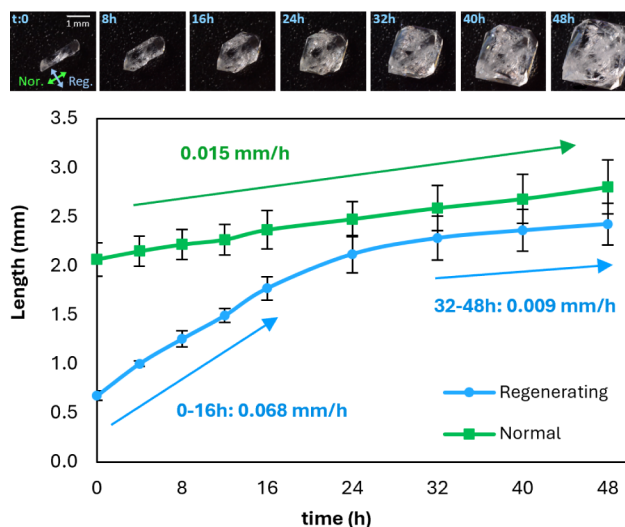


Figure 2. Appearance over time and dimensional growth trends for two-sided paracetamol regeneration in ethanol ($n = 3$). The period of 0–32 h corresponds to the regeneration time, and the period of 32–48 h corresponds to the crystal growth after regeneration.

under the same conditions, the regenerating dimension was reported to grow at a rate of 0.037 mm/h during the first half of the regeneration period.¹⁶ Therefore, the measured rate of 0.068 mm/h for two-sided regeneration, which is approximately twice that of 0.037 mm/h, indicates that regenerating surfaces do not compete in the two-sided regeneration case, thereby fastening the growth rate of the overall dimension. Notably, after regeneration, the ratio of the growth rates for the regenerating dimension (0.009 mm/h) to the normal dimension (0.015 mm/h) was around 0.6. As reported earlier,¹⁶ a growth rate ratio of around 0.7 is expected after regeneration, which is dictated by PCM's regular shape dimensions in ethanol.

Outcomes of this study demonstrate the potential of utilizing regeneration as a seeding tactic. Accordingly, crystal seeds tailored to expose their internal cleavage planes can facilitate faster crystal growth through regeneration. Thus, for instance, the process time needed to achieve target crystal mass and resource consumption can be reduced. Likewise, breakage tactics targeted to expose the crystals' internal cleavage planes can be explored (e.g., certain agitator types) and implemented for process optimization.

3.2. Crystal Regeneration Kinetics. Surface integration kinetics of crystal regeneration were explored for the PCM–ethanol system, within a supersaturation (S) range of 1.027–1.237 and a temperature range of 14–30 °C. The study started with the detection of the surface integration-limited growth regime. Given that the mass transfer rate has a linear dependence on concentration whereas the surface integration rate increases exponentially ($1 \leq g \leq 2$) with it, the rate regime was investigated for the highest supersaturation under study ($S = 1.237$). Thus, the detected agitation rate for a surface integration-limited regime would be valid for the whole supersaturation range. The results of this study are visualized in Figure 3a. As seen, the growth rate of (010) surface increases from $7.6 \pm 0.4 \mu\text{m}/\text{min}$ without agitation to $18.3 \pm 1.8 \mu\text{m}/\text{min}$ at 125 rpm and to $27.1 \pm 1.1 \mu\text{m}/\text{min}$ at 250 rpm. When the agitation rate increased further up to 625 rpm, the

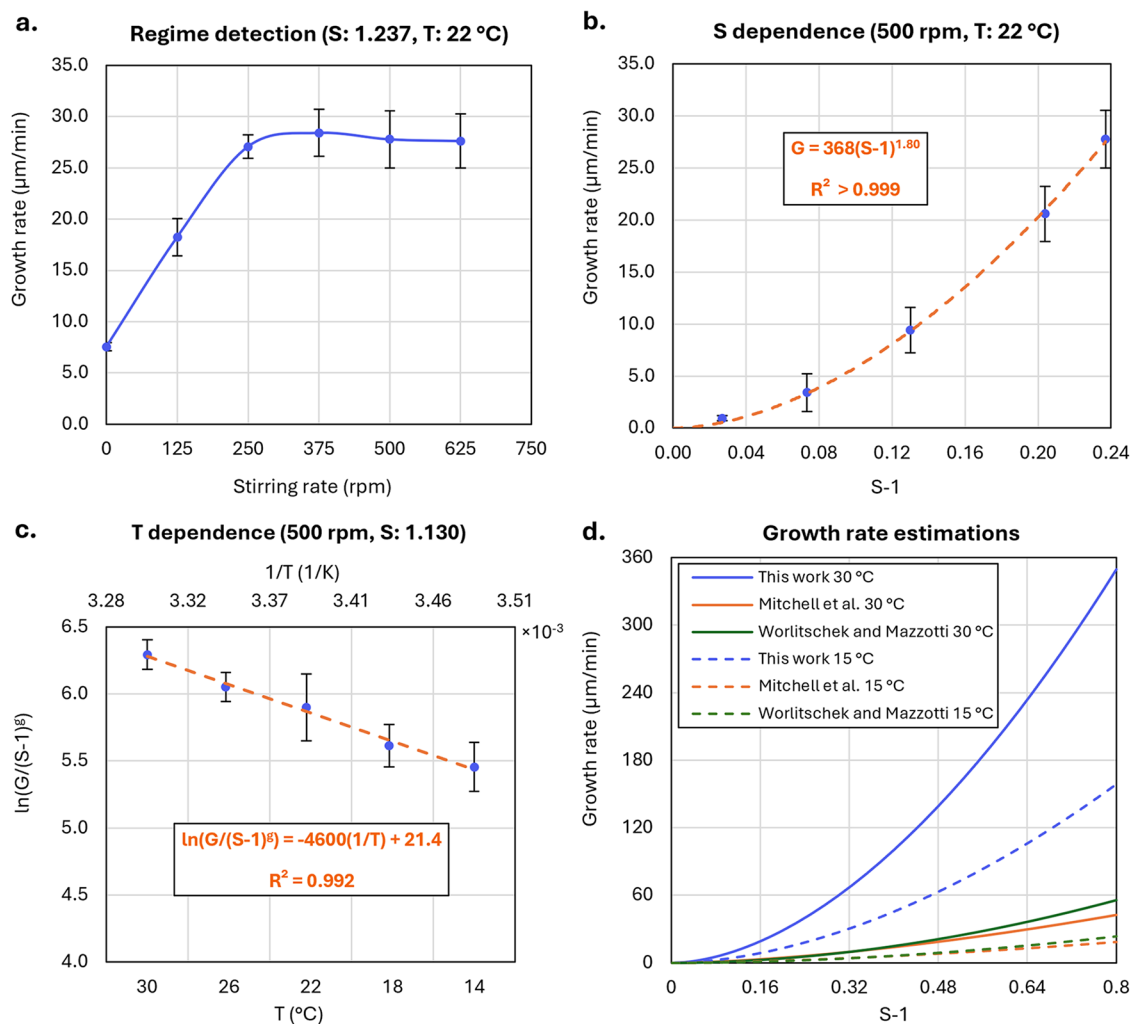


Figure 3. (a) Growth rate of the exposed (010) surface by stirring rate at 22 °C and $S = 1.237$ ($n = 3$). (b) Growth rate of the exposed (010) surface by the degree of supersaturation at 22 °C and a stirring rate of 500 rpm ($n = 3$). (c) Arrhenius plot for the growth rate of the exposed (010) surface at $S = 1.130$ and a stirring rate of 500 rpm ($n = 3$). (d) Estimated growth rates for paracetamol in ethanol by supersaturation at 30 and 15 °C for crystal regeneration based on results of the presented work, for unbroken crystal growth based on Mitchell et al.,¹⁹ and for unbroken crystal growth based on Worlitschek and Mazzotti.²⁶

growth rate did not meaningfully change. Hence, under these conditions, agitation rates of 250 rpm and higher result in a surface integration-limited regime, with the demarcation point indicated to be within 125 and 250 rpm. It was therefore decided to study the supersaturation and temperature dependencies at 500 rpm agitation rate, ensuring operation in the surface integration-limited regime.

Subsequently, the effect of supersaturation was quantified. Kinetic measurements were conducted at 22 °C and a stirring rate of 500 rpm at S values of 1.027, 1.073, 1.130, 1.204, and 1.237. As seen in Figure 3b, the growth rate of the (010) surface increased with an exponent of 1.80 ($R^2 > 0.999$) depending on the degree of supersaturation. The outcome is solidified by the fact that the exponent g is expected to be in the range of ($1 \leq g \leq 2$), and 1.80 falls within this range.

Finally, the effect of the temperature was studied. Isothermal crystallization tests were performed at a stirring rate of 500 rpm and the median studied S of 1.130. Experiments were conducted at temperatures ranging from 14 to 30 °C with 4 °C increments. After quantifying the exponent g , rearranging eq 1, surface growth rates were adjusted to $\ln\left(\frac{G}{(S-1)^{1.80}}\right)$ terms and

plotted against inverse of absolute temperature (K^{-1}) to determine the activation energy and the pre-exponential factor (Figure 3c). Consequently, the activation energy and the pre-exponential factor were, respectively, calculated as 38.2 kJ/mol (Figure 3c, $-\text{slope} \times R$) and $2.05 \times 10^9 \mu\text{m}/\text{min}$ (Figure 3c, $e^{\text{intercept}}$). The pre-exponential factor of $2.05 \times 10^9 \mu\text{m}/\text{min}$ is equivalent to 34.1 m/s in SI units, as conventionally reported. Thus, the surface integration kinetics for the regeneration of PCM in ethanol are formulated in eq 2:

$$G = A_0 \exp\left(-\frac{E_a}{RT}\right)(S-1)^g$$

$$= (34.1 \text{ m/s}) \exp\left(-\frac{38.2 \text{ kJ/mol}}{RT}\right)(S-1)^{1.80} \quad (2)$$

This study showcases the determination of surface growth kinetics for post-breakage regeneration for the first time. Thus, the methodology can be likewise used to determine kinetic equations for various systems that show regenerative growth.

Considering the outcomes, the activation energy tends to be around 10–20 kJ/mol for mass transfer-limited growth

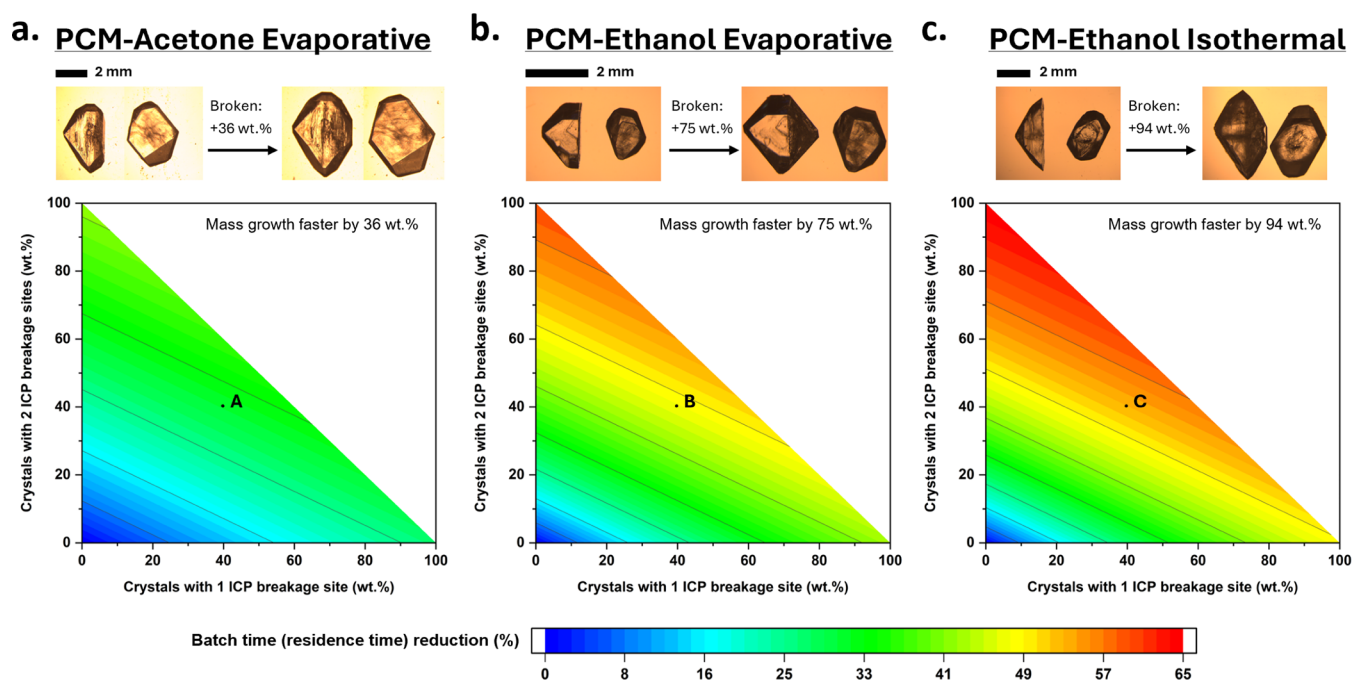


Figure 4. Visual developments of broken and unbroken crystal pairs and projected crystallization process time reductions by weight fraction of one-sided and two-sided regenerating seeds for a) paracetamol–acetone evaporative crystallization at room temperature ($n = 4$), b) paracetamol–ethanol evaporative crystallization at room temperature ($n = 3$), and c) paracetamol–ethanol isothermal crystallization at 15 °C ($n = 9$). Internal cleavage plane is abbreviated as ICP.

regimes, while the expected range is 40–60 kJ/mol for surface integration-limited cases.²⁰ Thus, the detected activation energy of 38.2 kJ/mol indicates a relatively small activation energy for the regenerative growth of PCM in ethanol, given the surface integration-limited operation. For PCM growth in ethanol without breakage, in the literature, A_0 values of 9.979 m/s¹⁹ and 21 m/s,²⁶ E_a values of 40.56 kJ/mol¹⁹ and 41.6 kJ/mol,²⁶ and g values of 1.602¹⁹ and 1.9²⁶ were reported. Differences in crystal growth rates estimated by these kinetic equations are plotted in Figure 3d, visualizing the significantly faster rate of regeneration compared to regular growth across different temperatures and supersaturations. The difference in growth rates is reflected by a higher A_0 and a lower E_a for regeneration, whereas the detected g is within the reported values for regular growth. The increased A_0 is linked to the significant instability of the newly exposed (010) facet, intrinsically increasing the frequency of solute attachment events.⁹ The lower E_a is attributed to the more nonpolar nature of the (010) facet compared to the facets on the exterior of unbroken paracetamol crystals,¹⁴ reducing the desolvation energy barrier for incoming solute molecules.²⁷

In addition to estimating surface growth rates based on temperature and concentration, the detected kinetic formulation can also be useful for implementation into crystallization process models (as detailed in the Introduction section) to enable accurate process modeling and optimization.

3.3. Impact of Crystal Regeneration on Mass Growth. Inspired by the faster growth trends observed in regeneration compared to regular growth, the potential of regeneration to enhance industrial crystallization processes was explored via translating its benefits into mass growth. In this study, the conventional single-crystal experiment technique was modified to design “two-crystal experiments,” in which two crystals (one broken and one unbroken) with similar initial masses were grown in the same crystallization setup to comparatively

analyze their growth. Three cases were studied: PCM–acetone regeneration with evaporative crystallization, PCM–ethanol regeneration with evaporative crystallization, and PCM–ethanol regeneration with isothermal crystallization.

The outcomes of the two-crystal experiments for the respective crystallization cases are provided in Figure 4. During regeneration, compared to their unbroken counterparts, the broken crystals grew faster by 36 ± 8 wt % for evaporative crystallization in acetone, by 75 ± 19 wt % for evaporative crystallization in ethanol, and by 94 ± 34 wt % for isothermal crystallization in ethanol. Mass growth measurements from the studied cases are also provided in Table S5. Therefore, regenerative growth has been demonstrated to enhance mass production rates in processes. Moreover, the findings of relatively higher increases for the cases with ethanol compared to acetone are in line with the literature, since PCM regeneration has been reported to proceed at faster rates in ethanol compared to acetone.¹⁶

3.4. Scale-up Potential of Crystal Regeneration. The potential for regeneration in terms of faster mass growth has been demonstrated in this work, in addition to the findings that simultaneous regeneration of multiple crystal surfaces is feasible. These findings motivated the exploration of regeneration’s scale-up potential to optimize crystallization processes. Accordingly, faster mass growth rates can be harnessed to reduce process batch times (or residence times, considering continuous processing), thus improving productivity as well as resource efficiency.

Equation 3 is formulated for the scale-up projections, with the term α describing the additional crystal growth rate induced by regeneration. Accordingly, the process time reductions are based on the time it takes for 100 mass units of crystals to grow an additional 100 mass units. Thus, seeds with one exposed breakage side and two exposed breakage sides are adjusted with additional growth rates of α and 2α ,

respectively. Based on our findings, α is given a value of +36 for PCM–acetone evaporative crystallization, +75 for PCM–ethanol evaporative crystallization, and +94 for PCM–ethanol isothermal crystallization.

Process time reduction (%)

$$\cong 100(1 - 100/[100(\text{wt \%}_{\text{Unbroken}}) + (100 + \alpha)(\text{wt \%}_{\text{One-sided}}) + (100 + 2\alpha)(\text{wt \%}_{\text{Two-sided}})]) \quad (3)$$

The projected impact of regeneration on multi-crystal processes is visualized in Figure 4a, b, and c for the respective crystallization cases. The figures describe corresponding process time reductions based on the weight fractions of one-sided and two-sided regenerating seeds. Given that the overall fraction of crystals adds up to 100 wt %, the graphs have a pyramidal shape. For instance, if a system contains 40 wt % crystals with one breakage site, there can be up to 60 wt % crystals with two breakage sites, as the 60 wt % also includes unbroken crystals in that case. As an example, the condition of 40 wt % crystals with one breakage site and 40 wt % crystals with two breakage sites (therefore, the remaining 20 wt % being unbroken) is marked with points A, B, and C in the respective graphs. For this condition, as shown, the respective process time reductions are estimated as 30%, 47%, and 53%. Therefore, overall, harnessing solely one-sided regeneration is estimated to reduce processing times by up to 26%, 43%, and 48% for PCM–acetone evaporative crystallization, PCM–ethanol evaporative crystallization, and PCM–ethanol isothermal crystallization, respectively. When two-sided regenerating crystals are also involved, the respective processing time reduction potentials are estimated to be up to 42%, 60%, and 65%. Although these estimations are not highly detailed and are based on single-crystal studies that differ considerably from large-scale units in aspects such as hydrodynamics, they demonstrate the sizable potential of regeneration to improve industrial processes. To actualize this potential, the effect of different breakage inducers (e.g., agitator types) on the resulting breakage mechanism (i.e., the fraction of crystals which are broken to expose their internal cleavage plane) in multi-crystal systems can be investigated as a future study.

4. CONCLUSION

In this study, regeneration of crystals with multiple cleavage sites was demonstrated for the first time. PCM crystals, cleaved parallelly from two sides, were grown back into their pre-breakage shape. The overall growth rate of the regenerating dimension was around twice as fast for two-sided regeneration compared to one-sided regeneration, indicating that regenerating surfaces do not inhibit the growth of each other. The growth kinetics of PCM regeneration in ethanol were studied in a surface integration-limited regime, yielding the equation $(34.1 \text{ ms}^{-1}) \exp(-38.2 \text{ kJmol}^{-1}/RT) (S - 1)^{1.80}$. With a higher pre-exponential factor and lower activation energy, regenerative growth is estimated to proceed faster than the growth of unbroken crystals across different temperatures and supersaturations. The kinetic equation can also be implemented into crystallization process models, improving accuracy and capability for cases involving crystal breakage. A modified “two-crystal” setup was designed to monitor the growth of a broken and an unbroken crystal with a similar initial mass in the same crystallization dish. Two-crystal experiments were

conducted for PCM–acetone evaporative crystallization at room temperature, PCM–ethanol evaporative crystallization at room temperature, and PCM–ethanol isothermal crystallization at 1.1 supersaturation. In the respective cases, broken crystals grew faster by $36 \pm 8 \text{ wt \%}$, $75 \pm 19 \text{ wt \%}$, and $94 \pm 34 \text{ wt \%}$. Based on these outcomes, the effect of regeneration on mass production was projected to multi-crystal systems, and regeneration was estimated to reduce crystallization processing times by up to 42%, 60%, and 65%, respectively. This study reports the feasibility of crystal regeneration for particles with multiple breakage sites, a methodology to formulate regenerative growth kinetics and its implications, the translation of regeneration to improve mass production rates, and its potential to enhance the productivity and efficiency of crystallization processes.

5. HIGHLIGHTS

- Crystal regeneration is demonstrated for crystals with multiple breakage sites.
- Growth kinetics for paracetamol regeneration in ethanol followed $(34.1 \text{ ms}^{-1}) \exp(-38.2 \text{ kJmol}^{-1}/RT) (S - 1)^{1.80}$.
- Regeneration significantly improves crystal mass growth rates and can remarkably reduce processing times.

■ ASSOCIATED CONTENT

Supporting Information

- The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.cgd.5c00806>.

Details of the evaporative crystallization setup (Figure S1); Details of the isothermal crystallization setup (Figure S2); Solubility curve for paracetamol in ethanol (Figure S3); Temperature and supersaturation conditions for kinetic studies (Table S4); Mass measurements from the two-crystal experimental studies (Table S5) (PDF)

Video of two-sided crystal regeneration of paracetamol in ethanol (Movie S1) (MPG)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

D.E. acknowledges the Department of Chemical Engineering at Imperial College London for a PhD Departmental Scholarship, as well as BASF (PA6590) for its funding. The authors also extend their gratitude to all their colleagues in the Heng Research Group for insightful discussions, with special thanks to Hamish Mitchell for developing the Python protocol for the integration of the robotic arm in the evaporative crystallization experiments.

■ REFERENCES

- (1) *Crystallization: basic Concepts and Industrial Applications*; Beckmann, W. Eds.; Wiley-VCH Verlag: Weinheim, Germany, 2013.
- (2) Yang, Y.; Pal, K.; Koswara, A.; Sun, Q.; Zhang, Y.; Quon, J.; McKeown, R.; Goss, C.; Nagy, Z. K. Application of Feedback Control and in Situ Milling to Improve Particle Size and Shape in the Crystallization of a Slow Growing Needle-like Active Pharmaceutical Ingredient. *Int. J. Pharm.* **2017**, 533 (1), 49–61.
- (3) Zhang, F.; Shan, B.; Wang, Y.; Zhu, Z.; Yu, Z.-Q.; Ma, C. Y. Progress and Opportunities for Utilizing Seeding Techniques in Crystallization Processes. *Org. Process Res. Dev.* **2021**, 25 (7), 1496–1511.
- (4) Chen, W.; Li, X.; Guo, M.; Link, F. J.; Ramli, S. S.; Ouyang, J.; Rosbottom, I.; Heng, J. Y. Y. Biopurification of Monoclonal Antibody (MAb) through Crystallisation. *Sep. Purif. Technol.* **2021**, 263, 118358.
- (5) Etit, D.; Ögmundarson, Ó.; Zhang, J.; Krogh Jensen, M.; Sukumara, S. Early-Stage Economic and Environmental Impact Assessment for Optimized Bioprocess Development: Monoterpenoid Indole Alkaloids. *Bioresour. Technol.* **2024**, 391, 130005.
- (6) *Engineering Crystallography: From Molecule to Crystal to Functional Form*; Roberts, K. J.; Docherty, R.; Tamura, R. Eds.; Springer: Dordrecht, The Netherlands, 2017.
- (7) *Handbook of Industrial Crystallization*; Myerson, A. S.; Erdemir, D.; Lee, A. Y. Eds.; 3rd ed; Cambridge University Press: Cambridge, United Kingdom, 2019.
- (8) Bosetti, L.; Mazzotti, M. Population Balance Modeling of Growth and Secondary Nucleation by Attrition and Ripening. *Cryst. Growth Des.* **2020**, 20 (1), 307–319.
- (9) Bade, I.; Verma, V.; Rosbottom, I.; Heng, J. Y. Y. Crystal Regeneration - a Unique Growth Phenomenon Observed in Organic Crystals Post Breakage. *Mater. Horiz.* **2023**, 10, 1425–1430.
- (10) Szilágyi, B.; Lakatos, B. G. Model-Based Analysis of Stirred Cooling Crystallizer of High Aspect Ratio Crystals with Linear and Nonlinear Breakage. *Comput. Chem. Eng.* **2017**, 98, 180–196.
- (11) Bao, Y.; Zhang, J.; Yin, Q.; Wang, J. Determination of Growth and Breakage Kinetics of L-Threonine Crystals. *J. Cryst. Growth* **2006**, 289 (1), 317–323.
- (12) Reeves, S. M.; Hill, P. J. Mechanisms Influencing Crystal Breakage Experiments in Stirred Vessels. *Cryst. Growth Des.* **2012**, 12 (6), 2748–2758.
- (13) Randolph, A. D. Effect Of Crystal Breakage On Crystal Size Distribution In A Mixed Suspension Crystallizer. *Ind. Eng. Chem. Fundam.* **1969**, 8 (1), 58–63.
- (14) Heng, J. Y. Y.; Bismarck, A.; Lee, A. F.; Wilson, K.; Williams, D. R. Anisotropic Surface Energetics and Wettability of Macroscopic Form I Paracetamol Crystals. *Langmuir* **2006**, 22 (6), 2760–2769.
- (15) Sun, C. C.; Kiang, Y. H. On the Identification of Slip Planes in Organic Crystals Based on Attachment Energy Calculation. *J. Pharm. Sci.* **2008**, 97 (8), 3456–3461.
- (16) Bade, I.; Etit, D.; Heng, J. Y. Y. *The Effect of Solvents on Crystal Regeneration*. In Peer Review.
- (17) Jiang, L.; Chen, W.; Zhou, L.; Xu, L.; He, F.; Heng, J. Y. Y.; Shehzad, H.; Ouyang, J. Uncovering Crystal Growth and Regeneration Mechanism to Control Crystal Morphology: The Case Study of Aceclofenac. *Sep. Purif. Technol.* **2024**, 347, 127577.
- (18) Aisling, L.; Åke, R. Crystal Growth of Single Salicylamide Crystals. *Cryst. Growth Des.* **2019**, 19 (12), 7230–7239.
- (19) Mitchell, N. A.; Óciardhá, C. T.; Frawley, P. J. Estimation of the Growth Kinetics for the Cooling Crystallisation of Paracetamol and Ethanol Solutions. *J. Cryst. Growth* **2011**, 328 (1), 39–49.
- (20) Mitchell, H. M.; Jovannus, D.; Rosbottom, I.; Link, F. J.; Mitchell, N. A.; Heng, J. Y. Y. Process Modelling of Protein Crystallisation: A Case Study of Lysozyme. *Chem. Eng. Res. Des.* **2023**, 192, 268–279.
- (21) Sitapure, N.; sang-Il Kwon, J. Introducing Hybrid Modeling with Time-Series-Transformers: A Comparative Study of Series and Parallel Approach in Batch Crystallization. *Ind. Eng. Chem. Res.* **2023**, 62 (49), 21278–21291.
- (22) Cruz, P.; Rocha, F.; Ferreira, A. Crystallization of Paracetamol from Mixtures of Ethanol and Water in a Planar Oscillatory Flow Crystallizer: Effect of the Oscillation Conditions on the Crystal Growth Kinetics. *CrystEngcomm* **2021**, 23 (47), 8301–8314.
- (23) Soto, R.; Verma, V.; Lynch, A.; Hodnett, B. K.; Rasmuson, Å. C. Crystal Growth Kinetics of Pharmaceutical Compounds. *Cryst. Growth Des.* **2020**, 20 (12), 7626–7639.
- (24) Zhang, Y.; Zhao, S.; Ma, Y.; Xu, C.; Hu, X.; Li, C.; Tang, W.; Gong, J. Mathematical Modeling and Experimental Validation of a Novel Multi-Stage Cascade Batch Reactive-Heating Crystallization in MSMPR Crystallizers. *Chem. Eng. Sci.* **2025**, 304, 121059.
- (25) Zheng, Y.; Wang, X.; Wu, Z. Machine Learning Modeling and Predictive Control of the Batch Crystallization Process. *Ind. Eng. Chem. Res.* **2022**, 61 (16), 5578–5592.
- (26) Worlitschek, J.; Mazzotti, M. Model-Based Optimization of Particle Size Distribution in Batch-Cooling Crystallization of Paracetamol. *Cryst. Growth Des.* **2004**, 4 (5), 891–903.
- (27) Turner, T. D.; Dawson, N.; Edwards, M.; Pickering, J. H.; Hammond, R. B.; Docherty, R.; Roberts, K. J. A Digital Mechanistic Workflow for Predicting Solvent-Mediated Crystal Morphology: The α and β Forms of L-Glutamic Acid. *Cryst. Growth Des.* **2022**, 22 (5), 3042–3059.



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