Extended Abstract of PhD Thesis: Optimizing the Crystallization of Pharmaceutical Compounds Using Additives

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1 Summary

The distinguishing feature of crystallization is the formation of products that are both highly pure and in the solid state. However, purity is not the only important aspect in crystallization, i.e., it is a well-known fact that the quality of a crystalline product also depends on its size and shape distribution. These properties are influenced by many characteristics of a crystallization process, such as the supersaturation, the temperature and the chemical environment in which the crystals are formed. The main goal of my PhD thesis was to understand how a different chemical environment changes the crystal size and shape and how this chemical environment can be altered such that a desired crystal size and shape distribution is obtained from a crystallization process.

While this work focuses on crystallization processes from solution and more specifically on batch cooling crystallization, the findings and techniques could be generalized to continuous manufacturing processes or to other types of crystallization processes, such as melt crystallization. The influence of solvents and additional shape modifiers (so called additives) on the crystal morphology and the particle size distribution was investigated using a widespread array of techniques and on various size scales (from the molecular level to the process level) which led to the following results:

- A simple screening procedure was developed that allows finding combinations of solvents and additives altering crystal morphology successfully. This screening procedure was carried out for the model compound urea and generalized to other compounds by defining screening heuristics.
- The interaction of additive molecules with crystal surfaces was investigated on a molecular level using molecular dynamics simulations on the model system urea (crystal), water (solvent) and biuret and acetone (additive molecules). This study yielded in depth insight on the mechanisms of crystal growth and how the presence of the additive molecules changed the evolution of crystal growth of urea. The results of this investigation were found to be consistent with the results of the screening procedure mentioned above.
- Nucleation and growth kinetics in the presence of additives were estimated from experimental data and a population balance equation model for the small molecular pharmaceutical Ibuprofen in the presence of the polymeric additive Pluronic F127 in solvent mixtures of ethanol and water.

Another focal point of my PhD thesis was the use of models to describe crystallization processes over multiple time- and size-scales, i.e., from the short-term stochastic phenomenon of nucleation, to the growth of crystals, to Ostwald ripening processes, which typically progress slowly. To this aim, a comparison between two types of models was carried out: models based on classical population balance equations and models based on the kinetic rate equation. The results of the two models were compared in a wide range of operating conditions while considering nucleation, crystal growth and Ostwald ripening simultaneously. The advantages and disadvantages of the two types of models were thoroughly assessed.

In the following the key results of my PhD thesis [1] will be briefly summarized in Sections 2–5.

2 Development of a screening procedure for additives and solvents

The factors influencing the outcome of a crystallization process in terms of crystal structure and crystal morphology can be grouped into two categories: chemical composition of the solution from which particles are formed and the process operating conditions. While the former includes the effect of solvents and additives, the latter includes the effects of

supersaturation, temperature and the hydrodynamics of the crystallizer (e.g., stirring rate, mixing conditions). This work focuses on the latter set of influence factors. Despite the many recent advances made in the prediction, rationalization and modeling of crystal morphology, an experimental investigation is - at least with standard tools and methods – often easier to apply and faster than its predictive alternatives.

These properties already made screening techniques a standard procedure for the discovery of solid state forms (polymorphs, solvates, etc.) in the pharmaceutical industry, as recently reviewed by Aaltonen et al. [2]. Despite this widespread use of HTS to find solid state forms, little attention has been paid to the fact that the existing HTS equipment can additionally be used for the screening of different crystal morphologies. The use of additives to change the morphology of product crystals during HTS appears to be a promising extension, which could be performed concurrently with the solid state form screening that is already in place. Therefore, a general screening procedure for additives and solvents was formulated, taking both the solid form and crystal morphology into account. To this end, a series of batch cooling crystallization experiments with various combinations of solvents and additives was performed for the model substance urea. Batch cooling crystallization was chosen as the method to generate supersaturation and form crystals because of its relatively simple implementation and its high reproducibility. Furthermore, the generation of a whole population of crystals guarantees a more robust investigation of the resulting crystal shapes than single crystal experiments.

After carrying out the screening procedure (details in Chapter 2 of the PhD thesis), the product particles were characterized by shape and solid state form (solvatism, polymorphism, ...) using light microscopy and differential scanning calorimetry and X-ray diffraction analysis, respectively. This yielded several "hits" in terms of additive and solvent combinations that allowed to reduce the aspect ratio of urea crystals in a consistent manner. In particular, the presence of amide groups in the additive molecules and polar solvents was found to yield the best results. For the sake of brevity, the results of this screening procedure are not repeated here and the interested reader is referred to Chapter 2 of my PhD thesis. Subsequently, the results were interpreted with a view on the surface chemistry of different facets of urea crystals and the molecular structure of the additive molecules. To generalize the screening procedure heuristics were defined that will allow to apply the screening procedure to any system under investigation.

3 Uncovering Molecular Details of Urea Crystal Growth in the Presence of Additives

While a screening procedure can produce useful results based on direct inference from experimental data, it is in no way predictive and essentially relies on educated guesses what combination of additives and solvents might be successfully used to improve the shape of crystals (the alternative is an exhaustive screening of many possible combinations). Given the steady increase in computational power and the ever continuing development of appropriate simulation algorithms and methods for enhanced sampling, molecular simulations have emerged as a viable approach to build a comprehensive picture of the molecular phenomena involved in crystallization processes [3].

In my PhD thesis and the corresponding publication [4] this was illustrated by performing standard and enhanced sampling molecular dynamics simulations of the crystal growth of urea and its interaction with different additives. More specifically a full atomistic description of the surface dynamics and thermodynamics of the fast-growing {001} and the slow-growing {110} faces was provided. The crystal growth of urea from water and methanol solutions was recently modeled by Piana et al. who used a combination of Molecular Dynamics (MD) and kinetic Monte Carlo (kMC) simulations, which enabled an accurate description of the shape of a growing crystal [5, 6]. However, the accuracy of this approach relied on the delicate extraction of appropriate rates for the kMC simulations from the MD simulations, which typically involves some tuning. Contrary to this, a direct atomistic description of crystal growth mechanisms in the presence of additives using molecular dynamics simulations was sought in my PhD thesis. Such a molecular description of the effects of additives on crystal growth is a challenging topic that has seldom been tackled in the literature; with the studies reported typically only exploring the very limited time scale of a few nanoseconds [7–9]. However, it is well established that simulations in the hundreds of nanoseconds are needed to properly observe the (relatively) rare events that characterize the crystal surface dynamics, such as the formation of 2D nuclei on a crystal surface or the adsorption/desorption of additive molecules.

As an alternative to running exceedingly long simulations, one can enhance the occurrence of such rare events through the use of enhanced sampling methods. In this work well tempered (WT) metadynamics simulations were used to sample adsorption and desorption events, thus allowing for a quantitative estimation of the associated free energies for both urea and additives on individual faces of urea crystals. WT metadynamics is a state-of-the-art enhanced sampling MD technique [10], which enables an efficient sampling of rare events and a convergent estimation of free energies.

In order to study the face-dependent growth dynamics (through standard MD) and to estimate the free energy of adsorption (through WT metadynamics), slabs of crystalline urea exposing a single face to a solution consisting of urea, water and additive molecules were prepared. Due to periodic boundary conditions on each side of the box such a simulation can be imagined as the simulation of an infinite plane exposing a specific facet (either a fast-growing {001} or a slow-growing {110} facet) on both sides of the slab.
From a standard MD simulation the evolution of the number of crystalline and the number of liquid molecules can be tracked over time (details are reported in Chapter 3 of my PhD thesis and the respective publication [4]), which is shown for two exemplary simulations in Figure 1. The increase in crystalline molecules, as well as the total number of urea molecules in solution are shown. In both simulations crystal growth depletes the number of urea molecules in the liquid phase leading to a stationary state where no net growth is observed. However, the evolution up to this stationary state is entirely different for the {001} and the {110} face: For the fast-growing {001} face a continuous profile is observed, while the simulation of the slow-growing {110} face exhibits a stepwise profile. This can be interpreted as the signature of two different growth mechanisms, i.e., rough growth for the fast-growing and 2D nucleation for the slow-growing face. In the case of crystal growth by 2D nucleation the formation of a nucleus on the otherwise macroscopically flat crystal surface is the rate-limiting step. After the formation of such a 2D nucleus the growth proceeds quickly until a complete layer of the crystal is completed, which causes this two-step process to start anew. This finding was subsequently confirmed by analyzing the growth behavior of individual crystal layers evolving during the simulation, i.e., it was found that in the case of the fast-growing facet multiple crystal layers are growing at once, which makes the crystal macroscopically rough, while on the slow-growing facet only one crystal layer is growing at a time. Additionally, the presence of different growth mechanisms on these two faces is corroborated by atomic force microscopy images reported in the literature [5].

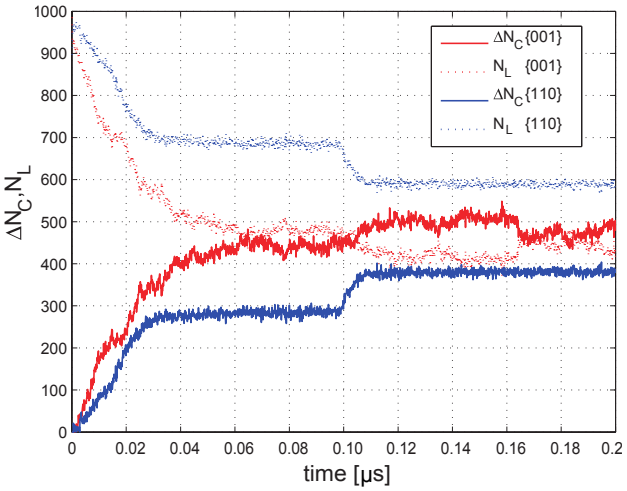


Figure 1: MD simulations of {001} and {110} urea facets in water (red and blue lines, respectively): evolution of the urea molecules incorporated into the crystal (solid lines) and of the number of urea molecules in solution (dashed lines).

Table 1: Free energies of adsorption and $S_{\{001\},\{110\}}$ for acetone, biuret and urea.

molecule	$\Delta G_{\mathrm{ads},\{001\}}$ [kcal/mol]	$\Delta G_{\mathrm{ads},\{110\}}$ [kcal/mol]	$S_{\{001\},\{110\}}$ [-]
acetone	-0.66 ± 0.38	-1.47 ± 0.45	0.26
biuret	-4.55 ± 1.02	-2.48 ± 0.43	32.44
urea	-3.22 ± 0.83	-1.7 ± 0.39	12.98

In order to investigate the effect of additives on crystal growth, their adsorption behavior on the afore-mentioned crystal surfaces was investigated. To this end, WT metadynamics simulations were performed with the goal of extracting the free energy of adsorption from them. These facet-dependent energies were determined for three types of molecules: for the urea molecule itself, for biuret and for acetone, with the two foreign molecules representing an effective and an ineffective additive (based on their ability to influence crystal growth such that compact urea crystals are obtained).

The obtained free energies of adsorption are reported in Table 1. This data was rationalized using the face-selectivity, $S_{\{001\},\{110\}}$, defined as the ratio of the adsorption equilibrium constants which is reported in the same table. The face-selectivity allows to quantify the preferential interaction of a

given molecule between two specific crystal faces. In particular the values of ΔG_{ads} and $S_{\{001\},\{110\}}$ show that the interaction of the biuret molecule with the urea crystal faces is much stronger than that of the acetone molecule and also that the selectivity of the biuret for the fast {001} face is remarkable. This evidence allows us to demonstrate the selective adsorption of biuret molecules on the {001} faces of the urea crystal and thus to rationalize why biuret is such an excellent growth inhibitor for these faces: biuret has a higher probability to interact with the fast face than with the slow one and at the same time has a free energy of adsorption comparable to urea itself on the same face. These two properties are caused by the capability of biuret to fill a lattice site on the {001} faces nearly perfectly, which was investigated in detail in the corresponding publication [4]. It was discovered that the biuret molecule adsorbs in five different preferential configurations on the {001} faces, each of them different in distance from the solid/liquid interface and its orientation.

The study of the paradigmatic case of urea on a molecular levels allowed to identify some key ingredients that could be used in the design of additives capable of avoiding the formation of needle-shaped crystals. High affinity and high selectivity for the fast growing face of a needle crystal emerged as crucial for a potential shape-affecting effect. These features are inherently related to the structure of the additives, that should exhibit moieties capable of reversibly bind the lattice sites exposed on the fast growing crystal face thus limiting its growth rate.

4 Characterization of the nucleation and growth rates of Ibuprofen crystals in the presence of the polymeric additive Pluronic F127

In order to investigate the effect of additives on the crystallization kinetics of a whole population of crystals in a quantitative manner and under realistic conditions present in a batch crystallizer a study on the crystallization kinetics of the pharmaceutical Ibuprofen in the presence of the polymeric additive Pluronic F127 (PF127) was conducted during my PhD thesis. While less specific than "tailor-made" additives, polymeric additives have two distinct advantages: they are very unlikely to be incorporated into the crystal lattice of a compound since they differ from the solute molecules both structurally and in size and they are often already approved as excipients in the formulation of pharmaceuticals, so that their use in a manufacturing process could be accomplished without overcoming major regulatory hurdles.

Early studies theorized that polymers adsorb on the crystal faces and thus inhibit or slow down crystal growth. It was for example reported that the polymers form net-like structures on the crystal surfaces during crystal growth.[11] The influence of polymeric additives on the nucleation rate was also investigated and their retarding effect on the nucleation was explained by interactions of the polymer molecules with the solute molecules through hydrogen bonding, therefore hindering their precipitation.[12] Polymeric additives also influence viscosity, thereby possibly introducing mass transfer limitations to crystal growth and nucleation. However, in most of the studies published on the subject the phenomena of nucleation and crystal growth are not separated, thus making it rather difficult to directly infer the mechanism of action for the additive investigated, so that the authors frequently resorted to qualitative observations rather than a quantitative investigation of the effect.

The crystallization kinetics of Ibuprofen in the presence of Pluronic F127 were quantitatively investigated in my PhD thesis using a two-step procedure: first, the crystal growth kinetics are independently investigated by designing seeded isothermal batch experiments at moderate supersaturation levels and a high seed loading. This precludes the occurrence of a large number of nucleation events, so that the consumption of solute from the liquid phase can be entirely attributed to the growth of seed crystals, hence effectively decoupling the phenomena of nucleation and crystal growth. Second, unseeded cooling crystallization experiments are conducted from which the primary (heterogeneous) and secondary nucleation rate can be quantitatively estimated.

Focusing on crystal growth initially, a number of seeded isothermal desupersaturation experiments was conducted for which the evolution of the solute concentration in the liquid phase was monitored using in-situ attenuated total reflectance infrared spectroscopy (ATR-FTIR) coupled with an appropriate calibration model (details reported in Chapter 4 of my PhD thesis and in the corresponding publication [13]). The experimental dataset covers different supersaturation levels, temperatures and concentrations of the additive molecule. A process model based on the population balance equation and constitutive equations for the growth rate equation and the solubility was then fitted to the experimental data by minimizing the difference between the

modeled and the experimental concentration profiles. Since there is a variety of growth rate models described in the literature, a model identification step was performed by comparing the goodness of fit of each of these models to the experimental data. It was concluded that the growth rate mechanism of Ibuprofen in the presence of Pluronic F127 in the supersaturation and temperature range investigated follows a birth and spread (i.e., 2D nucleation) mechanism. The so-obtained growth rate is shown for different additive concentrations in Figure 2. It is worth making two remarks. First, the net effect of the additive's presence is the decrease of the growth rate. This is due to the adsorption of the additive, which hinders growth. Secondly, such growth rate decrease could be due to two mechanisms caused by the presence of the additive, namely either hindrance of surface diffusion or hindrance of solute incorporation in the kink sites blocked by the additive; these two mechanisms might coexist. While analyzing the latter would require a different type of experimental investigation beyond the scope of this work, the former mechanism can be discussed by considering its likely dependence on the viscosity of the environment in a similar way as the diffusivity in the solution. The diffusion coefficient is predicted by the Stokes-Einstein equation to be inversely proportional to the viscosity in solution. By measuring the viscosity of ethanol/water mixtures containing different concentrations of PF127, it was found that the presence of PF127 in solution increases the viscosity and therefore decreases the diffusion coefficient (and thereby also decreases the surface diffusion coefficient). Therefore, the conclusion was drawn that the difference in growth rate shown in Figure 2 stems mainly from a reduced surface diffusion coefficient, which was in turn interpreted as an effect of the adsorption of PF127 molecules on the surface of the crystals, thereby hindering the diffusion of the solute molecules on the crystal surface. The nature of this adsorption seems to be isotropic, since comparing the final crystals obtained for runs carried out with different concentrations of PF127 did not show any appreciable differences in crystal habit. While this might not be a proof for the isotropicity of the adsorption between the PF127 molecules and the crystal surfaces, it is at least an indication that the adsorption cannot be strongly anisotropic.

After the determination of the crystal growth rate, the nucleation kinetics of Ibuprofen in the presence of PF127 were investigated using unseeded batch cooling crystallization experiments. To this end, a set of experiments using different cooling rates (thereby

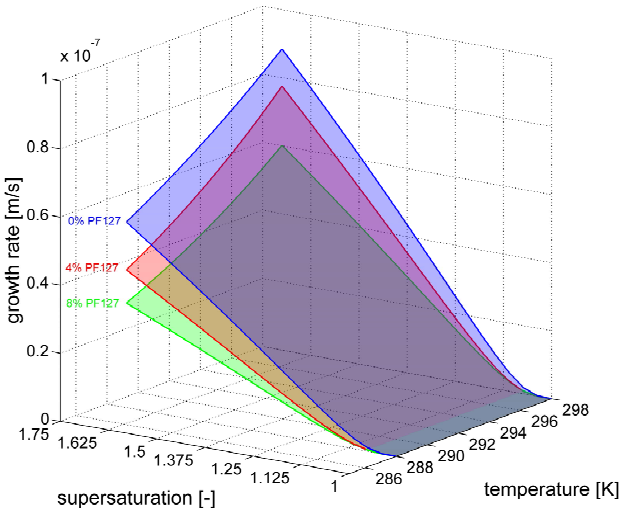
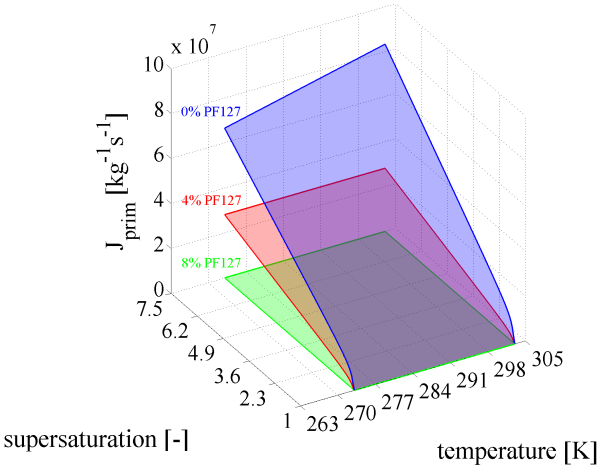


Figure 2: Growth rate of Ibuprofen crystals in dependence of supersaturation and temperature for concentrations of 0, 0.04 and 0.08 kg PF127/$kg_{solvent}$.

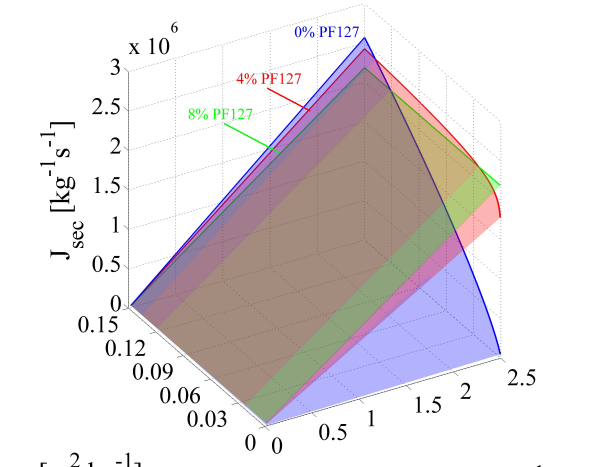
also altering the average supersaturation level) and additive concentrations was performed. Experimental data was again recorded in the form of concentration profiles measured by ATR-FTIR. Additionally, the particle size distribution at the end of the process was characterized using a Coulter Multisizer. Employing two measurement devices rather than one was deemed necessary because the estimation of nucleation rates from concentration profiles is notoriously inaccurate because crystals of very small size have only a minute impact on these profiles. The population balance equation model described above was extended to incorporate primary (heterogeneous) and secondary nucleation and was then again fitted to the experimental data, i.e., the difference between the model and the experimental data was minimized by adjusting the kinetic parameters in the nucleation rate expressions. Two different sources of experimental data will never be in perfect agreement with each other because they are subject to different experimental errors. Hence, a procedure to identify the optimal trade off between the two measurements was used in the estimation of nucleation rate parameters. The thusly estimated primary and secondary nucleation rates for different operating conditions are reported in Figure3a and Figure 3b, respectively. It can clearly be seen that the estimated primary nucleation rates are smaller for higher concentrations of Pluronic F127 over a wide range of supersaturations and temperatures with the primary nucleation rate for 0.08 kg PF127/$kg_{solvent}$ being more than an order of magnitude lower than the nucleation rate in absence of the polymeric additive, while the nucleation rate at

0.04 kg PF127/$kg_{solvent}$ is an intermediate case in the whole supersaturation and temperature range investigated. Considering the secondary nucleation rate on the other hand (cf. Figure 3b), one sees that that the estimated secondary nucleation at high values of $\Delta c = (S-1)c_*$ is only slightly affected by the addition of PF127. However, the addition of PF127 strikingly reduces the influence of Δc on the secondary nucleation rate.

In contrast to the study of the crystal growth rate presented above the constitutive equations used to fit the experimental data were of an empirical nature as first principle expressions did not fit the experimental data reasonably well. One should therefore refrain from an overinterpretation of the obtained parameter values (hence they are not further discussed here). However, from the identified decreased primary nucleation rate, one can conclude that nucleation in the presence of PF127 is inhibited. Whether this inhibition is due to a change in the interfacial tension between crystal and solution or a hindered diffusion of solute molecules (as in the case of the growth rate, see above) or some other reason could not be conclusively determined. The resulting effect in the context of cooling crystallization experiments from clear solution is that the metastable zone broadens with the addition of PF127, which might widen the operating range of crystallization processes that try to avoid the generation of additional nuclei by homogeneous nucleation.



(a)



(b)

Figure 3: Fitted nucleation rate of Ibuprofen for concentrations of 0, 0.04 and 0.08 kg PF127/$kg_{solvent}$. The nucleation rate is split into its primary and secondary part. (a) Primary nucleation rate in dependence of supersaturation and temperature (b) secondary nucleation rate in dependence of the surface area of all crystals, μ_2, and $\Delta c = (S-1)c_*$

5 Modeling Nucleation, crystal growth and ostwald ripening in crystallization processes

Crystallization can essentially be described as a combination of several mechanisms: the formation of the new phase (nucleation), growth of crystals and secondary effects such as agglomeration and breakage. The combination of these effects determines the evolution of the particle size distribution (PSD) until the supersaturation of the solution is depleted. When starting from an initially solid-free system, nucleation is dominant at the beginning of the process, when typically the difference in chemical potential between solution and the solid phase, or supersaturation, is high. Crystal growth becomes significant as soon as crystals are present in the suspension and will dominate the decrease of supersaturation after some time. After the depletion of supersaturation, a mechanism known as Ostwald ripening (also referred to as coarsening, aging, or simply ripening) takes over and further influences the evolution of the particle size dis-

tribution, while breakage and agglomeration can continue to act on the crystals.

Though very powerful in numerous applications, classical population balance equation models cannot describe Ostwald ripening and nucleation simultaneously. This is because the nucleation models assume a constant critical size, while the Ostwald ripening models require the critical size to be a function of the supersaturation. This problem is often resolved by using two separate population balance equation models to describe a complete crystallization process: one to describe nucleation and growth and one to describe Ostwald ripening using a size-dependent growth rate (see for example Iggland and Mazzotti [14]). This situation is unsatisfactory, both conceptually and practically, since the basic mechanisms behind both nucleation, growth and ripening are the same and in some applications, e.g., precipitation of multiple polymorphs [16], nucleation and growth or ripening occur for different solid phases at the same time. A model which includes all these steps has been presented by Kashchiev [15] (which will be termed the kinetic rate equation model (KRE) in the following). The KRE model describes particles based on attachment and detachment of single molecules, or of clusters of molecules, according to the pseudo-reaction scheme

$$A_n + A_j \underset{h(n+j,n)}{\overset{g(n,j)}{\rightleftharpoons}} A_{n+j} \tag{1}$$

Here, A_n denotes a crystal of size n, $g(n,j)$ is the rate constant of the two-particle attachment "reaction" of a crystal of size n to a crystal of size j, and $h(n+j,n)$ is the rate constant of the one-particle detachment of a crystal of size j from a crystal of size $n+j$. It is noteworthy that the attachment reaction accounts for both crystal growth (when n or j is 1) and agglomeration, whereas the detachment reaction accounts for both dissolution (when n or j equals 1) and breakage. Nucleation is not described explicitly as in the population balance equation model (where it is described using a boundary condition at a fixed size), but occurs naturally as a result of the interplay of the ensemble of reactions in Equation 1, provided attachment and detachment rates are properly defined.

In my PhD thesis (Chapter 6) and the corresponding publication [17] a thorough comparison between population balance equation models and the above-mentioned model was presented. To this end, dedicated simulations for nucleation, crystal growth and Ostwald ripening were performed in a wide range of process conditions and the behavior of the two models was confirmed to be well-aligned. In a final set of simulations complete crystallization processes were simulated, i.e., from the nucleation of particles well into the time when Ostwald ripening occurs. Such simulations are unique to the above-presented model and could not be performed using a classical population balance equation model. An example of such a simulation is shown in Figure 4, where the particle size distribution, $\tilde{n}\tilde{Y}$, is plotted as a contour plot against dimensionless time and the size (in number of molecules). Two points are noteworthy about this plot: first, in this plot a horizontal slice of the contour plot would yield the PSD at a certain instant of time and second, the dashed black line represents the critical particle size over time. The simulated process can thus be interpreted to consist of several phases: initially, there are no particles present as the whole PSD is below the critical size (some people refer to these particles as "embryos"), then these subcritical particles overcome the critical size and nucleation occurs. The concomitant nucleation and growth decreases the supersaturation in solution, which causes the critical size to increase according to classical nucleation theory. At even later times, a focusing of the size distribution is observed, i.e., a bimodal PSD is formed, containing both subcritical clusters and a population of particles with sizes around the critical size. Note that the focusing phase is rather short and that it is directly followed by Ostwald ripening. While this is unusual, it is simply caused by the small size of the precipitated particles (around 10^4 molecules). Ostwald ripening can be easily identified in this plot by the simultaneous evolution of the critical size and the PSD. This example shows that the KRE model is able to describe the whole crystallization process from nucleation to Ostwald ripening including subcritical particles.

In the corresponding publication [17] further simulations under different process conditions are presented and the parameters in both models types are investigated in detail. While the classical population balance equation approach is an irreplaceable tool for a wide variety of processes, the unifying description of the KRE model presented above has conceptual and practical merits for certain applications. From a conceptual point of view, the mechanisms of nucleation, crystal growth and Ostwald ripening should be described as different aspects of the same fundamental driving force (the difference in chemical potential) since they all involve the transfer of solute molecules from a disordered liquid phase to an ordered crystalline phase. Consequently, the mechanisms should also be described in a consistent fashion. It is our strong belief that such a unifying, continuous description of these mechanisms, without artificially decoupling them, can be achieved by implementing and solving the KRE model.

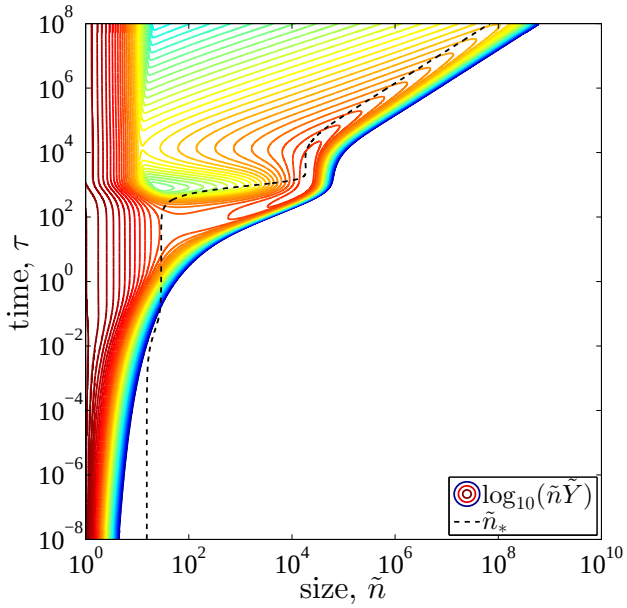


Figure 4: Example simulation using the kinetic rate equation model displayed in a plot of dimensionless size vs. time. The color of the contours relates to the logarithmic value of the PSD and the black dashed line is the critical size.

From a practical perspective, the way the KRE model has been formulated allows for the accurate description of crystals below the critical size also during process stages where nucleation is present (or even dominating). In the light of recent studies that have shown that agglomeration of subcritical crystals might be an important aspect in nucleation [18], the possibility to model these effects for the subcritical crystals is an important feature. Although not investigated in my PhD thesis, such a mechanism could be implemented in a model based on the kinetic rate equations, while an implementation in a classical PBE model that describes nucleation to occur directly at the critical size would only be reflected in a correction of the nucleation rate (i.e., it would be increased), which is an unsatisfying oversimplification of the underlying physics.

6 Importance and impact

The influence of impurity or additive molecules is manifold in crystallization and touches the main area of crystallization (the purification aspect), as well as other areas, due to their influence on the particle size and shape distribution. In my PhD thesis progress was made with respect to the latter aspect. To investigate this demanding problem a variety of techniques (screening, predictive techniques, estimation of kinetics, etc.) was used from the molecular to the process level.

While the characterization of kinetics and screening techniques will continue to play an important role in crystallization in the near future (and my PhD thesis contained its fair share of them, see Sections 2 and 4), progress has also been made on modeling techniques that are based on first principles and describe crystallization on the molecular level (see Section 3). The progress on these aspects presented above has been achieved during my PhD thesis, however, further insights were gained in later studies. For instance, the results presented in Section 3 were essential to the creation of a more predictive study carried out on urea in a variety of solvents [19]. This study combined predictions performed using WT metadynamics simulations with a detailed crystallization model and compared it to experimental findings. It was found that our predictions were in very good agreement with experimental findings, i.e., the models where able to predict crystal shapes ranging from needles to perfect tetraeders from a variety of solvents. This line of work is currently continued by Dr Matteo Salvalaglio and continues to be a successful cooperation between the research groups of Prof. Mazzotti and Prof. Parrinello.

The difficulties encountered in the quantitative estimation of nucleation rates due to its stochasticity and the underlying complicated phase diagram of the Ibuprofen/water/ethanol system (see Chapter 5 in my PhD thesis for details) has provided the initial motivation for two PhD projects currently ongoing in the research group of Prof. Mazzotti.

Parallel to the works presented above, I was involved in the design, construction and evaluation of a measurement device capable of measuring the shape of a population of particles in an on-line fashion. [20–22]. An improved version of this setup [23] is currently used by three PhD students in the measurement of multidimensional growth rates of crystals [24], the direct quantification of agglomerates and various other applications.

Summarizing, my PhD thesis covered a wide subject area, produced some interesting results and sparked research leads which are currently being followed by several PhD students and one postdoc in the research group of Prof. Mazzotti.

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