Influence of Seed Surface Pre-Processing on Crystal Growth Behavior in Cooling Batch Crystallization

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Abstract

Product quality and yield of pharmaceuticals produced by traditional industrial seeded batch cooling crystallization-operations is subject to large fluctuations as a consequence of seed surface quality. In this research, effects of seed pre-treatment by dry- and wet-milling were investigated on subsequent performance in crystallization behavior by measuring crystal growth rate, with comparative reference, in both stagnant and suspended, turbulent media. It has been shown that pre-processed paracetamol-seeds grew at a lower rate compared to non-processed seeds in stagnant conditions, whereas examination of the effect of seed surface healing increased growth rates. Separate experiments with suspended seeds of paracetamol and lactose in turbulent media, analyzed by *in situ* crystal size-measurements on growth rate, were found subject to attrition and agglomeration respectively. Consequently, processing of image-analysis, relating to crystal growth, was found inadequately performed.
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1. Introduction

Production of the current variety of consumer goods available for all kinds of applications requires a lot of complex processes with various degrees of quality demands. Numerous examples can be provided from oil refinery, food production, metal-extraction from ores, but also specialty chemicals, such as coatings, resulting in a wide range of different processes. In order to fulfill the needs and demands in both quantity and quality, these operations consume large quantities of energy and (raw) materials and leave a lot of waste and use energy inefficiently. The current global trend, stimulated through increasingly stronger law enforcement, requires these production processes to be intensified, for example by maximizing synergistic effects in partial processes. Since a large amount of the total industrial energy consumption is used for separation and purification in manufacturing a marketable product, an enormous gain in reducing costs (and therefore also an increased marketing position), by energy- and material savings can be achieved.

Crystallization is one of the available (industrial) separation technologies, others examples being distillation and membrane-separation. This solid-liquid separation process is widely used in branches producing polymers, inorganic and organic salts and pharmaceuticals. Pharmaceuticals require, certainly due to stringent quality aspects on bio-toxicity and effectiveness (by possible controlled delivery at specific organs), extra attention with respect to process-control and optimization, considering the purpose of medicines.

Generally, crystallization being carried out in batch reactors, of such drugs from a clear solution (by primary nucleation), results in highly undesirable batch-to-batch-variations through small fluctuations in (local) conditions in the reactor and process control and thus a low reproducibility with respect to purity and crystal size distribution, thus impeding further downstream-processing. The resulting large amounts of non-marketable/off-spec products in combination with low yields therefore demand improved yields-per-batch, while maintaining quality, presenting a major challenge. An even larger challenge accompanied by these variations in the production process is posed to the performance of the drug. Here, drug effectiveness and possible controlled delivery at specific organs are at stake, which is of too much of a compliance considering the purpose of medicines.

Process control of extensive variables, such as temperature and composition, is a large scale enhancement, where two dominant operations are present to control crystallization. Direct nucleation control (DNC) involves control of the number of particles, i.e. population of crystals, by inducing a sudden temperature change of the system (temperature-swing), which results in crystal formation occurring in a single outburst. In this case, the initial amount of crystals formed is then to be preserved in order to control the crystal size distribution (CSD) for the remainder of the batch. Operation limits considering crystal morphology depending on the initial supersaturation after the temperature change have been successfully determined\[^{[1]}\], although control of the number of crystals is difficult due to the non-linear dependency of primary nucleation on supersaturation. However, it has been shown that using heat cycles, attrition and agglomeration of crystals is reduced and re-dissolving of small crystals, results in improved control of the number of crystals present and thus of the final crystal size distribution (CSD), with on average a larger crystal size and a narrower CSD obtained per batch, compared to uncontrolled crystallization\[^{[2,3]}\].

On the other hand, supersaturation control implies that the driving force for crystallization is controlled, such that for example constant growth rate for crystals might be achieved by
implementing calculation and solving of the population balance and adjusting system parameters accordingly\textsuperscript{[4,5]}. However, since supersaturation control extends batch time by low cooling rates at the start and operation is in the metastable region during the entire batch, this strategy is sensitive to process disturbances, e.g. cooling slightly from optimal the optimal rate might result in a second event of uncontrolled crystal formation, although these can be limited\textsuperscript{[6]}.

One of the options frequently used for enhancement of the product quality is seeded batch crystallization, which eliminates the strong non-linearity in crystal formation from primary nucleation (unseeded batch crystallization), thus improving process control. This involves input of small seed crystals (usually of the same compound) on which the dissolved component can be crystallized by providing an initial surface area. Thermodynamic analysis states that lattice-integration occurs more controlled and consistent as a consequence of lower entropy compared to crystallization from clear solution. However, in practice, it has been shown that seeding in batch crystallization is complicated by uncertainty\textsuperscript{[7,8]} about the timing of the seed point the optimal amount and size of seed crystals and on the quality of the seed crystals\textsuperscript{[9]}. Research on the effects on the final product quality with respect to the choice of the seed point and the amount and size of the seed crystals has been published\textsuperscript{[10-15]}, while not much is known about the effect of the quality of the seed crystals which is related to the origin and treatment of the crystals prior to the application in the crystallizer\textsuperscript{[16,17]}.

This research therefore intends to contribute to the improvement of cooling crystallization processes for specialty products (in this case medicines) through an investigation on the crystallization-behavior of paracetamol/acetaminophen and lactose monohydrate by varying initial seed quality-conditions through milling, thus deliberately introducing alteration of the surface properties. The subsequent influence of seed surface quality, by observing/identifying respective growth rates, on the evolvement of the crystallization process is not correlated, while contributing as a major factor on product quality. Hereto, seeds are produced from primary nucleation by cooling, which are accordingly sieved into two fractions, where the larger fraction, anticipating on size reduction, is intended for pre-processing by milling. After which a portion of seeds is dry-milled and another part wet-milled, these are sieved to the similar diameter fraction as the initial smaller fraction (used as un-pre-processed seeds for reference) to minimize disturbances, with subsequent examination of shape, size, polymorphy and surface texture.

As growth rates are a measure for seed performance, it is convenient to first observe single crystal growth of the different seed-types in stagnant conditions in a growth cell, whereas afterwards, a small scale-up to suspended solutions, as an initial examination towards translation into industrial applicability, is performed. Here, the \textit{in situ}-combination of crystal size-development by image-analysis and solution-concentration measurements by ATR-FTIR is tested, with the aim of improved monitoring (and control) of the crystallization process. From growth rate data collected from single seed experiments a comparison for the suspension can be made in order to determine deviations and possibly their respective influences in multi-particle systems as a guide for further scale-up. This should direct to a better understanding of the mechanisms involved in the crystallization steps, which in turn can be optimized and implemented. The optimization and implementation are not within the scope of this research.

In order to develop understanding with the reader of the activities performed, interpretation of results and following conclusions during this research, the basic principles behind and phenomena occurring during crystallization will be treated in the next sections, from single crystal formation to transport phenomena in multi-particle systems. The next chapters will
describe the set-ups used and a theoretical approach thereof, along with experimental conditions, interpretation of results and conclusions.

1.1 Solubility and crystallization type

At first, some of the terms frequently used in crystallization have to be clarified. As already mentioned in the introduction, crystallization is a solid-liquid separation process. In this case, the solid will precipitate from a liquid containing the component to be crystallized. In this liquid, known as the solvent or mother liquor, the compound to be crystallized is known as dissolved in the solvent or otherwise is said to be in a dissolved state. As might be expected, not an infinite amount of the solid can be dissolved in a solvent. There is a maximum in solubility, which is dependent on temperature and material properties/interactions of the solid and the solvent. For a binary system, only one parameter will describe the maximal solubility or saturation curve and this can be captured graphically in a concentration vs. temperature-plot (Figure 1.1), although these usually originate (but can be directly translated) from Van ‘t Hoff-equations of the form Eq. (1.1) by setting the activity coefficient for the solute $\gamma_2 = 1$ for ideal solubility$^{[18]}$.

\[
\ln(x_2\gamma_2) = \left(\frac{\Delta H_m}{R} \left(\frac{1}{T_m} - \frac{1}{T}\right)\right)
\]

(1.1)

Figure 1.1: Equilibrium concentration as a function of temperature for paracetamol, dividing the plot in an undersaturated (below saturation curve) and supersaturated region (above saturation curve). The dashed line represents the metastable zone limit.
The saturation curve implicitly postulates that there are two distinct areas in the graph accordingly. The lower region under the saturation curve is called undersaturated, since at a particular temperature more solute can be maintained in solution and is thus not saturated. On the other hand, the upper region is interpreted as being supersaturated, explained by the solution containing too much of the solute. A third region (in between the saturation curve and the dotted line) is also identified, which is known as the metastable zone. In this region, although situated in the general supersaturated region, the solute might still be fully in the dissolved state rather than in the crystalline state. The subject of the metastable zone and especially the origin thereof is still under large debate and not yet fully understood, however, it is not within the scope to provide such explanations, while at least it might be stated that the inherent thermodynamic instability of a system being in the metastable zone provides the solute to precipitate/crystallize into the solid form. The amount of solids formed can be determined via two different ways, depending on the crystallization method chosen. The two most common methods to obtain a supersaturated solution are evaporative and cooling crystallization, with other options being anti-solvent crystallization and precipitation. Evaporative crystallization increases the concentration of the solute by evaporating the solvent, whereas cooling crystallization achieves the critical soluble amount by decreasing temperature. Usually, for pharmaceuticals, batch-wise cooling crystallization is used as these (mostly) poorly soluble organic compounds require large purity of crystals and energy-consumption is less compared to evaporative crystallization. Therefore, only this crystallization type is used in this research. Besides separation processes being defined and manipulated through thermodynamics, product quality and therefore overall efficiency of the process is determined by limitations introduced by kinetics, e.g. concentration polarization in membrane separations or mass transfer in adsorption. Crystallization is no exception and it is thus convenient to discuss various phenomena encountered, ranging from single crystal formation to multi-particle systems on a larger scale, and their respective correlation/origin with respect to (modifiable) system-parameters as well as the effects on the final product.

1.2 Crystal formation

As mentioned in the previous paragraph, the metastable zone is an important factor in crystallization behavior, where solute-molecules are orientating towards each other, contrary to random orientation while in the undersaturated region. From this point, a small cluster of oriented molecules or nucleus (plural: nuclei) is considered, where the balance of the Gibbs free energy of the surface area relative to the total volume of the cluster determines whether or not this cluster will form a crystal. Formulation of the (mathematical) functions for these area- and volume-energies yields the nucleation work function (see Figure 1.2), a type of activation energy-barrier. For nucleation, i.e. the spontaneous formation of small crystals, to occur, a single nucleus is to overcome this initial energy-barrier by acquiring enough molecules, i.e. \( r > r_c \), which consequently decreases total Gibbs energy of the system. Nucleation can be achieved in various ways, correspondingly named primary, which can be further subdivided, and secondary nucleation. Ultimately, a subsequent phase of crystal growth for stabilization of the newly formed crystal (as well as the thermodynamic state of the mother liquor) is entered. These different phases of crystal formation and growth are summarized in Figure 1.2 for clarity and each step is described in more detail in the remainder of this paragraph.
1.2.1 Primary nucleation

Principally, primary nucleation is defined as crystallization from a clear solution, where formation of the small cluster of molecules required for crystallization can be achieved in two ways, either in the absence or presence of a host-particle in the system. When such host-particles are absent, a cluster will solely consist of molecules of the solute and is therefore termed homogeneous nucleation. However, in practice, deviation from ideal solutions, i.e. solutions containing only the solvent and solute, by disturbing factors for solvent-solute interaction, such as superimposed conditions (e.g. external electrical charge) or impurities\textsuperscript{11}, is frequently observed, thereby altering properties of crystallization mechanisms and thus final crystal properties. For example, a small dust-particle present in the system might act as a cluster and thus subsequent orientation of solute-molecules around these particles. In this case, a crystal is not considered pure and crystal formation of this type is therefore conveniently named heterogeneous crystallization.

In retrospect with Figure 1.2 the difference between homogeneous and heterogeneous (primary) nucleation can be expressed as the previous starting from a cluster size of a single solute-molecule, since no apparent initial nuclei are to be found and, in accordance with the example of a dust-particle (or generally an impurity), heterogeneous nucleation having some initial cluster size larger than a single molecule. From this, it can be concluded that additional acquisition of solute-molecules (and implicitly: total Gibbs-energy) is always less for heterogeneous nucleation. As impurities in a specific system are almost unavoidable (due to (other) thermodynamic equilibria or nano-particles being present), heterogeneous crystallization is therefore the pre-dominant mechanism for primary nucleation, which is captured in Eq. 1.2\textsuperscript{21}.

![Graphical display of energy function for surface and volume of solute clusters, along with the net result, where $r_c$ determines the minimal critical radius for developing a crystal from a clear solution and subsequent growth of the crystal can occur.](image)

\textbf{Figure 1.2: Graphical display of energy function for surface and volume of solute clusters, along with the net result, where $r_c$ determines the minimal critical radius for developing a crystal from a clear solution and subsequent growth of the crystal can occur.}
$$B^0 = A \exp \left( \frac{-16\pi^2 V_c^2 \sigma^3 N_A}{3v^2 R^3 T^3 \ln S^2} \right)$$

(1.2)

However, as a consequence of this (usually relatively large) energy-barrier and unknown initial nuclei sizes, nucleation is highly dependent on and sensitive to local conditions in a system, e.g. local temperature being lower near the edges or cooling coils compared to bulk temperatures, thus locally decreasing solubility, resulting in statistically larger probabilities for nucleation in these regions\(^{22}\).

This results in primary nucleation being an uncontrolled/uncontrollable phase in crystallization behavior of the compound of interest and is therefore undesirable, certainly with respect to consumer products produced in different batches. Moreover, as crystallization processes require scale-up on an industrial level, the inherent discrepancy between (and therefore the influence of) local conditions becomes larger and is probably one of the hardest issues involved to circumvent.

### 1.2.2 Secondary nucleation

While mechanical stirring is naturally used to limit differences/gradients on local scales, this introduces other phenomena in crystallization processes, as the crystals present might collide with the stirrer. On impact, a crystal might be fragmented, a phenomenon called attrition, essentially introducing a new (number of) crystal(s). While attrition rates (Eq. 1.3) are highly dependent on solid content of slurries\(^{23}\), material properties\(^{24,25}\) and stirring speed\(^{26}\), the total volume of the initial crystal is conserved, however, more importantly, the total surface area is increased (besides the number of crystals).

$$B^0 = k_s \sigma^b M^1 N'$$

(1.3)

If the fragment(s) is/are of smaller size than the surface-to-volume ratio required for the nucleation work-barrier, this can be viewed as a type of homogeneous primary nucleation. However, usually crystal chips from attrition are of sufficient size, i.e. surpassed the activation energy-barrier, and thus immediately act as a new crystal and this type of crystal formation is therefore termed secondary nucleation\(^{12}\). In this latter case, although the number and size of the additional fragments is usually unknown, an outburst of nuclei in the metastable zone by primary nucleation is prevented, since a system containing both solids and the mother liquor is already thermodynamically stable. Therefore, the concept of secondary nucleation can be used to improve controllability of crystallization in separation technology, although in a modified manner, by seeding.

### 1.2.3 Seeding

Basically, seeding is the introduction of small crystals composed of the desired compound to be crystallized, which results in an extension of batch-operated crystallization parameters alongside conventional thermodynamic and kinetic control. These include selection of seed size, seed amount/loading and seed point.

A specified product size range and yield might be determined from the first two, combined with mass balances, from which a pre-determined seed size might be selected to optimize crystallization rates for individual crystals. However, growth rate dispersion, attrition and agglomeration (collision of crystals as opposite to attrition) introduce discrepancies between
the predicted size and obtained crystal size distributions to various extents\cite{27-29} alongside small fluctuations in seed size. The seeding point, i.e. the moment which the seeds would be deposited into the solution during the process, is usually chosen in the metastable zone slightly below the saturation temperature, i.e. initial supersaturation is present, of the component as to assure crystal growth occurs immediately. Whereas seeding is discussed later, at first, an overview of relevant parameters as a consequence of crystal formation is treated.

1.3 Crystal properties

With crystal formation discussed from an energy-perspective, resulting crystal properties are usually influencing following unit operations, such as slurry handling as a function of particle density, weight content, etc.. Therefore, a summary of relevant topics is given below.

1.3.1 Crystal morphology and polymorphism

The orientation of solute-molecules is dependent on the solute-solvent interaction, similar to solubility, however is also subject to solute-solute interaction, for example by hydrogen bonding, steric hindrance, ionic strength, \(\pi-\pi\)-interactions, etc.. This creates a spectrum of possible formations of molecules and thus defines crystal structure, by extension of the principal unit cell. An example is given in Figure 1.3 for paracetamol-crystals grown in aqueous solution and a mixture of water - acetone – toluene\cite{30}, whereas impurities can also contribute to a substantial degree\cite{31}.

![Figure 1.3: Example of solvent-composition influencing crystal morphology of paracetamol.](image)

As in this case, it was found by X-Ray Powder Diffraction (XRPD) and Differential Scanning Calorimetry (DSC) that the unit cell was maintained, this is usually not the case and thus results in polymorphy, i.e. the ability of the molecules to arrange in differently, which might be predicted to some extent\cite{32,33}, thus resulting in altered crystal properties. While the issue of control/avoidance of polymorph formation remains\cite{34}, for downstream-processing, such as tableting, anisotropy of crystals as a consequence of polymorphism might be undesirable for final product quality. Crystal morphology can be captured in description of individual planes/faces, by denoting the reciprocal of (imaginary) intersections of the principal axes in a Carthesian coordinate-system with the reference [000], usually chosen as the centre of the crystal. Using the definition of square brackets as a single plane, e.g. [010] denoting intersection only with the \(y\)-axis, while braces describe a set of crystal planes (in this example \{010\} represents both [010] and [0\(\bar{1}\)0]) = [0,-1,0]), for further information about crystallography is referred to literature\cite{35}.
1.3.2 Crystal size distribution

Whereas the final product in industrial crystallization ideally consists of a uniform size, in retrospect with primary nucleation being difficult to influence directly and seed size and quality subject to fluctuations, a range of sizes or crystal size distribution (CSD) is usually obtained (see Figure 1.4). In addition, residence time distribution in continuous operations also plays a role. From this, a variety of statistics concerning mean values and percentiles might be applied in order to obtain information relevant for specific fields. For full explanation and usefulness, the reader is referred to textbooks\cite{36,37}.

Again, considering population balances and other factors influencing, theoretical approaches might limit size dispersion\cite{38}. Furthermore, attrition and agglomeration contribute also to broadening of the distribution as well as fines. These very small crystals, initially attached to crystals, might come off, especially when dried crystals are brought in solution, alter the size distribution by disturbing the number of crystals, while total volume is conserved, resulting in a shift to lower average mean size.

![Figure 1.4: Crystal size distribution and the cumulative, displaying difference in particle sizes of individual crystals with respect to the total population.](image)

1.4 Crystallization phenomena and parameters

In this section, parameters in crystallization processes are discussed as to complete the basic understanding of limitations and the consequences for the performance thereof.

1.4.1 Supersaturation

For all chemical reaction and separation processes, it holds that there is a predefined thermal equilibrium at some given temperature, pressure and composition. In order to acquire the desired product, a shift in this equilibrium is to achieved as a result of a difference in the chemical potential $\mu$ from starting conditions, which can be externally applied by e.g. lowering the temperature, which, for crystallization, results in precipitation of the solute. While the driving force for crystallization of the solute (L) on the crystal (S) is described by:

$$\Delta \mu = \mu_L - \mu_S$$  \hspace{1cm} (1.4)
Substituting the temperature dependence of $\mu_i = \mu_i^0 + RT \ln a$ results in:

$$\Delta \mu_2 = \left(\mu_2^0 + RT \ln a\right)_L - \left(\mu_2^0 + RT \ln a\right)_S$$

(1.5)

Since it is assumed that the crystal is in equilibrium with the solution (else it dissolves), while the solute is not in equilibrium with the solvent, Eq. 1.5 can be rewritten as:

$$\Delta \mu_2 = \left(\mu_2^0 + RT \ln a\right)_L - \left(\mu_2^0 + RT \ln a\right)_{eq} = RT \ln \frac{a}{a_{eq}}$$

(1.6)

Furthermore, assuming a fair degree of dilution and low supersaturation, the expression for the activity $a_i = x_i \gamma_i f_i$ can be simplified by setting $\gamma_2 \approx 1$ and $f_2 \approx 1$ and thus, it follows that:

$$\Delta \mu_2 = RT \ln \frac{a}{a_{eq}} \approx RT \ln \frac{x}{x_{eq}} \approx RT \ln \frac{C}{C_{eq}} \approx \frac{C - C_{eq}}{C_{eq}} = \sigma$$

(1.7)

where an approximation for $\ln(1)$ is also inserted.

Now that a more profound derivation for the general driving force in crystallization is provided, crystallization kinetics with some additional background are discussed.

### 1.4.2 Lattice integration and kinetic models

As previously mentioned, orientation of solute-molecules towards the crystal surface is a key factor in determining the rate of crystallization. For example, crystallization of $\alpha$-lactose $\cdot$ H$_2$O, is known experiencing issues concerning this as the relatively large molecules, along with polarity (and therefore large solubility, which enhances solute-solute-interaction, thus further decreasing tendency for orientation) and mutarotation$^{[39]}$.

In addition, crystal faces are on a molecular not ideal planes/terraces as depicted in Figure 1.5. Surface defects/vacancies are present or rather just end points of a plane as discontinuities in the crystal lattice, where strain is inherently present, which in turn results into energetically favorable sites for crystallization, since the molecules are not fully incorporated in a unit cell. Thus, the tendency of molecules on the edges of a crystal to attract solute-molecules is apparent as to minimize the exposed surface area (and thus minimizing deficiencies). In general, three types are recognized (vacancies, step- and kink-sites), where a detailed analysis of the lowering of

![Figure 1.5: Schematic representation of crystal surface structure showing kink and step sites on the edges of the terraces as well as vacancies$^{[40]}$.](image)
activation energy barriers and respective crystal growth rate for each of the types with respect to ideal planes is omitted and can be found elsewhere\(^{[41]}\). Furthermore, the increasing instability of the solute-solvent-interaction with increasing supersaturation, reflects in crystallization behavior governed by different mechanisms in combination with surface defects. Three mechanisms (see also Table 1.1) for lattice integration to occur, each with different kinetics are posed, where the predominant one depends on the relative supersaturation.

Spiral growth occurs when a screw dislocation is present, resulting in helical structures on crystal surfaces. With each subsequent layer added during the growth process, the result is that a new dislocation arises (which continues upon termination). Therefore solute-molecules experience no difference with respect to new layers, which in turn result in fast kinetics. The birth- and spread-model assumes the formation of a 2-D nucleus on the surface of a crystal, from which uniform, lateral growth over a crystal plane occurs, such that the initial plane is covered with a new sheet after completion. Since a activation barrier for nucleation is to be surpassed, this occurs at larger supersaturation, i.e. chemical potential difference supplying this, as compared to (spiral) growth.

The last mechanism considered is rough growth. In this case, when supersaturation becomes even larger than required for birth and spread to prevail, activity of the solute to leave the solution overruns the (desire for) orientation for optimal lattice integration and thus crystallization takes place in a rapid and uncontrolled manner, resulting in substantial crystal defects and (usually) amorphous crystals.

### Table 1.1: Summary of kinetics of crystal growth mechanisms as a function of lattice defects/strain and supersaturation.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Surface integration</th>
<th>Diffusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiral growth</td>
<td>( R \approx k_r \sigma^2 )</td>
<td>( G = k_s \sigma )</td>
</tr>
<tr>
<td>Birth and spread</td>
<td>( R \approx k_n \sigma^n )</td>
<td>( G = k_p \sigma )</td>
</tr>
<tr>
<td>Rough growth</td>
<td>( R \approx k_r \sigma )</td>
<td>( G = k_s \sigma )</td>
</tr>
</tbody>
</table>

However, crystal defects do not only come forth from (random) molecular events or superimposed process variables, but also might be introduced mechanically. When breaking crystals by e.g. milling, initially surrounded and probably well-arranged molecules from the inner regions are now exposed to unfavorable conditions as well as additionally induced vacancies from chips broken off or dislocated molecules/planes from impact. As this can be captured in seed surface quality, growth rate difference between milled and unmilled seeds is expected. When assuming initial seed size of qualitatively different seeds to be equal, the difference in (and quantification of) growth rate is known as growth rate dispersion\(^{[27]}\). Furthermore, the ratio of surface area to volume, when considering uncontrolled seed size during batch operation, is also increased, which causes even more strain to the molecules. Although mixed solutions are assumed to eliminate local gradients by convection, viscous forces near stationary surfaces, i.e. crystallizer walls or crystal planes prevent crystallization rates being directly proportional to supersaturation. Thin film models, assuming a stagnant (and thus only diffusional rearrangement) region as a separation barrier between the bulk solute and the crystal planes, are usually applied to incorporate delays in mass transfer. As it is difficult to measure either surface integration or diffusion within the film layer, it might be stated that the total rate of crystallization is found as a combination of both and an apparent rate is therefore observed.
1.4.4 Seed size and seed mass

From the previously described phenomena, considering driving force and mass transfer, an overall growth rate equation is obtained, defining \( k_g \) as the apparent mass transfer coefficient and the power \( n \) as an integrated parameter from surface integration and volume diffusion in the film layer, since surface integration and thin film diffusion are in series and the sum of both equals observed growth rate.

\[
G = k_g \sigma^n
\]  

(1.8)

As was indicated, the influence of seeding, independent of solubility, has a large effect on final product size and thus selecting initial conditions for seeds is important, where error-propagation is to be limited. Considering the desired solute mass to be crystallized, Eq. 1.9 represents a one-dimensional relation of the ratio of selected seed size and mass with respect to final product size and the total mass crystallized from solution, i.e. initial solute concentration - final solute concentration, determined by the solubility curve.

\[
m_s = \frac{L_s^3}{L_p^3 - L_s^3} V \Delta C
\]

(1.9)

It should be noted that crystal morphology, captured in crystal shape factors, is not included and it is assumed that particle number is constant, i.e. no attrition or agglomeration and/or primary nucleation.

When examining crystal seed growth, ideally for a single particle, the equation simplifies the seed mass to \( m_s = p_{cr} \cdot \Delta V \). However, since \( \Delta V = A(L \cdot A) = A\cdot \Delta L \), it is apparent that growth rate of single crystal faces is also dependent on the surface area of the plane under consideration, which modifies linear growth rate measurements to some extent\[28,42\].

As growth rate rate dispersion and size dependent growth might occur simultaneously, the respective influence on the broadening of the CSD is difficult to predict, hence limitations in product specification control by seeding remain, although less compared to primary nucleation.

1.4.5 Seeding point

Where consequences on the final CSD of seed parameters in batch crystallization are apparent, selection of process variables, especially with respect to initial supersaturation experienced by the seed crystals, are of importance. Returning to growth mechanisms previously discussed, it might be stated that product quality is dependent on the mode (cooling vs. evaporative, batch vs. continuous and seeded vs. unseeded) chosen as well as control of kinetics. The ideal seeding point might vary with mode and crystal and process characteristics\[43\]. Where these might be determined experimentally for individual systems, it is should be noted that in general, the seeding point should be chosen within the metastable zone of the compound.

1.5 Crystallization phenomena in multi-particle systems

Scale-up for industrial production rates usually requires larger equipment/systems and therefore, in crystallization, simultaneous growth of a manifold of single particles, i.e. multi-
particle systems. It is known that direct translation, extension or extrapolation of single particle-development to larger scales involves a variety of other concepts, influencing the general crystallization behavior. An example of attrition, resulting in a multi-particle system by secondary nucleation and consequently affecting individual particles’ growth rate, was already given. On the other hand, it is also possible that a shift in the relevant factors, such as size dependence growth or present number of fines, determining crystallization behavior, during scale-up accounts for different overall observations with respect to product quantity and/or quality\textsuperscript{[37,42]}. The main objectives in seeded batch crystallization are usually given by minimizing size variation and additional nuclei formed and batch time, which translates to maximizing product yield with respect to a specified average size and seed growth rate\textsuperscript{[44]}. Implicitly and ideally, when compared to single crystal growth discussed previously, this states the number of particles should remain equal throughout the entire operation, which is formulated in the general population balance equation:

\[
\frac{\partial f_n}{\partial t} = -\frac{\partial (f_n G)}{\partial L} + \frac{f_n \phi_{\text{in}}}{V} - \frac{f_n \phi_{\text{out}}}{V} \quad (1.10)
\]

Where the number density function \( f_n = f_n(L,t) \) to include non-uniform growth rate as a function of initial size. For batch cooling crystallization, the two latter terms are set to 0 as flow is not added or withdrawn (for anti-solvent crystallization this is thus not the case), from which the initial condition follows that \( f_n(L,0) = f_{n,\text{seed}}(L_0) \). However, as the reduced equation for batch crystallization appears simplified, in general lengthy mathematical solutions are required to solve it completely for a modeled final CSD as \( G \) is dependent on supersaturation, crystal size, mass transfer and growth mechanism. Whereas it might be attempted to fully model the population balance with the intent to theoretically predict a CSD and adjusting process parameters accordingly, incorporating attrition- and agglomeration-rates, relative influence of growth mechanisms compared to dispersion, etc., this is not within the scope of the research and is therefore referred to elsewhere.
2. Materials & Methods

2.1 Chemicals

In this research, two important pharmaceutical components were investigated, from which one is the painkiller paracetamol (or acetaminophen, ≥ 99%, Sigma-Aldrich, CAS 103-90-2). Lactose is known to exist in two forms, α and β, with the difference being the position of the two OH-groups at 4th position in the rings of galactose (left ring) and glucose (right ring) conjunct through an oxygen-atom between both rings. The most common and stable form, thus used, is the α-Lactose and an additional water-molecule is present, translating in a monohydrate. α-Lactose · H₂O (4-O-β-D-Galactopyranosyl-α-D-glucose, ≥ 99%, Sigma-Aldrich, CAS 5989-81-1) is used as a tableting compound, for its desirable compressibility properties. Chemical structures are depicted in Figure 2.1[45]. As solids might adopt various macro-visual appearances, crystal morphology as a function of parameters, e.g. initial supersaturation, solvent-solute interaction, etc., discussed in the previous chapter, structures are also depicted in Figure 2.1[46,47].

![Chemical structures of Paracetamol / Acetaminophen and α-Lactose · H₂O](image)

Figure 2.1: Chemical structures and the main polymorphic appearance, i.e. paracetamol-crystals grown in water at high supersaturations (S > 1.2) and α-Lactose · H₂O formed in of the compounds used in this research.

In order to mimic systems used in industrial crystallization of these components, solvents are chosen accordingly, i.e. water is used to dissolve paracetamol as well as for α-Lactose · H₂O. Minimizing effects on crystallization behavior of dissolved salts, available demineralized water was used, deionized by a PureLab Ultra-system.
Solubility-curves (Figure 2.2) for both compounds are taken from literature as a Van ‘t Hoff-equation for paracetamol\cite{48} and soluble concentrations for α-Lactose · H₂O via an intermediate from the original source through e-mail correspondence\cite{49} and converted in concentration vs. temperature-dependence by using exponential fits for the data range available in the form of Eq. 2.1, where \( A \) represents the \( C_0(T_0) \) [mg mL\(^{-1}\)] for the selected range \( B \) [K\(^{-1}\)] the correction factor for temperature dependence, which can be found along in Figure 2.2.

\[
C_s(T) = A \cdot \exp(B \cdot T)
\]  

(2.1)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{solubility_curves.png}
\caption{Solubility-dependence on temperature of paracetamol (upper) and α-Lactose · H₂O (lower), with corresponding exponential fits.}
\end{figure}
Other properties, such as solid density, required for data-analysis are displayed in Table 2.1.

Table 2.1: Summary of some of the relevant chemical properties of components used.

<table>
<thead>
<tr>
<th>Property</th>
<th>Weight [g mol(^{-1})]</th>
<th>( \rho ) [kg m(^{-3})]</th>
<th>( k ) [W m(^{-1}) K(^{-1})]</th>
<th>( C_p ) [J kg(^{-1}) K(^{-1})]</th>
<th>Refractive index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>151.17</td>
<td>1293</td>
<td>-</td>
<td>-</td>
<td>1.643</td>
</tr>
<tr>
<td>( \alpha )-Lactose ( \cdot ) H(_2)O</td>
<td>360.31</td>
<td>1525</td>
<td>-</td>
<td>-</td>
<td>1.533</td>
</tr>
<tr>
<td>Water</td>
<td>18.02</td>
<td>1000</td>
<td>0.596</td>
<td>4.185 ( \times ) 10(^3)</td>
<td>-</td>
</tr>
<tr>
<td>Quartz glass</td>
<td>-</td>
<td>2210</td>
<td>1.4</td>
<td>730</td>
<td>-</td>
</tr>
</tbody>
</table>

2.2 Seed production and pre-processing

A well-defined crystal structure of both components, serving as a template for both untreated, conventional seeds and further processing, is attempted to achieve by re-crystallization. Schematically, the set-up used is shown in Figure 2.3, which consists of circulated, temperature controlled cooling water flowing through a continuously (overhead-)stirred \( \sim \) 1 L jacketed vessel.

![Figure 2.3: Schematic representation of the set-up used for re-crystallization with temperature controlled cooling bath (left) and a 1 L jacketed vessel (not on scale).](image)

Afterwards, seeds are sieved in order to obtain more narrowly distributed crystal sizes to enhance comparison between different experiments.

Pre-processing of a part of the re-crystallized seeds from a larger sieved fraction (due to preceived size loss) of the same batches is performed by milling in a conventional ball mill (Fritsch, Pulverisette 7), where dry- and wet-milling are considered as pre-treating parameter. Wet-milling of seeds is conducted in anti-solvent, for which absolute ethanol (\( \geq \) 99.8\%, Sigma-Aldrich, CAS 64-17-5) was a suitable selection for \( \alpha \)-lactose \( \cdot \) H\(_2\)O. Paracetamol, on the other hand, dissolves in absolute ethanol and therefore \( n \)-hexane (VWR BDH Prolabo, mixture of isomers, technical grade, CAS 110-54-3) was chosen. Particle size-analysis was conducted by laser diffraction (Anaspec, Microtrac S3500) in anti-solvent with a sample delivery-controller.
2.3 Growth cell

2.3.1 Experimental set-up

Measuring seed growth rate after preparation in stagnant solutions is performed in a quartz glass growth cell of 10 x 33 x 10 mm with glass thickness of 1 mm under a microscope (Nikon PTIPHOT 200) by taking snap-shots in time. Cooling of the growth cell is performed externally by a cooling bath with temperature control (Lauda, edition 2000) The set-up is depicted in Figure 2.4.

Figure 2.4: Overview (A) of the set-up used for determining crystal growth rate in stagnant solution, showing the optical microscope (1) and the thermostat (2). B) Larger picture of the microscope (magnification range: 5 – 50x) with camera (3) and the growth cell (4). C) Growth cell (5) and in-/outlet tubes (6) surrounded by the cooling water (7) supplied by the thermostat. D) Schematic picture of cooling flow circulation of the overall set-up.

Sections of entrance- and exit-tube to the growth cell outside the temperature-controlled region of the disk as well as the outer circumference thereof are assured slightly above saturation temperatures by a thermally heated wire to avoid crystallization in these regions of the set-up as a result of natural cooling (not shown in Figure 2.4 for clarity). The flow of the cooling water approximates the growth cell at roughly 45°.
A seeding vessel (on the right of the microscope, shown in Figure 2.4.D) is placed in series of the cooling cycle before the growth cell in order to assure that this part is warmer than the growth cell. The main reason is to prevent recrystallization on seeds before the experiment is started.

Saturated solutions at a chosen temperature are prepared and brought into both the growth cell and the seeding vessel and will accordingly be equilibrated for some time. Then, after equilibration, the seeding vessel is manually connected via a thin tube to the growth cell entrance and subsequently a small amount of seeds is brought manually in the seeding vessel. Beforehand, a syringe was connected to the exit tube of the growth cell, through which the solution with the seeds could be drawn from the seeding vessel into the growth cell by vacuum aiming to obtain a single crystal and no air bubbles in the growth cell.

### 2.3.2 General assumptions

It is apparent from Figure 2.4 that the growth cell is isolated from the surrounding cooling water for mass exchange. A schematic overview of the series of physical transport phenomena is presented in Figure 2.5, since the cooling water allows heat transfer through both the quartz glass-walls of the cell and the metallic entrance- and exit-tubes.

![Figure 2.5: Schematic representation of physical transport phenomena occurring in the growth cell, which can be divided into two conductive parts in water and quartz glass. The temperature of the solution - glass-interface might be solved as the temperature of the interface equates on both sides with their respective fluxes. The heat transfer coefficient \( h \) at the glass - coolant boundary is to be determined via Nusselt-relationships.](image)

The latter statement implies firstly, that heat loss through these tubes is significant due to the metallic nature (compare \( k_{Fe} \sim O(10^2) \) and \( k_{H2O} \sim O(10^3) \) with thickness of tube walls roughly equal compared to inner radius (~ 0.5 mm)) and thus is assumed that solution in the tubes is of temperature of the cooling water. Secondly, the small volume of the tubes states that mass of solute in the tubes is negligible compared to the total solute mass in the system, i.e. growth cell plus tubes. From both these conclusions, it is assumed that the influence of the tubes on the total system is relatively small with respect to the cell and are thus neglected in further analyses.
Therefore, the total system, hereafter just mentioned as growth cell, is regarded as a rectangular cuboid with dimensions given above, which gives the following total energy-balance for the solution in the growth cell, consisting of a heat loss-term by cooling and a heat release-term gained from crystallization enthalpy (Eq 2.2):

\[
\frac{dE}{dt} = \frac{d(\rho V C_p T)}{dt} = \rho V C_p \frac{dT}{dt} = -\phi q A - \Delta H_{cr} r_{cr}
\]

(2.2)

where \( E [\text{J}] \) describes energy, \( \rho_s [\text{kg m}^{-3}] \) solution density, \( V [\text{m}^3] \) the volume of the growth cell, \( C_p [\text{J kg}^{-1} \text{K}^{-1}] \) solution heat capacity, \( T [\text{K}] \) the temperature of the solution in the growth cell, \( \Delta H_{cr} [\text{J mol}^{-1}] \) enthalpy of dissolution and \( r_{cr} [\text{mol s}^{-1}] \) the rate of solute crystallizing, additionally assuming constant solution density (\( \rho_s \neq \rho_s(T) \neq \rho_s(t) \)) and constant solution heat capacity (\( C_p \neq C_p(T) \)).

Initially, it is assumed that \( C_p \cdot \Delta T \) of the growth cell is much larger \( \Delta H_{cr} \) and the latter term is negligible as a contribution in the energy-equation.

### 2.3.3 Heat transfer and temperature calibration

As is clear from Figure 2.5, energy is transferred from the growth cell to the surrounded cooling fluid by convection. From the cooling of the outer wall, energy is conducted, according to thermodynamics, within both the solution and the quartz glass as a consequence of the temperature difference.

#### 2.3.3.2 Convective heat transfer

Heat loss by the convective transport described by Newton’s Cooling Law (Eq 2.3), an overall heat transfer coefficient might be estimated using appropriate Nusselt-relations by e.g. Eq 2.4.

\[
\phi q = U \Delta T = U (T_q - T_c)
\]

(2.3)

where \( \frac{1}{U} = \frac{1}{h} + \frac{k_d}{d_d} + \frac{k_s}{d_s} \)

\[
\text{Nu} = \frac{hd}{k} = 0.332 \text{Re}^2 \text{Pr}^{1/3}
\]

(Flat plate parallel to flow, \( \text{Re} < 3 \cdot 10^5 \)\(^{[50]} \))

(2.4)

where \( \text{Re} = \frac{\rho v L}{\mu} = \frac{1000 \cdot 3.5 \cdot (3.3 \cdot 10^{-2})}{1.002 \cdot 10^{-3}} = 1.15 \cdot 10^5 \) and \( \text{Pr} = \frac{1.002 \cdot 10^{-3} \cdot 4185}{0.596} = 7.03 \)

where \( h \) is dependent the Nusselt-number (Nu), which is defined as the heat transfer coefficient [J m\(^2\) s\(^{-1}\) K\(^{-1}\)], \( d \) the characteristic length of heat penetration [m], \( k \) the thermal conductivity coefficient of the respective phase [J m\(^{-1}\) s\(^{-1}\) K\(^{-1}\)]. The Reynolds-number (Re) is determined by \( \rho \) the fluid (i.e. coolant) density [kg m\(^{-3}\)], \( v \) the fluids velocity [m s\(^{-1}\)], \( L \) the
flow length [m] along the cell wall $\mu$ the (dynamic) viscosity of the fluid [Pa s] and Prandtl-number (Pr) by $C_p$ the coolant’s heat capacity and other variables defined above. It should be mentioned that in the Re-calculation, for simplicity, density- and viscosity-values of water are taken around 20 °C as exact values as a function of temperature are considered as surpassing the goal of an engineered approach concerning the growth cell. The average velocity of the circulating coolant is in duplo experimentally roughly determined by measuring the weight of liquid (water) pumped out in time (681 g in 5.04 s and 696 g in 5.17 s) with the tube diameter being 7 mm, which gives:

$$v = \frac{\phi_v}{A} = \frac{1}{\rho_c A} \frac{M_c}{t} = 3.5 \text{ m s}^{-1}$$

(2.5)

From this, it follows that:

$$\text{Nu} = \frac{h d}{k} = 0.332 \text{Re}^2 \text{Pr}^{\frac{1}{3}} = 216$$

and thus $h = 3895 \text{ W m}^{-2} \text{ K}^{-1}$

(2.6)

However, as indicated in Figure 2.4.C, the approximating angle of the cooling flow might induce a propagated error in the estimation of the heat transfer coefficient as a result of eddies when properly modeled. As in general it is known that convective heat transfer appears much faster than diffusive heat transfer (compare time-scales $t = L/\nu$ (convective, linear) and $t = L^2/D$ (diffusive, quadratic), this is most likely not to be the case. Therefore, the main resistance is expected to be in the conductive parts, which is confirmed from the calculation of the heat transfer coefficient, from which it follows that $h >> k/d$, using values from Table 2.1, which was also found by Cristiana Virone.[67]

### 2.3.3.2 Conductive heat transfer

As a temperature step change in ideal form cannot be accomplished, the corresponding temperature profiles with respect to instationary heat transfer need to be accounted for, resulting in three distinct regions. An example of experimentally determined profiles is given in Figure 2.6, where an ideal and a non-ideal step change in temperature are depicted and . The initial phase (I) just after the start might be complex, as penetration of heat from the bulk solute towards the outer wall is limiting as was shown. In phase II, it can be seen that $\Delta T = \text{constant}$. Thus instationary heat transfer is described for both the quartz glass and the solution by:

$$\frac{dT}{dt} = a \cdot \nabla T$$

(2.7)

Although heat transfer is directed 3-D, from here, a simplified one-dimensional view is adopted, where $x = 0$ is referenced as the centre of the growth cell and $x = d$, the half width of the growth cell. For a thin slice within the solute, it holds that:

$$\frac{dT_s}{dt} = \frac{A}{\rho_s VC_{p,s}} \left( \phi_s |_{x} - \phi_s |_{x+dx} \right) = -\frac{k_s A}{\rho_s VC_{p,s}} \frac{\partial T}{\partial x} |_{x} = -\frac{k_s A}{\rho_s VC_{p,s}} \frac{\partial T}{\partial x} |_{x+dx} = a_s \cdot \frac{\partial^2 T}{\partial x^2}$$

(2.8)
with boundary conditions:
\[
\frac{\partial T}{\partial x} \bigg|_{x=0} = 0 \quad \text{from symmetry}
\]
\[
T(x = \pm d) = T^*
\]
\[
T(t = 0) = T_0
\]

**Temperature profiles**

Figure 2.6: Temperature-profiles for the coolant and the growth cell, showing a time-delay in step change as well as temperature difference between the growth cell wall and the cooling water being non-constant as a consequence of fluctuating heat flux in regions I and III.

For the quartz glass, a similar expression is obtained by:

\[
\frac{dT_q}{dt} = a_q \cdot \frac{\partial^2 T_q}{\partial x^2}
\]  \hspace{1cm} (2.9)

with boundary conditions:
\[
T(x = \pm(d + d_q)) = T_c
\]
\[
T(x = \pm d) = T^*
\]
\[
T(t = 0) = T_0
\]

Equating fluxes solves for the boundary temperature \(T^*\) for heat penetration, where \(T_{centre} = T_0\) in the initial phase I between the solution and the glass as a function of the coolant temperature \(T_c(t)\):

\[
\phi_{q,quartz}^* = \frac{k_q}{\sqrt{\pi a_q t}} (T^* - T_c(t)) = \phi_{q,s}^* = \frac{k_q}{\sqrt{\pi a_q t}} (T_{centre} - T^*)
\]  \hspace{1cm} (2.10)
Considering that resistance to heat transfer was concluded in the conductive phases, i.e. either the solution or the quartz glass, the Fourier-number, with \( a = k/\rho C_p \) the thermal diffusivity coefficient [W m\(^{-2}\) K\(^{-1}\)], is given by Eq. 2.8,

\[
 Fo_q = \frac{at}{d^2} \tag{2.12}
\]

the characteristic time-scales for heat conduction in the saturated solution (approximated as water) and the quartz glass\(^{[51]}\) are calculated respectively, where it should be stated the simplified one-dimensional view for characteristic lengths for both phases is taken as the thickness of the quartz glass \((d_q = 1 \text{ mm})\) and the half-width of the growth cell \((d/2 = 5 \text{ mm})\), as:

\[
\frac{d_q^2}{a_q} = 1.2 \text{ s} , \quad \frac{d_w^2}{a_w} = 175 \text{ s}
\]

From this, it can be concluded that overall process time is much larger than time required for heat penetration. Using the critical value \( Fo < 0.1 \) for which penetration theory holds, the value is determined as 17.5 s from the start\(^{[52]}\). Furthermore, it is expected that heat transfer is governed by the thermal conductivity of the saturated solution rather than the quartz glass, from which it might be stated that the main resistance is in this phase. For further analysis is referred to others\(^{[67]}\).

Considering the linear phase II in Figure 2.6, it is concluded that the temperature difference between the coolant and the quartz glass and also the quartz glass and the solution is constant. Furthermore, it follows that \( T_{centre} \) is not constant anymore, thus the average temperature in the growth cell is to be measured in order to relate to the solubility.

Therefore, a calibrated TC-08 thermocouple with a data-logger (Pico Technology) is used to determine the temperature in time while cooling for the cooling bath, assuming with the aforementioned fluid velocity that heat loss through the circulation path of the coolant is negligible, the inner wall (quartz glass) of the growth cell and the centre of the growth cell.

### 2.3.4 Mass transfer and crystal growth

Then Fick’s Law (Eq. 2.8) is to be applied, solving for the resulting mass diffusional fluxes of the solute within the growth cell:

\[
\vec{\phi}_s = -D \nabla C \tag{2.13}
\]

For crystal growth to occur, this diffusion is directed towards the seed crystal(s). However, referring back to Figure 2.5, in combination with the solubility expressions and the position of
the seed crystal(s) on the bottom of the growth cell, direct translation into concentrational (diffusive) fluxes through solubility-curves is not apparent. Since on the top of the cell is assumed of the same temperature as the bottom, it can be concluded that in the upper part of the cell mass diffusion is enhanced as a result of the central temperature being larger and thus a relatively larger solubility in addition to free convection as a consequence of slight density differences. Contrary, in the bottom half, conflicting mechanisms occur as solute tends to diffuse both upwards the warmer centre and downwards to the seed crystal. As it is difficult to determine and/or quantify the influence of these counteracting mechanisms it is assumed that diffusion is only towards the crystal and is to be quantified through application of an averaged temperature throughout the growth cell, additionally ignoring edge effects.

Figure 2.7 displays a thin film model separating bulk solute-concentration from seed crystal with the corresponding mass transfer equations.

\[ x^i dx \rightarrow \frac{dC}{dt} = -D \nabla^2 C \]

**Bulk solute**

\[ \frac{dC}{dt} = -k_{na} \nabla C \]

**Thin film**

\[ \frac{dC_s}{dt} = G \cdot A \cdot k \cdot A \cdot (x, y, z, t) \cdot \sigma^n = \frac{dC}{dt} \]

**Crystal plane**

Figure 2.7: Mass transfer of solute from the bulk in the growth cell through a thin film-layer (thickness \( \delta \)) with lattice integration. Equal to the heat transfer in the entire growth cell, it consists of a series of resistances.

As mass is transported from the bulk solute to the boundary layer, it can be stated that the mass lost in the bulk is gained on the crystal (by conservation of mass):

\[ \frac{dC_{s,b}}{dt} = \frac{dC_{cr}}{dt} \] (2.14)

From the perspective of the crystal, the growth rate equation is generally given by:

\[ G = k_s \sigma^n = k_s \left( \frac{C_s - C_{eq}}{C_{eq}} \right)^n = k_s \sigma^n \] (2.15)

where \( G [\text{m s}^{-1}] \) is the crystal growth rate, \( k_s [\text{m s}^{-1}] \) the mass transfer coefficient, \( \sigma [-] \) the relative supersaturation ratio, consisting of \( C_s [\text{mg mL}^{-1}] \) the solute bulk concentration and \( C_{eq} [\text{mg mL}^{-1}] \) the equilibrium concentration, i.e. solubility, and \( n \) a power usually governed by the type of growth mechanism occurring on the crystal (see Section 1.4.3). The ratio (and driving force of crystallization) of bulk- and equilibrium-concentrations is usually expressed as the relative supersaturation \( \sigma [-] \).

With the manipulation of taking the natural logarithm on both sides of Eq. 2.15, a linear expression in the form of \( y = a + b \cdot x \) is obtained, where \( a = \ln(k_s) \) and \( b = n \) (Eq 2.16):
\[ \ln(G) = \ln(k_e) + n \cdot \ln(\sigma) \]  

(2.16)

From this, a plot might be constructed in order to determine the values of the unknown mass transfer coefficient and the power \( n \). Furthermore, the expression in Eq 2.14 and Eq.2.15 can be combined to relate growth rate as a function of supersaturation-depletion, i.e.:

\[ \frac{dC_{s,z}}{dt} = \rho_{cr} \sum_{i=1}^{n} G_{ij} A_{ij} \]

\[ \frac{dC_{s,b}}{dt} = -\rho_{cr} \sum_{i=1}^{n} G_{ij} A_{ij} \]

where \( n \) [-] the number of seed crystals in the system, \( i \) crystal index number, \( G_{ij} [\text{m s}^{-1}] \) growth rate of crystal plane \( j \) of crystal \( i \), \( A_{ij} [\text{m}^2] \) surface area of crystal plane \( j \) of crystal \( i \) and \( \rho_{cr} [\text{kg m}^{-3}] \) crystal density. Integration yields, using the boundary condition \( C(t = 0) = C_0 \):

\[ C_s(t) = C_{s,0} - \rho_{cr} \sum_{i=1}^{n} G_{ij} A_{ij} \]  

(2.17)

As the number of seeds, next to the investigated crystal, in the growth cell is determined and the original particle size of all crystals is assumed equal for all, the consummation of supersaturation might be found. Therefore, crystal growth rate, by incorporating crystal morphology, for particular faces (see Section 2.1) can be correlated for determination of parameters in Eq 2.17. Here, it is assumed that \( A_{ij} \) is constant in time and thus growth rate is determined linearly rather than volumetric. This is a consequence of the loss of information by converting the 3-D crystal into a 2-D picture thereof for example the area of \{110\} being dependent on the relative growth of (all) neighbouring faces. From this, it is decided to take snapshots in time with the microscope to calculate the crystal growth rate and at this point, supersaturation is calculated and averaged throughout the growth cell, from which a theoretical growth is calculated.

Analogous to Eq. 2.8, a similar expression is obtained for the mass flux. However, the considering kinetic transport limitations, mass transfer from the bulk solute to the crystal is assumed directed towards the crystal, from which it follows that the symmetry boundary condition of Eq. 2.8 is not valid. In this case, the thin film boundary layer is considered.

\[ \frac{dC_{s,b}}{dt} = D \frac{\partial^2 C_s}{\partial x^2} \]  

(2.18)

with boundary conditions:

\[ \frac{\partial C}{\partial x} \bigg|_{x=\delta} = -k_m \Delta C = -k_m (C^* - \rho_{cr}) \]

\[ C_s(x=\delta) = C^* \]

\[ C_s(t = 0) = C_{s,0} = C_{eq} \]

From an experimental and modeling point of view, this implies discretization (in time steps) might be used to cycle between calculation of crystal plane and the bulk concentration.
Whereas full modeling is not aimed for in this research, considering the dependency of the mass transfer coefficient on the Sherwood-number with diffusive fluxes acting as equivalent to heat transfer, described above, and the sensitivity thereof (in stagnant media) with respect to molecular properties, such as lattice integration preceded by solute molecule orientation (especially for complex (polar) components as lactose and paracetamol (with an additional non-polar methyl-group)), simplifications are required. For stagnant media the Sherwood-number \( Sh = 2 \), thus:

\[
Sh = 2 = \frac{k d}{D}
\]  

(2.19)

where diffusion coefficients for paracetamol and lactose in water are calculated at \( 6.44 \cdot 10^{-10} \) m\(^2\) s\(^{-1}\) (by interpolation)\(^{[53]}\) and \( 4.97 \cdot 10^{-10} \) m\(^2\) s\(^{-1}\) (extrapolated from a correlation of sucrose)\(^{[54,55]}\) respectively. The characteristic length \( d \), considering instationary mass transfer can substituted for the penetration depth \( x_p \), given by:

\[
x_{m,p} = \sqrt{\frac{\pi D t}{\pi}}
\]  

(2.20)

resulting in the mass transfer coefficient:

\[
k(t) = \frac{D}{\pi t}
\]  

(2.21)

### 2.4 Online monitoring of crystal size distribution and supersaturation

Alternatively, seed growth in turbulent conditions as a next step to extend to industrial applications is investigated through use of a novel, combined implementation of \textit{in situ} image-analysis and \textit{in situ} concentration-measurements. The previous to be performed by a built-in camera in a Crystalline with temperature-control (Avantium Technologies version 2.11), whereas information about the solution-concentration is obtained through Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (Bruker Optics, Matrix-MF with IN351-probe (diameter 3 mm)), abbreviated from here as ATR-FTIR. Innovative is the online-analysis of both apparatuses for the total mass balance, where supersaturation-depletion equaling crystal growth rate should be complementary. The setup with both apparatuses is shown in Figure 2.8.

In general, compared to the growth cell, the temperature gradient within the solution (and the prediction of this phase being the main resistance) is eliminated as it is assumed to be ideally mixed. Furthermore, since therefore bulk concentration is assumed to be constant throughout the solution, mass transfer limitations are now considered only dependent on the thin film model. Although, the influence of Eq 2.7 is eliminated, seed growth is still described by Eq. 2.8. As the purpose of the two analyses-techniques is to measure both the unknown parameters \( <G> \) from \( \sum_{i=1}^{n} G_{ij} A_{ij} \) (average growth rate) and \( C_s(t) \), Eq. 2.17 should readily be cross-validated, from which the parameters in Eq 2.9 are found. However, since not within the scope of this research, full analysis is not performed and it is thought sufficient explanation of
transport phenomena is given in Section 2.3, where simplifications (by elimination of resistances and adjusting dimensionless correlations with respect to conditions) of presented formula can be applied.

Figure 2.8: Crystalline set-up (1-3) for image-analysis with the temperature-control device (1), software-handling of temperature-control and images (2) and the camera’s (3) along with the Matrix-MF (4-6) to perform in situ concentration-measurements, consisting of the infrared spectroscopy apparatus (4), control-software (5) and the 3mm-ATR-FTIR-probe (6).

2.4.1 Crystalline set-up

Crystalline consists of eight reactors (labeled A - H), connected to a computer, where software is available for temperature-programming, where the program is to be executed by an externally linked water bath. Attached to reactors E - H, particle viewers (or camera’s) are found, which have a fixed position near the bottom of the vial (diameter 16.6 mm, approximate height 40 mm), such that both a magnetic stirrer bar and an overhead-stirrer can be used without influencing photos taken. As the aspect ratio (radius-to-height) of the vial-dimensions is considerable, it should be noted that the overhead-stirrer (propeller positioned at \( \sim \frac{1}{2}h \)) might induce flow patterns, thus resulting in non-ideal(ly mixed) suspension. Additionally incorporated in the software is a particle analysis-tool, from which, for example, particle size can be analyzed during the experiments.

2.4.2 Image-analysis by Crystalline

Image-analysis by Crystalline is performed through taking snapshots in time and separating crystals from the clear solution (considered background) through intensity-differences. Accordingly, the area of the 2-D depicted crystal is converted into an area-equivalent circle, with radius \( r \) determining particle size. From the cumulative of crystal sizes in a single image, percentile values can be found, which is defined as the maximal size for a specific percentage of crystals. Crystalline calculates \( d_{10^-} \), \( d_{50^-} \) and \( d_{90^-} \)-values, with subscripts denoting the percentile, from which a CSD in time is determined. As crystals grow during experiments, these values will correspondingly increase and growth in time can be followed. For certainty, a time-averaged manipulation is performed to minimize statistical effects of e.g. only one crystal in a single image or images only containing the relatively large crystals, while smaller ones are coincidently not in the image. Development of percentiles is not only interesting for
average growth rates, however, the relative shift between these is also a qualitative indicator for growth rate dispersion and might indicate attrition/agglomeration with respect to predicted growth.

Furthermore, particle shape factor is determined via ISO/CD 9276-6 through computation of a Legendre-ellipsoid and consequently extracting the ratio of the principal axes.

\[
Elliptical\ shape\ factor = \frac{x_{L,\min}}{x_{L,\max}}
\]  (2.22)

Following the trend of the shape factor in time, the general relative growth of crystal faces can be observed as e.g. ibuprofen in \( n \)-hexane\(^{[56]} \) forms needle-like crystals, this would result in substantial increase in the shape factor\(^{[57,58]} \), while crystal growth might not be observable considering the manipulation for particle size measurement. However, considering the orientation of the particle towards the camera, especially for low shape factors, quality of image-analysis is reduced and is probably subject to increased statistical randomness.

2.4.3 Matrix-MF

Another additional measurement technique, attenuated total reflectance Fourier transform infrared (ATR-FTIR), was also introduced for quantification of the concentration of the component to be crystallized in combination with the known temperature-profile and CSD from Crystalline.

At first, a calibration set within the selected operating range (temperature or concentration) by carefully selecting characteristic wavenumbers for the component of interest (solute paracetamol and lactose) and excluding sample noise regions should be performed. Then, Matrix-MF would fit multi-variate parameters by interpolation into a predictive function by partial least squares regression from individually attained infrared spectra, which incorporates the absorbance intensity as a function of concentration and broadening as a function of temperature. This prediction should accordingly be validated by presenting the ATR-FTIR a sample of the original calibration set (internal validation/cross-validation) and a sample of known concentration (external validation) and consequently calculating and implementing the root-mean-squared errors (of cross-validation and prediction), thus improving the robustness of analysis\(^{[59]} \).

From this point, if the model is correctly formulated, an initial background-spectrum is taken, which is to be subtracted during the experiment for the spectra obtained and solute concentration during the experiment can be monitored.
3. Experimental section

The objective of growth rate-determination for different surface qualities for seeds of paracetamol and lactose monohydrate by milling is to be achieved by proper selection of experimental conditions. This section describes parameters involved and variations thereof.

3.1 Seed production

Seed crystals for paracetamol and α-Lactose · H₂O were obtained by primary nucleation from a stirred (an overhead-stirrer was used) clear solution in a 1 L jacketed vessel, using cooling crystallization with temperature control at a rate of -0.5 °C min⁻¹. Additionally, temperature and stirring rate were maintained for at least one hour to enhance Ostwald-ripening for acquiring larger crystals and increasing smoothening of the crystals, i.e. crystal defects on the surface are minimized. After this, the solution containing the crystals is filtered by vacuum filtration using a filter pore size of 11 µm, where residual seeds were manually removed from the filter paper with a spatula and dried for at least 15 h at 50 °C. Finally, a sieving step is performed from which the fraction 90 - 125 µm is used as the untreated seeds, leaving further treatment. A larger fraction of 125 - 200 µm is pre-treated as milling reduces size.

3.2 Seed pre-processing

Now that the template for seed crystals is performed, subsequent pre-treatment was performed by milling. In this case, 3.0 g of a component was brought into a bowl and milled with a ball mill, varying rotational speed, milling time and milling type.

3.2.1 Dry- and wet-milling

As a rapid selection of milled seeds, an iterative qualitative determination (by inspection under the microscope) of conditions was required. In this case, the larger sieve fraction (125 - 200 µm) was used.

It was found that for dry-milling, using selection criteria of crystal roundness and size range after milling, that dry-milling at 1000 rpm for 10 min was sufficient. Without further treatment, these milled seeds were sieved to the desired fraction of 90 - 125 µm for comparability to unhandled seeds.

Wet-milling was performed in 20 mL of anti-solvents n-hexane for paracetamol and (absolute) ethanol for α-Lactose · H₂O. Here, the conditions were 250 rpm for 10 min. Acquaintance and purification of wet-milled seeds was performed similarly as with the production. Finally, a sieve fraction, also of 90 - 125 µm was obtained.

Table 3.1 shows the pre-processing conditions for seeds investigated in the growth cell and suspensions. Afterwards, microscope- and SEM-images were acquired to examine milling effectiveness on surface properties considering fines, etc. XRPD was used to identify if polymorphy was maintained compared to unprocessed seeds.
Table 3.1: Overview of parameters used to obtain qualitatively altered seeds subsequently examined on growth rate behavior in the growth cell and turbulent suspensions.

<table>
<thead>
<tr>
<th>Component</th>
<th>Milling type</th>
<th>Amount of anti-solvent</th>
<th>Starting size range [μm]</th>
<th>Milling time t [min]</th>
<th>Rotational speed [rpm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>Dry</td>
<td>-</td>
<td>125 - 200</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>Wet</td>
<td>20 mL n-Hexane</td>
<td>125 - 200</td>
<td>10</td>
<td>250</td>
</tr>
<tr>
<td>α-Lactose · H$_2$O</td>
<td>Dry</td>
<td>-</td>
<td>125 - 200</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>Wet</td>
<td>20 mL Ethanol</td>
<td>125 - 200</td>
<td>10</td>
<td>250</td>
</tr>
</tbody>
</table>

3.2.2 Milling parameters

With equal spacing in time and speed, series of 200, 400, 600, 800 and 1000 rpm, using similar conditions with respect to the amount of anti-solvent, starting sieve fraction and number of balls, were sampled at 2, 4, 6, 8 and 10 min with sample quantities roughly between 50 - 100 mg for both materials and subsequently analyzed with particle size measurements in anti-solvent. These included (mean) volume- and number-distributions, after setting the correct refractive indices (see Section 2.1). A summary for paracetamol and α-Lactose · H$_2$O processing conditions can be bound in Table 3.2.

Furthermore, it should be noted that first, a conventional measurement was executed and thereafter, using the same sample, an ultrasound-input of ~ 20 s (in and by the apparatus) with another size measurement was performed. The latter was operation was thought to weaken the physical interaction of fines with the seed crystal and thus would also suspend them in the anti-solvent. Qualitative, although quantitatively measured, information about such fines might therefore be extracted.

Table 3.2: Sampling of milling parameters for dry- and –wet-milling with subsequent particle analysis for paracetamol and lactose monohydrate. A reference without pre-treatment was also measured (in triplo).

<table>
<thead>
<tr>
<th>Milling type</th>
<th>Anti-solvent</th>
<th>t [min]</th>
<th>0</th>
<th>200</th>
<th>400</th>
<th>600</th>
<th>800</th>
<th>1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry</td>
<td>-</td>
<td>0</td>
<td>Ref</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Ref</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>Ref</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>Ref</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>Ref</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>Ref</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

3.3 Growth cell

Considering growth cell experiments, at first, a saturated solution had to be prepared within the selected temperature range. Given the low solubility in water of paracetamol, it was chosen as a starting saturated solution temperature of 40 °C as a balance between having observable growth in time, i.e. proportional supersaturation, mass transfer limitations (reduced by small relative supersaturations) and practical handling, such as microscope magnification of 50x and required manual contact of the growth cell. Hereeto, 23.23 g was weighed and 1 L of demineralized water was added. Stirring and heating to 60 °C would ensure rapid and total dissolving of the amorphous paracetamol crystals.

Saturated solutions for α-Lactose · H$_2$O were prepared, using the same cooling bath as for experiments, by adding a surplus of the solid to 1 L water and maintaining a temperature of 20 °C, stirring overnight and vacuum filtering the presumed saturated solution off, mainly because of its high solubility and thus proportional errors if the solution was prepared by
weight. The saturation temperature of 20 °C was chosen to limit excessive growth, while using a similar linear cooling rate in the experiments as with paracetamol. First, the cooling bath was brought 5 °C above the respective saturated temperatures for paracetamol and lactose, thereby limiting crystallization in following operations by natural cooling. Washing and cleaning of the growth cell was performed with water and ethanol flushed through at least three times and thereafter, the pre-heated (at ~ 55 °C) 30 mL total of solution was injected in three times, before adding the solution used in the experiment. Besides, 10 mL of saturated solution was added to the stirred seed vessel (placed in series, see Section 2.3.1). The growth cell and the seeding vessel were then equilibrated to its saturation temperature for at least an hour. Conditions are given in Table 3.3.

Table 3.3: Experimental conditions used for growth rate determination of single seeds.

<table>
<thead>
<tr>
<th>Component</th>
<th>Seed type</th>
<th>Aging [min]</th>
<th>(T_{sat}) [°C]</th>
<th>(C_{eq}) [g L(^{-1})]</th>
<th>Size [μm]</th>
<th>(T_{sat}) [°C]</th>
<th>(C_{eq}) [g L(^{-1})]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>Unmilled</td>
<td>-</td>
<td>40</td>
<td>23.2</td>
<td>~ 100</td>
<td>35</td>
<td>19.7</td>
</tr>
<tr>
<td></td>
<td>Dry-milled</td>
<td>-</td>
<td>40</td>
<td>23.2</td>
<td>~ 100</td>
<td>35</td>
<td>19.7</td>
</tr>
<tr>
<td></td>
<td>Wet-milled</td>
<td>5</td>
<td>40</td>
<td>23.2</td>
<td>~ 100</td>
<td>35</td>
<td>19.7</td>
</tr>
<tr>
<td>(\alpha)-Lactose · H(_2)O</td>
<td>Unmilled</td>
<td>-</td>
<td>20</td>
<td>191.7</td>
<td>~ 100</td>
<td>15</td>
<td>167.0</td>
</tr>
<tr>
<td></td>
<td>Dry-milled</td>
<td>-</td>
<td>20</td>
<td>191.7</td>
<td>~ 100</td>
<td>15</td>
<td>167.0</td>
</tr>
</tbody>
</table>

Next, a few seed crystals were investigated under the microscope, where it was manually tried to remove/reduce agglomerates or broken crystals in order to enhance qualitative suitable seeds. The remaining seeds were then brought into the seed vessel, from which a part of the solution was sucked into a syringe, which was attached to the growth entrance tube. The valves of the growth cell were opened and the seed solution was brought in. Then the valves were closed and a quick inspection under the microscope would reveal if there were only a few suitable crystals were present as ideally only one seed crystal was present. If this criterion was fulfilled, one of the seeds was selected for experimental investigation by proposing an additional criterion of the distance of the seed at least 0.2 mm from the side of the growth cell, to minimize edge effects. Else, the aforementioned activities were repeated. It should be mentioned that air bubbles were tried to be minimized by holding the growth cell vertical while injecting the seed crystal solution. The entire procedure from suspending seed crystals in the seed vessel up to the microscope positioned and focused just for the start of the experiment, lasted some 5 minutes.

Finally, the experiment was started by simultaneously adjusting the temperature of the cooling bath 5 °C lower (step change) and initiating microscope-software for image-acquisition with beforehand implemented settings of an exposure time of 1 s at a magnification of 50x and a total of 100 photo’s with a single picture 30 s.

3.4 In situ growth rate experiments

For in situ-experiments, for paracetamol, also a saturation solution at \(T = 40 \, ^\circ\text{C}\) \(23.23\, \text{mg mL}^{-1}\) was used, prepared similarly as with the growth cell-experiments. For \(\alpha\)-Lactose · H\(_2\)O the saturation temperature was chosen at 40 °C as natural cooling is limited, since the vial is completely enclosed in the Crystalline and temperature gradients within the vial are
eliminated by stirring. In this case, the saturated solution was made by weighing 332.23 g of solute and adding 1 kg water.

Temperature programming in Crystalline is performed by heating 3 dummy-vials with 5 mL water to 45 °C by 5 °C min⁻¹ from room temperature and then switching these with one vial containing 5 mL pre-heated saturated solution and two others 3 mL of the same saturated solution for the experiment(s) respectively (all stirred with an overhead-stirrer at 700 rpm). This procedure was implemented as to avoid delay in dissolution when heating a slurry (with similar amounts of solute and solvent) from room temperature, where non-dissolved crystals would act as (additional) seed crystals. From this point, the temperature was maintained at 45 °C for 10 min for equilibration.

Next, a linear cooling rate of -0.3 °C min⁻¹ was implemented towards an end temperature of 20 °C in order ensure supersaturation ratio to be close to unity during the entire experiment. The seeding point was chosen within the metastable zone of both compounds (i.e. below the saturation temperature), where, in order to prevent/limit rough growth of seeds, seed points in the experiments were chosen at relatively low supersaturations, i.e. $\sigma < 1.1$. 3 mL of pre-heated and equilibrated solution from the 5 mL saturated solution-vial was just before the seed point transferred into a second continuously stirred vial containing a weighed amount of seeds. From this, 250 μL was pipetted off, assuming ideal mixing and inserted in the third vial with 3 mL saturated solution for the experiment. Seed loading was chosen relatively low as a balance between acquiring crystal-absent or -overcrowded pictures and expected final product size. Practically, it was found that 1000 - 1500 seed crystals in the system satisfied these requirements, which results from calculation that initially ~ 10 mg seeds of either paracetamol were weighed.

Setting that Crystalline, considering the length of the experiments and associated limited software-memory available, takes one snapshot per 5 s crystal size in time should complement in accordance with supersaturation-depletion measured in solution concentration by ATR-FTIR.

Table 3.4: Conditions for experiments with suspended seed crystals, using an overhead-stirrer at 700 rpm.

<table>
<thead>
<tr>
<th>Component</th>
<th>Seed type</th>
<th>Cool rate [°C min⁻¹]</th>
<th>$T_{sat}$ [°C]</th>
<th>$C_{eq}$ [g L⁻¹]</th>
<th>Seed point at $\sigma$</th>
<th>$T_{sat}$ [°C]</th>
<th>$C_{eq}$ [g L⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>Unmilled</td>
<td>-0.3</td>
<td>40</td>
<td>23.2</td>
<td>1.095</td>
<td>20</td>
<td>12.5</td>
</tr>
<tr>
<td>$\alpha$-Lactose · H₂O</td>
<td>Unmilled</td>
<td>-0.3</td>
<td>40</td>
<td>332.2</td>
<td>1.062</td>
<td>20</td>
<td>191.7</td>
</tr>
</tbody>
</table>

For ATR-FTIR to develop a precise relation between solution concentration and the alteration of the absorbance spectra as a function of these, solutions with saturation temperatures of 20, 25, 30, 35, 40 and 45 °C for paracetamol was prepared. The ATR-FTIR-probe was inserted through a small opening in the lid of a vial while using a magnetic bottom stirrer.
4. Results & Discussion

4.1 Seed production

Seed crystals were produced via primary nucleation according to the procedures described in Section 3.1. First the produced crystals were analyzed based on microscope- and SEM-pictures to investigate whether single non agglomerated crystals were obtained with low amounts of fine particles on their surface. In addition, an attempt was made to quantify specific surface area of the seed crystals. For paracetamol and α-lactose · H₂O, produced by primary nucleation, considered as unprocessed seeds after sieving in the range of 90 - 125 µm, some of these pictures are presented below (Figure 4.1 & 4.2).

![Microscope- and SEM-pictures of paracetamol crystals](image)

Figure 4.1: Microscope- (A-B) and SEM-pictures (C-D) of paracetamol-crystals formed from re-crystallization, showing a few agglomerates. Crystal planes are clearly visible, however, some crystals exhibit crystal defects. Fines are present in small numbers. Generally, quality of template-crystals is sufficient.

From Figure 4.1, it can be seen that the largest part of crystals is within the desired sieving fraction range. Furthermore, paracetamol-crystals (Figure 4.1.A-B) show well-defined crystal planes as well as the morphological (macro-visual) appearance of the stable, monoclinic form I. SEM-photos (Figure 4.1.C-D) confirm this. However they also show a wide variety of crystals from fragmented/broken crystals to only having slight surface defects. Fine particles
of roughly < 5 µm, agglomerated at the larger particles’ surfaces, are in a fairly low degree visible (Figure 4.1.D).
Small numbers of aggregates were also identified (see Figure 4.1.A), as well as crystals in twinned form (not visible in Figure 4.1), which is known to be common for pharmaceutical\textsuperscript{[60]}, due to various possibilities for hydrogen-bonding and thus lattice-integration.
For experiments with the growth cell, these aggregates might be avoided by selection of suitable, single crystals under the microscope, concluding that production of paracetamol-seeds in the range of 90 - 125 µm is successfully accomplished.

![Figure 4.2: Images of α-lactose · H\textsubscript{2}O, taken with microscope in anti-solvent ethanol (A-B) and SEM (C-E), showing tomahawk-shaped crystals. Anti-solvent loosens fines from the surface as indicated by the large number of black ‘dots’ (A). During drying, single particles form aggregates as can clearly be seen from SEM-pictures (C). Lack of transparency of crystals under microscope indicates fines on the surface, which is confirmed by SEM (D). Different aspect ratios for single crystals are observed (D-E), while existence of elongated crystals (E) is minor.](image)

Considering α-lactose · H\textsubscript{2}O, the distinct, stable tomahawk-shape is found for the lactose-crystals. While in general most single particles appear as depicted in Figure 4.2.D, elongated crystals are also found (Figure 4.2.E). However, Figure 4.2.C, shows a substantial amount of aggregated crystals, especially after drying processes. For sieving, this means that only a small percentage consists of single crystals rather than aggregates.
In addition to this, fines are also abundant on the surfaces, despite heating cycles used to re-dissolve small crystals. Adding a few drops of anti-solvent ethanol confirmed this as fines were detached and fines were ‘flowing’ (indicated by the numerous small dots), which can be seen in Figure 4.2.A. Additional washing steps with either a slightly undersaturated solution at room temperature or in ethanol were found to remove only a small fraction of fines and were thus unsuccessful.

An explanation for these observations is provided by the relative large solubility of $\alpha$-lactose $\cdot$ $\text{H}_2\text{O}$ combined with a metastable zone-width, as experienced, sometimes exceeding 20 °C, corresponding to $S > 1.8$. Both of these are a consequence of the structure of the lactose-molecule, which exhibits a large number of OH-groups. Firstly, this favors solute-solvent-interaction and secondly, lattice-integration is hampered as the orientation of a molecule in solution in the vicinity of a crystal might not fit the unit cell. The large metastable zone width causes upon nucleation, a large number of small crystals to be formed, increased frequency of colliding crystals and thus a large agglomeration rate is expected. Subsequent crystal growth at these (initial) supersaturations results in rough growth.$^{[61,62]}$

Furthermore, caking of the crystals in drying processes seems inevitable and therefore is decided to continue with current seeds, since it is believed that single crystals can be found (as shown in Figure 4.2.D). Therefore, experiments with the growth cell can still be performed.

In contrast, difficulties for experiments in suspension under turbulent conditions might be expected, where possible disintegration of aggregates introduce deviations for surface area available. Nevertheless, these seeds will be used for research as improved quality is unlikely to be attained.

Although various batches were produced for acquisition of sufficient amounts for further pre-treatment, all batches showed similar qualitative and quantitative (with respect to sieving) results.

Naturally, at least one other analysis technique is needed to confirm having formed the desired crystals with their polymorphic morphology. XRPD was used for confirmation, but results from this are presented in the next section after pre-processed crystals were produced.

### 4.2 Seed pre-processing

Now that the basis for seed crystal-production is discussed, subsequent pre-treatment was performed by milling a larger sieve fraction of 125 - 200 $\mu$m. In this case, 3.0 g of a component was brought into a bowl and milled with ball mill, varying rotational speed, milling time and milling type with specific conditions mentioned in Section 3. In order to obtain a qualitative measure for dry-milled crystals, samples were taken at various elapsed times. Visual inspection under a microscope (suspended in a small amount of anti-solvent) was conducted to determine the degree of crushing by examining the roundness of edges of crystals and searching for dents in planes.

#### 4.2.1 Dry-milling

For dry-milling, it was found that at the maximum of 1000 rpm and milling for 10 minutes, for both paracetamol and $\alpha$-lactose $\cdot$ $\text{H}_2\text{O}$, from the larger sieve fraction of 125 - 200 $\mu$m obtained from seed production (see Experimental Section), crystal shape and size were sufficiently changed, with very low yield of the desired fraction of 90 - 125 $\mu$m.
Extra SEM-pictures (after sieving) were taken for closer, micro-visual examination of surface structure compared to general crystallinity observed from microscope-pictures.

Compared to the untreated seeds for paracetamol, a large fraction of crystals in black/opaque particles was found (see Figure 4.3.A). Figure 4.3.B shows more explicitly that, besides roundness of edges and irregular circumference, relatively large fines are present (on the right-hand side of the crystal). SEM-images (Figures 4.3.C-D) coincide very well as similar observations were made and from these, the chipped fractions are found as fines, in low amount, adhering to the original, larger crystals and are determined at a size of 10 - 20 µm as compared to a rough maximum of 5 µm for unhandled seeds (see previous section). Although the general crystal morphology can still be recognized, it is clear that surfaces of crystal planes are significantly changed, indicating that either crystal planes are defect or presence of a larger number fines on the surfaces or a combination thereof. Both will result in a substantial loss of refraction (of light detected through the microscope) compared to initial transparency of intact crystals, which is confirmed by SEM-images. These pictures coincide very well with observations from the microscope as indeed edges have rounded and planes have irregular surface structures (with cracks or pieces chipped off), concluding that dry-milled paracetamol seed crystals are qualitatively suitable for intended growth rate-experiments.

Figure 4.3: Dry-milled paracetamol crystals under microscope (A-B) and SEM (C-D). Opaque crystals (A-B) indicate reduction of refraction by either surface roughening or fines attached on the surface (or both). Damage of crystals (C-D) is clearly visible with SEM, as well as (large) fragments on the surface.
Dry-milled lactose-crystals (Figure 4.4.A-D) exhibit similar optical properties as paracetamol crystals. Here, a number of opaque crystals are found under microscope, although less than in dry-milled paracetamol. This might be explained from Figure 4.4.D, where it can be seen that large surfaces are relatively intact as compared to the faces at the sides of the crystal ((010), (110), (100), (110), (150), (010), etc.) and their respective position towards microscope (Figure 4.4.A), since most are lying on this gravitationally stable large surface (011).

Though the number of fines is increased as a result of the milling process, sizes of these fines are of ~ 1 - 5 µm, which allows for more regular surface-coverage as compared to chips from paracetamol. Visual inspection under the microscope with addition of anti-solvent produced similar observations as with unprocessed seeds, i.e. loosening of fines.

In contrast with dry-milled paracetamol, the general morphology (from the non-handled lactose-seeds), i.e. the characteristic tomahawk-shape, of a large part of the crystals is absent. However, it is assumed that crystal planes will re-form in growth experiments.

4.2.2 Wet-milling

Use of anti-solvent wet-milling as a variation in seed pre-treatment is an interesting where it was found that paracetamol is insoluble in n-hexane, whereas for α-lactose · H₂O anti-solvent (absolute) ethanol was used.

By visual inspection under the microscope after milling at 1000 rpm for one minute, it was...
observed that crystal size was severely reduced (<< 100 µm), from which it was decided that lower rotational speeds were required in order to have sufficient yields of seed crystals. At 250 rpm for 10 minutes, still a large part was smaller than the desired range of ~ 100 µm with small crystal fragments, presumed to attach as fines upon drying, commonly found. For the purpose of having quantity and quality, it is thought that these conditions are sufficient with removal of (a large fraction of) these fines by vacuum-filtration (with filter pore size 11 µm), where it should be mentioned that this is an empirical trade-off.

Figure 4.5 represent the qualitative results for wet-milled seeds of paracetamol. It is clear that crystal damage is less than with dry-milled seeds (taking transparency as a measure for reasons mentioned before) (Figure 4.5.A-C), which is expected, since kinetic energy is less compared to dry-milling conditions (due to lower rpm) and, in addition, the liquid will act as an impact-absorber. Microscope- and SEM-images (Figures 4.5.C and 4.5.E) still show a comparable number and size of fines on crystal surfaces as with dry-milling, indicating that wet-milling in combination with vacuum-filtration, is not a major contributing factor to fine-removal/-limitation.
Contrary to dry-milled seeds, cracks in crystals are commonly found (Figure 4.5.E), which is unexpected. Cracking, i.e. dislocation of crystal planes into the interior of the particles is unlikely to be caused by impact, however might be introduced by partial dissolution and thus impaired interaction with subsequent collision, although also quite improbable as wet-milling is conducted in anti-solvent. A reasonable explanation for this is to be provided by further investigation, which is out of the scope of this research.

Although sieved, aggregates formed from fragments are abundant (Figure 4.5.D), which leads to a large portion of the seeds being unsuitable for growth rate experiments. Growth cell experiments can nonetheless be performed as single seed crystals are present.

In general, considering the comparability with dry-milled paracetamol-seeds, it might be expected that growth rates for wet-milled seeds are lower, since seed properties seem similar except the degree of surface roughness and edge roundness.

Wet-milled α-lactose · H₂O-seeds are of another category (see Figure 4.6). The fines, already perceived at the surfaces of untreated seeds have largely increased in number, confirmed by adding absolute ethanol. Again, black dots become visible (Figure 4.6.A-B). Furthermore, examining SEM-pictures (Figure 4.6.C-D) resulted in a network of interconnected fines, original crystals and fragments thereof. As indicated in Section 4.1, drying processes had a large influence on aggregate-formation. Where the milling process
Introduces favorable crystallization sites, moreover, upon drying, crystals are now experienced to have crystallized with their neighboring particles. Whereas for microscope-pictures (Figure 4.6.A-B), anti-solvent could be added to distinguish at least the general morphology to a certain extent. SEM-images are improper to extract information. Due to the amount of particles crystallized on the original surfaces, it is presumed that removal of those, while maintaining the processed conditions, is impossible as re-dissolving is inaccurate and would influence the surface texture. Therefore, it is decided that wet-milled α-lactose \( \cdot \) H\(_2\)O-seeds are not further investigated for the remainder of this research, since this interferes with the objective.

4.2.3 XRPD

Further confirmation of seeds being of the stable, industrially used polymorphic state (other than examination of crystal morphology and surface structure) was examined by acquisition of XRPD-patterns (X-Ray Powder Diffraction). In this case, untreated and pre-processed seeds are compared with polymorphs known from literature. The effect of a polymorphic change could have been induced as a consequence of high impact/kinetic energy of rotating balls on crystals. Therefore, additional XRPD-patterns were obtained, which are shown in Figure 4.7 and 4.8 for paracetamol and α-lactose \( \cdot \) H\(_2\)O, along with spectra for known polymorphs. It should be noted that the Open Crystallographic Database (OCD)\[^{[63]}\] is used as a primary source for the reference spectra, whereas unavailable patterns were acquired using GetData Graph Digitizer v. 2.25 from JPEG-files\[^{[64-66]}\]. The latter method induced only coarse (and sometimes incomplete) patterns, but can nonetheless be used for comparison. Furthermore, it should be noted that intensities are not of interest, rather positions of peaks. Spectra are probably obtained in two parts as a small shift of peaks is observed for \(2\theta \geq 20^\circ\) (obtained from oral conversation), however spacing between peaks seems still relative compared to patterns from literature.

In the previous section, it was already indicated that the most common forms for paracetamol (monoclinic form I) and lactose (monoclinic α-lactose monohydrate) were probably acquired after recrystallization. Paracetamol seeds show indeed a similar diffraction pattern (with respect to peak position) as the stable form I from peaks at \(2\theta \approx 14^\circ\) and \(2\theta \approx 24^\circ\). Lactose seeds have also been determined as the stable, common polymorph as the three peaks around \(2\theta \approx 20^\circ\) are specific for the monohydrate. Comparing unhandled seeds with pre-processed seeds by milling shows crystal structure remained unchanged after pre-treatment. For these two components, it can therefore be concluded that qualitative pre-treatment, while maintaining crystal structure, is achieved.
Figure 4.7: XRPD-patterns for produced paracetamol seeds and reference spectra obtained from either Open Crystallographic Database or articles containing the remaining polymorphic forms. All seed-spectra coincide very well with each other, where these, in turn, show a similar pattern as the identified stable polymorph I.

Figure 4.8: Spectra of lactose seeds and lactose polymorphs. From three characteristic peaks for the monohydrate around $2\theta \approx 20^\circ$, it can be concluded that all seeds are of this stable polymorph.
4.2.4 Milling parameters

Particle size analysis as a function of milling time and rotational speed is measured in order to have a fundamental basis of size reduction for initial seed size, which, by Eq. 1.9, determines the CSD of the product. Here, it should be noted that surface structures, fines, etc. as a measure for quality is not taken into account. Therefore, additional information should be acquired, however generalized principles for ball mills are difficult to develop with respect to adjustable parameters (number of balls, milling time, milling type, rotational speeds, etc.) and also fixed properties differing per compound such as crystal anisotropy and hardness (also with respect to hygroscopicity). The balance of quality vs. quantity of seeds is thereby specific for each system and should not be interpreted as cross validation or be extrapolated.

Figures 4.9 and 4.10 present mill plots for paracetamol- and α-lactose · H₂O-seeds from starting sieve fractions of 125 - 200 µm with and without ultrasound (US). For paracetamol, the low solubility would require a multifold in batches and material, whereas lactose-crystals in single batches are difficult to grow to the required size and thus yields a low amount per batch. Due to these intensive experimental procedures to obtain a sufficient amount of seeds in this fraction (3 g per series, thus 15 g in total for a single mill plot as five different speeds are investigated), it was decided to limit this quantification/these mill plots to single series and only for dry-milling.

Additionally, it was found afterwards that scratches on lenses of the analysis apparatus (Microtrac S3500) were present, which might have hampered (adequate) particle size analysis by laser diffraction to an unknown degree, e.g. the volume distribution with US for paracetamol (lower left of Figure 4.9)

For both paracetamol and α-lactose · H₂O, the initial milling time of 2 min is most efficient, where after decline of average particle size is only minor, except for paracetamol milled at 200 rpm, while generalizing analysis-fluctuations and starting sample-variations.

The number-distribution in combination with the volume-distribution for paracetamol indicates that a large amount of (very) small chips were present after milling, increasing the overall number (steep decrease), while maintaining a relatively large amount of volume-averaged particles. This is in accordance with observations from microscope- and SEM-pictures. From comparison of number distributions with and without US, it is further supported that only a small amount of fines was present at the initial seed crystals, as these distributions are almost equal. Furthermore, as from practical experience it was found that still a sufficient amount of dry-milled paracetamol crystals was usable relative to the non-pre-processed seed fraction used, the average volume distribution at 1000 rpm and 10 min indicates a value of ~ 80 µm, which along with the previous statement of a small number of fines, coincides very well with these observations.

Furthermore, it should be noted that the outliers in the mean volume-distributions for paracetamol might be caused by either inadequate analysis (as a consequence of the lens) or aggregates formed from the milling process.

α-Lactose · H₂O-mill plots show, compared to paracetamol, a smaller initial crystal size, which was also found in visual observation (see previous sections). Another confirmation, concerning the large number fines is also found when comparing the initial number distributions with and without US. It is clear that the rough difference of 105 µm is caused by the loosening of the fines by the ultrasound-input. Although measurements with US at 200 and 600 rpm produced unreliable results, it can be seen that milling time does not really influence particle size.
Generally comparing the volume and number distributions without US considering fines, a similar conclusion with respect to paracetamol is indicated, however this contradicts with previous observations and is probably caused by the net balance of a large number of small fines for α-Lactose · H₂O and a small number of larger fines for paracetamol, resulting in qualitatively similar mill plots. Upon milling the initial smaller lactose-crystals, the result is averaged out over the milled crystals, the chips thereof, possibly from a similar size as the initial crystal, and fines (thus: initial seeds and chips are large, fines are small), while for paracetamol a substantial amount of the volume distribution after milling consists of initial seeds, while small in number compared to the chips and fines, the latter two in a similar size range. As a result it is expected and confirmed that number- and volume-distributions of lactose are less steep than for paracetamol.

Figure 4.9: Mill plots representing a correlation between milling time, rotational speed and average particle size for paracetamol. In the upper part no ultrasound is used before particle size measurement, while measuring volume- and number-distributions. In general, with increasing milling time, particle size is decreasing, neglecting small fluctuations in measurement. From the volume-distribution without US, it might be concluded that at t > 200 rpm, particle size is not substantially dependent on milling time and a sufficient amount of particles in the desirable seed size range is available. Furthermore, as usage of ultrasound does not seem to result in relevant deviations, this suggests and supports the previous observation of a small number of fines (initially) present. Data point t = 10 min, rpm = 200 in the mean volume distribution without US has artificially been set to 0 as a consequence of a probable measurement (size = 455.9 µm) to maintain clarity.
Re-correlating diffusional fluxes from temperature with balances from Chapter 2, requires temperature-calibration of the stagnant solution in the growth cell, certainly with respect to transient behavior in the initial phase of growth inherently introduce. Therefore, time scales of step changes are of importance as ideally temperature would be equal in all dimensions immediately after the change has been made. In case temperature within the growth cell slowly adjusts to its surrounding temperatures, simplifications of mass balances no longer apply with result of incorrect comparison. Temperature calibrations for different saturated solutions used are displayed in Figure 4.11. As can be found in Figure 4.11 to complete the implemented step change takes about 350 s. Furthermore, in Section 2.3.2, a quick calculation resulted in the expectation that the main resistance would be in the saturated solution, which is confirmed when calculating the conductive fluxes (Eq 4.1.a-b) after 100 s in the quartz glass (~ 900 W m\(^{-2}\)) and the saturated solution (~ 50 W m\(^{-2}\) for one direction and should thus at

4.3 Single crystal seed growth

Re-correlating diffusional fluxes from temperature with balances from Chapter 2, requires temperature-calibration of the stagnant solution in the growth cell, certainly with respect to transient behavior in the initial phase of growth inherently introduce. Therefore, time scales of step changes are of importance as ideally temperature would be equal in all dimensions immediately after the change has been made. In case temperature within the growth cell slowly adjusts to its surrounding temperatures, simplifications of mass balances no longer apply with result of incorrect comparison. Temperature calibrations for different saturated solutions used are displayed in Figure 4.11. As can be found in Figure 4.11 to complete the implemented step change takes about 350 s. Furthermore, in Section 2.3.2, a quick calculation resulted in the expectation that the main resistance would be in the saturated solution, which is confirmed when calculating the conductive fluxes (Eq 4.1.a-b) after 100 s in the quartz glass (~ 900 W m\(^{-2}\)) and the saturated solution (~ 50 W m\(^{-2}\) for one direction and should thus at
least be reduced by a factor of 4, assuming \( x = y < z \) concerning growth cell dimensions), which is in agreement with results obtained by others\(^{67}\).

\[
\phi_{q_{\text{quartz}}} = k_y \frac{\partial T}{\partial x} \bigg|_{x=0} = k_q \frac{\Delta T}{d_y} \bigg|_{t=0} = k_q \frac{T_{\text{side}} - T_{\text{coolant}}}{d_y} \bigg|_{x=\frac{d_{\text{cell}}}{2}} = 1.4 \cdot \frac{40.6 - 39.9}{1 \cdot 10^{-3}} = 902 \text{ W m}^{-2}
\]

(4.1.a)

\[
\phi_{q_{\text{solution}}} = k_w \frac{\partial T}{\partial x} \bigg|_{x=0} = k_w \frac{\Delta T}{d_s} \bigg|_{t=0} = k_w \frac{T_{\text{centre}} - T_{\text{side}}}{d_s} \bigg|_{x=0} = 0.596 \cdot \frac{41.0 - 40.6}{5 \cdot 10^{-3}} = 46 \text{ W m}^{-2}
\]

(4.1.b)

![Temperature calibration of the growth cell](image)

Figure 4.11: Temperature in time for the cooling bath, the side and the centre of the growth cell for both different saturated solutions at 40 °C for paracetamol in water and α-Lactose · H₂O in water. Temperatures shown by the cooling bath deviate by some 1.5 °C and should be corrected for. Furthermore, temperature difference is largest between the inner side of the growth cell and the cooling water, validating the assumption of the main resistance being in the solution.

Furthermore, when considering the supersaturation profile, this can be computed via the temperature difference, using Eq 4.2, although in the initial phase, crystal size measurement was found impracticable as accurate reference marks on the images were unidentifiable. Kinetic parameters for the growth constant and the power-law type were therefore not determined, although specific values presented by others\(^{72}\) might be used, however, in this case primary nucleation was modeled.

\[
\sigma = \frac{C(t) - C_{eq}}{C_{eq}}
\]

(4.2)

Figure 4.12 depicts the supersaturation profile, assuming no crystal growth. Assuming total crystallization of solute, the expected mass for a seed crystal is found by:

\[
m_{cr,f} = m_{cr,0} + \frac{V_c(C_{eq,0} - C_{eq,f})}{n}
\]

(4.3)

thus relating to the final size of a spherical particle:
Relative supersaturation profiles for paracetamol and α-Lactose · H₂O

Figure 4.12: Relative superstation ratio-profiles calculated via initial temperature calibration and corrected for the experimental temperature range for lactose (20 - 15 °C). As mass should be conserved a correlation with the growth rate can be found (see Section 2.3.4)

\[ V_{cr, f} = \frac{\pi}{6} d_{cr, f}^3 = \frac{m_{f}}{\rho_{cr}} = \frac{m_{\text{seed,0}} + \frac{V}{n} (C_{eq,0} - C_{eq,f})}{\rho_{cr}} = \frac{\pi}{6} d_{cr, 0}^3 + \frac{V (C_{eq,0} - C_{eq,f})}{n \rho_{cr}} \]  \hspace{1cm} (4.4)

from which it follows:

\[ d_{cr, f} = \sqrt[3]{d_{cr, 0}^3 + \frac{6 V (C_{eq,0} - C_{eq,f})}{\pi n \rho_{cr}}} \]  \hspace{1cm} (4.5)

Thus, using values from Section 2.1 and 3.3, assuming uniform seed size of ~ 100 µm, the expected final size for a single crystal, i.e. \( n = 1 \), for paracetamol is 2590 µm and for α-lactose · H₂O 4392 µm.

From selected cross-sections at the edges of the crystals, the growth rates were calculated the different seed types by a linear fit. From this, the slope was derived and averaged over all cross-sections in the same experiment where possible, since \( G = \Delta L/\Delta t \), thus obtaining an averaged growth rate for the crystal. For paracetamol, the results are presented below in Table 4.1.

Growth rates for unmilled seeds show consistency to a large degree, with an average growth rate from three experiments determined as 1.80 µm min⁻¹. In general, wet-milled seeds grew at a slightly lower rate (1.57 µm min⁻¹) than seeds, whereas growth of dry-milled seeds (1.03 µm min⁻¹) was found less than both non-milled and wet-milled seeds. Experiments with dry-milled seeds aged for 5 min resulted in larger growth rates (1.03 µm min⁻¹) compared to the unaged crystals, however, also lower than unprocessed and wet-milled seeds. However, when examining results for dry-milled and wet-milled seeds, there is a clear difference.
Table 4.1: Overview of growth rates for unpre-treated, dry-milled and wet-milled seeds of paracetamol. The second experiment for unaged dry-milled crystals proved unfeasible for analysis from a lack of continuous reference points throughout the experiment. Growth rates for pre-treated seeds vary largely, although in general are lower compared to unprocessed seeds.

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Unprocessed</th>
<th>Dry-milled</th>
<th>Wet-milled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>unaged</td>
<td>5 min aged</td>
<td>unaged</td>
</tr>
<tr>
<td>1</td>
<td>1.85</td>
<td>1.18</td>
<td>1.35</td>
</tr>
<tr>
<td>2</td>
<td>1.66</td>
<td>-</td>
<td>1.12</td>
</tr>
<tr>
<td>3</td>
<td>1.88</td>
<td>0.87</td>
<td>-</td>
</tr>
<tr>
<td>Average</td>
<td>1.80</td>
<td>1.03</td>
<td>1.24</td>
</tr>
</tbody>
</table>

As the range of growth rates for wet-milled paracetamol spans 1.25 - 1.90 µm min⁻¹, this translates into a deviation of ~ 20% from the mean growth rate. Returning to Figure 4.5, it is suggested that the origin of this deviation is found from milling, as crystal appearance and surface texture show a larger variety compared to untreated seeds (Figure 4.1), from which it is suggested this qualitative aspect affects their respective growth rates. Assuming this 20% deviation is within a justifiable confidence interval, it is suggested that the largest value for the growth rate (1.90 µm min⁻¹) is comparable with those of unprocessed seeds. In this case, considering relatively low milling speeds and possible re-crystallization from the anti-solvent during milling, it might be suggested that surface quality for some wet-milled crystals is approximately equal to those of unmilled seeds (see also Figure 4.5), although this should be verified, concluding that only minor differences in growth rates are observed.

Dry-milled paracetamol seeds on the other hand show substantially lower growth rates with respect to unprocessed and wet-milled paracetamol. Comparison of growth rates with the latter type, considering the larger rotational speed during milling, is not expected, when referring to surface quality from Figure 4.3, showing a large number of deformed crystals. In order to investigate the effect of repair of crystals for the performance of dry-milled crystals, in two experiments with similar conditions as others, the seeds were maintained in the saturated solution for 5 min after suspending. As can be found in Table 4.1, growth rates increased by ~ 0.2 µm min⁻¹. In this case, since dry-milled paracetamol contained few fines, dissolution thereof was assumed not attributing to the concentration of the saturated solution, which would have limited the effectiveness. In addition, a large number of favorable crystallization sites is also available, considering the initial surface quality of the dry-milled seeds, concluding that the aging process was successful.

However, as the growth rate was measured linearly as in practice often is performed, this inherently introduces discrepancies as morphology is a consequence of different planes growing at various rates (see Introduction), also depending on initial supersaturation. Since, different morphologies were observed between seed crystals, also at the start of experiments, in combination with crystal orientation fluctuations therein propagate in the measurement of growth rates.

For a single experiment (no. 3) of unprocessed paracetamol, as an example, crystal face growth was determined (Figure 4.13). This was possible, in this case, due to a clear contrast between the different crystal faces in microscope-images from (the inner transparent) {011}-plane(s) and no (grown) fines disturbing the image as well as detectable edges of the crystal for the larger part of the experiment. From this, concerning the overall average growth rate by averaging the individual plane-growth, the value of $G_{av} = 1.42$ µm min⁻¹. Furthermore, considering the comparative sets (except for {100}), it is concluded that analysis of {201} by
measuring the perpendicular length of the opaque part (since \{100\} does not contribute to the length) was insufficient as the inner transparent part (\{001\}) (also) induced refraction, thus, assuming growth of \{001\}, destabilizing the pre-determined reference point (over time). For the remaining two sets \{011\} and \{110\}, relating to the slope $G$, comparable results within the set can be found. Whereas for \{110\} the two measured cross-sections at $t = 20$ min differ $\sim 20$ µm, apparently growth of individual crystal planes is independent on the size, i.e. different area of the face. This is confirmed, although the size difference is smaller, considering \{011\} growth rates. Comparison of the averaged growth rate with the linear growth rate from Table 4.1, shows a deviation of $\sim 25 \%$, from which it can be concluded that growth rate determination is influenced by the analysis-method applied.

For $\alpha$-lactose · H$_2$O -seeds, results for experiments performed in triplo are presented in Figure 4.14. As can be seen, during the experiment, it was observed that the seed crystal was slightly smaller at the end of the experiment (in all cases), thus no growth was perceived. While, leakages in the system were excluded by flowing pressured air through the growth cell and no bubbling from nor fluid in the growth cell was observed, another explanation might be found in the possibility for oxidation. However, since the crystal partly dissolved, the outer oxidation layer would have been removed, from which it follows that internally the crystal should also have been oxidized.

Whereas $\alpha$-lactose in solution might transform into $\beta$-lactose through mutarotation, the possibility of the solution consisting largely of the latter arises. This has been investigated extensively for applications of lactose in the dairy industry. However, it was found that crystallization of $\alpha$-lactose · H$_2$O is independent of the content $\beta$-lactose in solution$^{[68]}$. 

---

![Crystal plane growth rate](image)
Considering the final size for a single crystal was calculated much larger than the dimensions of the growth cell and excessive presence of other seed crystals in the cell, i.e. $n < 10$, was not observed, concluding that other phenomena might influence the crystallization behavior. Furthermore, mutarotation appeared much faster than crystallization rates, i.e. crystallization is the limiting step\[69\]. Besides, at lower temperatures, the equilibrium between α- and β-lactose in solution shifts towards the α-form, from which it can be concluded that prolonged crystal growth of α-lactose · H$_2$O would occur, since mutarotation indirectly provides a larger apparent supersaturation\[68\]. Kinetic studies also confirmed increased growth rate with increasing supersaturation and the power law was found to be determined with $n > 1$, next to growth rate (relatively) independent of seed surface area\[70\]. A single experiment with dry-milled lactose crystals produced a similar result compared to the unhandled seeds (Figure 4.15).
4.4 Influence of mixing on seed crystal growth

Ultimately, the influence of other phenomena on the crystallization behavior of the seed crystals is investigated. In this case, *in situ* growth behavior in a continuously stirred vial with a larger amount of seed crystals is monitored to examine growth rate of the seeds in time and other factors occurring, such as agglomeration and attrition, which additionally determine the crystal size distribution (CSD) and thus final product quality.

At first, it has to be mentioned that ATR-FTIR-device was found performing insufficient during calibration. Therefore, results described below were acquired without explicit concentration-measurements first intended. Thus, temperature-calibration in order to re-calculate *in situ* solute-concentrations was desired.

4.4.1 Temperature-calibration

Thoroughly representing forthcoming experiments, 3 mL water, stirred at 700 rpm with a magnetic stirrer bar (at the bottom), is chosen as the calibrating solvent, where it is assumed from temperature calibration-data from the growth cell (not shown in Figure 4.11 to maintain clarity) that solutes (paracetamol and α-lactose \· H₂O) only contribute to a very small fraction of both overall solution-density and overall solution heat capacity, concluding negligibility for calibration. A temperature-profile is used with a simple linear cooling rate of -0.3 °C min⁻¹ in the range from 45 to 20 °C, the set start- and end-temperatures respectively.

Figure 4.16.A shows the set temperature-profile of the Crystalline (red line) and the measured (actual) temperature-profile by a calibrated thermocouple (blue line). Neglecting the delayed...
response in the heating start-up phases, difference in temperature in the cooling phase is evident. From this graph, it was concluded that a general offset of \( \sim 2.6 \, ^\circ\text{C} \) (for all small reactors used in this research (Reactors E - H)) is present for the centre of each of the continuously stirred vials and thus had to be corrected for.

Furthermore, computing \( \Delta T(t) \) (Figure 4.16.B), it was found that temperature-difference between the set temperature and experimentally determined values is increasing. However, due to the small value \( (O(10^{-2} \, ^\circ\text{C min}^{-1})) \), this is omitted for the remainder of experiments. Furthermore, assuming at larger cooling rates order of error increasing proportionally, it can be stated that cooling equipment used is sufficient in execution of programmed cooling rates of \( 0 \leq \Delta T \[ ^\circ\text{C min}^{-1} \] \leq 0.3 \). An overview of temperature-corrections can be found in Table 4.2.

Table 4.2: Overview of deviations from programmed temperature-profiles for each reactor used, showing an average offset of 2.6 \(^\circ\text{C}\).

<table>
<thead>
<tr>
<th>Reactor</th>
<th>( a ) [^\circ\text{C min}^{-1}]</th>
<th>( b ) [^\circ\text{C}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>0.012</td>
<td>2.7614</td>
</tr>
<tr>
<td>F</td>
<td>0.012</td>
<td>2.6139</td>
</tr>
<tr>
<td>G</td>
<td>0.012</td>
<td>2.4857</td>
</tr>
<tr>
<td>H</td>
<td>0.012</td>
<td>2.5404</td>
</tr>
</tbody>
</table>

4.4.2 Crystalline seeding experiments

With implemented corrections for the basic offset of the temperature-profiles, seeding experiments in turbulent conditions were performed for both paracetamol and lactose. Two sets of explorative \textit{in duplo} experiments were performed.

A first set with paracetamol, using 3 mL saturated (paracetamol-)solution at \( T_{\text{real}} = 40 \, ^\circ\text{C} \) (23.24 mg mL\(^{-1}\)) 11 mg seeds g pre-equilibrated solution\(^{-1}\) (from which 250 \( \mu \)L was taken
assuming ideal mixing), seeded at $S = 1.095$ ($T_{\text{real}} = 37.3 \, ^\circ\text{C}$), stirring with an overhead-stirrer at 700 rpm.
The second set consisted of $\alpha$-lactose · H$_2$O seed crystals (4 mg seeds g solution$^{-1}$), also using an overhead-stirrer at 700 rpm, seeded at $S = 1.062$ ($T_{\text{real}} = 37.8 \, ^\circ\text{C}$), using the similar procedure of seeding.
The supersaturation-profile following the temperature calibration is given in Figure 4.17. Analyzing images (Figure 4.18.A-B (paracetamol) and Figure 4.18.C-D ($\alpha$-lactose · H$_2$O) as a sample of a larger amount of investigated pictures) from experiments showed an increase in the total amount of particles. Furthermore, a relevant amount of agglomerates and fragmented crystals is observed, while intact particles after $\sim 10$ min from the seeding point seem of similar size compared to initial seeds.
Applying Eq. 4.5, also assuming an initial seed size of 100 µm and absence of attrition and/or agglomeration, it can be found that $n = \frac{m_{\text{cr, total}}}{\rho_{\text{cr}} \cdot V_{\text{cr}}}$, resulting in the number of seeds for the paracetamol experiment $n \sim 4061$ and for the lactose monohydrate $n \sim 1075$, from which it follows, that the expected final sizes are calculated as 239 and 856 µm respectively. From this, it is concluded that seed loading was not large enough to cause unobservable growth rates.
The increase in the amount of crystals might be caused by loosened crystals formed from initial breeding. Consequently, collision frequency is expected to increase, which results in larger agglomeration rates, where for the system paracetamol - water, the agglomerates detected with increased size and mass are therefore assumed to settle (towards the bottom of the vial).
Considering the newly formed particles from attrition, total average crystal size is decreased and the number of crystals enlarged. Per crystal, this means less supersaturation will be available to crystallize, which in turn reduces average growth rate. Since for this particular system (in this specific apparatus) the concrete rates for agglomeration-/attrition-rates and

**Relative supersaturation profiles**

![Relative supersaturation profiles](image)

Figure 4.17: Supersaturation profiles, assuming no crystal growth for suspended solutions with a starting temperature of 45 °C and end temperature 20 °C. Seeding points are also indicated.
their relative impact are unknown, average growth rates are difficult to quantify. On the other hand, experiments with α-lactose · H₂O - water showed a large increase in small particles, which might be caused by fines loosening or attrition. An example is displayed in Figure 4.18.C-D. Similar as with paracetamol, re-correlation additionally including equations known for various crystallization phenomena is advised.

Figure 4.18: Seeding experiments with paracetamol (A-B) (11 mg seeds/g solution, 700 rpm, $S = 1.095$) and α-lactose · H₂O (C-D) (4 mg seeds/g solution, 700 rpm, $S = 1.062$). Pictures A and C are just after the seed point, whereas ~10 min later, the number of agglomerates (1) and attrition fragments (2, B and D) is increased.
From visual inspection, it was found that at 700 rpm, using an overhead-stirrer, crystals were only swirling at the bottom of the vial, from which it is concluded that crystals are not fully suspended in solution, possibly by flow separation/different flow patterns (see Section 2.4.1), somewhat comparable with a fluidized bed reactor’s dense (bottom) and lean (top) phase. Since the camera is fixed near the bottom of the vial (within the apparatus), snapshots might not represent an average of either size or number of the crystals adequately. A test using a magnetic stirrer bar instead of the overhead-propeller in order to minimize gravitational separation provoked attrition as crystals were crushed underneath it. This option was therefore rejected.

When examining consecutive operations used by Crystalline-software (retrieved from the attached Help-file) on images for particle analysis, it was concluded that background-subtraction, i.e. eliminating particles out of focus by setting a certain light-intensity threshold, is performed inadequately as shown in Figure 4.19. Here, it can easily be seen in the image that particles out-of-focus of the camera partly overlap with a particle that should be accounted as an in-focus particle, while the background-subtraction-operation does not recognize the distinct particles. Accordingly, this results in particle’s average size increases and consequently introduces discontinuities when calculating overall growth rates. Lowering seed loading (to half its value) would then be a feasible option in order to minimize the number of particles per image, however, with incomplete suspension, some images were found containing no crystals, while others depicted average sizes smaller than the initial seed size used in the experiments.

Improved image-analysis could be achieved in various ways, which is not in the scope of this research and would consume time unavailable.

Figure 4.19 Examples of incorrect analysis of particles during an experiment with paracetamol seeds, showing particle overlap and increased area classification (1), particles, which should be considered background, but are nonetheless counted (2) and a discarded (relatively in-focus) particle, which might be incorporated in analysis (3).
At first, particles out-of-focus show a hazy and larger appearance, thereby also increasing the average size. Using thresholds of intensity-gradients rather than of actual intensity, the low-gradient background-particles can be discriminated more easily. Thus, with an additional background-subtraction, most of these particles are removed.

Secondly, when crystal morphology is implemented in processing data, overlapping particles will also become more distinguishable. Sharp edges of e.g. paracetamol crystals could then be extrapolated into the larger dark area remaining from the (first) background-subtraction, since out-of-focus particles also appear more rounded. This feature allows software, for well-defined morphologies, to determine which part of intensity is most probable to be considered as actual particle. Again with an additional background-subtraction, quality of subsequent particle size- and shape-analysis would be even further improved[^71].

With the additional information about CSD (Figure 4.20, where the blue line indicates the seed point) and particle shape factors processed by Crystalline per snapshot, it can be seen that

![Development of size-percentiles in time of conventional paracetamol seeds](image)

**Figure 4.20:** Size-development of untreated paracetamol seeds in time (11 mg seeds g solution⁻¹, 700 rpm). Blue line indicates seed point ($S = 1.088$). Below are images, taken during the experiment, presented. Initial growth is hardly observable (A-B), while attrition causes $d_{50}$ (C-E) to drop, whereas $d_{90}$ (B-D) remains approximately constant as a result of agglomerates, neutralizing out attrition, which decreases average size, and agglomeration (shifting average size up). Finally (D-F), this balance is decided in favor of attrition rates, thereby decreasing $d_{90}$ too. It is assumed this is a consequence of attrition fragments growing and again be subject to attrition. After image F, pictures become overcrowded with particles, which results in overlapping on a large scale, which causes $d_{90}$ rapidly to grow.
that both attrition and agglomeration produce irregular trends in time, especially for $d_{50}$- and $d_{90}$-values. A logical explanation can be provided as attrition contributes to the formation of a large number of new nuclei, in which case it is highly dependent on how many of these small fractions are captured in a single snapshot, determining one part of the $d_{50}$-value. On the other hand, $d_{50}$-values are also highly dependent on agglomeration-rates and thus the number of agglomerates in the snapshot. For snapshots at certain instants in time in combination with the size-profiles, it was found that the balance between attrition- and agglomeration-rates is progressively advantageous for attrition, which causes $d_{50}$ to decrease. Exponential increase of the number of small fragments as a consequence of cycling between attrition fragments growing and experiencing renewed attrition is thought to lower the value permanently. However, $d_{90}$-values were found to remain approximately constant for another few minutes as is explained by total particle area per snapshot roughly being equal. This suggests attrition-rates at the start of the experiment are minimal compared to agglomeration-rates as a small increase in $d_{90}$ can be seen. After ~15 minutes a turning point is reached (due to the exponential increase in particle number), which results in attrition dominating the system rather than agglomeration. This decreases then also the values for $d_{90}$, however increases ~7 minutes later. At this point, the number of particles visible becomes large and particle-overlap in analysis by Crystalline occurs frequently. This causes time-averaging growth rates to fluctuate, concluding that information about growth rates is difficult to extract.

Returning to a general perspective, experiencing practical issues of mixing and attrition/agglomeration in combination with software-performance currently available, it is concluded that in situ growth rate-determination was unsuccessful. It is therefore recommended to improve image-analysis software and to include population balances in data-analyses.
5. Conclusions & Recommendations

5.1 Conclusions

Optimization of product yield and quality in the pharmaceutical industry, often involving seeded batch cooling crystallization, demands for advanced tools to control product quality in these processes. As process variables are extensively monitored and controlled with respect to supersaturation profiles, undesired nucleation and seed mass and size, small-scale processes influencing the objectives from varying seed quality are not well-known.

In this research, paracetamol- and lactose monohydrate-seeds were produced by primary nucleation and subsequently exposed to different processing conditions by dry- and wet-milling and aging in saturated solution and analyzed on crystal size, morphology and the presence of fine particles. Crystal growth behavior was studied in stagnant solution in a growth cell and under turbulent conditions as a quantitative measure for performance dependent on surface quality.

SEM-pictures of dry-milled crystals showed deformations for paracetamol to a large extent and a low number of large fines, whereas lactose-crystals were rounded and were covered with a large number of small fines compared to conventional seeds. Wet-milled paracetamol-seeds were found relatively intact with number and size of fines resembling results for conventional seeds. Lactose was, after wet-milling and drying, found as a continuous aggregate/cake, covered with fines, from which it was concluded surface quality could not be examined in growth rate experiments.

Single crystal growth in stagnant solution for both untreated- and dry-milled lactose-seeds was not achieved. Unprocessed paracetamol seed crystals have shown consistent growth behavior with largest rates. Wet-milled seeds were found growing at slightly lower rates, which, related to altered surface quality from visual inspection, was expected. Experiments with dry-milled seeds resulted in a substantial lower growth rate compared to both untreated and wet-milled seeds, whereas aging for this seed type suggested repair of seed crystals, consequently increased growth rate, however not to a large extent. From an industrial perspective, use of wet-milled seeds is preferred as large amounts of small crystals are efficiently obtained by milling, while effects on growth rate are minor.

Suspended solution experiments for in situ growth rate-monitoring by online image-analysis for both paracetamol and lactose were found experiencing agglomeration and attrition to a large extent. In combination with processing software performing insufficient with respect to particle size-analysis, it was concluded that results were inadequate.

5.2 Recommendations

As practical handling with the growth cell with respect to seeding was experienced difficult to control, improvements could be achieved by introducing a flow circuit through a seeding vessel, which, manually controlled, should achieve the objectives of a single crystal in the cell, as well as avoiding natural cooling by uncircuited transfer, resulting in undesirable aging processes, interfering with the objectives of investigating seed surface quality. Furthermore, 3-D modeling of the growth cell with respect to heat and mass transfer and free convection,
which might influence experiments substantially considering the operating conditions.

Additionally, the mass transfer coefficient and the exponential growth rate parameter should be determined by cooling to lower end temperatures, such that crystal planes are clearly visible with measureable growth rate, while supersaturation is still generated. Considering image-analysis by Crystalline, two major improvements can be achieved. As it was concluded that particle background-subtraction by implementation of absolute thresholds, along with the geometry of the set-up, result in incorrect particle selection for analysis, it is advised to develop models using threshold gradients, from which particle-discrimination is improved. Additionally, incorporating crystal morphology as an extension for processing software to distinguish overlapping particles should also enhance online size measurements.
Acknowledgments

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List of symbols

Latin symbols

$a$  Activity of component $i$
$a$  Thermal diffusivity coefficient $k/(\rho \cdot C_p)$ [m$^2$ s$^{-1}$]
$B$  Nucleation rate [m$^3$ s$^{-1}$]
$C_i$  Concentration of component $i$ [kg m$^{-3}$]
$C_p$  Heat capacity [J kg$^{-1}$ K$^{-1}$]
$D$  Diffusion coefficient [m$^2$ s$^{-1}$]
$d$  Length/Thickness [m]
$E$  Energy [J]
$F_0$  Fourier-number [-]
$G$  Growth rate [m s$^{-1}$]
$H$  Enthalpy [J mol$^{-1}$]
$h$  Heat transfer coefficient [W m$^{-2}$ K$^{-1}$]
$k$  Thermal conductivity coefficient [W m$^{-1}$ K$^{-1}$] or mass transfer coefficient [m s$^{-1}$]
$L$  Length [m]
$M$  Molecular weight [g mol$^{-1}$]
$N$  Impeller speed [s$^{-1}$]
$N_A$  Avogadro’s number 6.022·10$^{23}$ [mol$^{-1}$]
$Nu$  Nusselt-number [-]
$Pr$  Prandtl-number [-]
$R$  Universal gas constant 8.314 [J mol$^{-1}$ K$^{-1}$]
$Re$  Reynolds-number [-]
$S$  supersaturation [kg m$^{-3}$]
$Sh$  Sherwood-number [-]
$t$  time [s] or [min]
$T$  Temperature [°C] or [K]
$V$  Volume [m$^3$]
$v$  velocity [m s$^{-1}$]
$x_i$  Mole fraction [mol $i$ mol]
$x$  Distance [m]

Greek symbols

$\beta$  Cooling rate [°C min$^{-1}$]
$\Delta$  Difference operator
$\gamma$  Activity coefficient [-]
$\mu$  Chemical potential [J mol$^{-1}$]
$\nu$  Viscosity [Pa s]
$\rho$  Density [kg m$^{-3}$]
$\sigma$  Relative supersaturation [-]
$\phi$  Flux of subscript $i$ [J m$^{-2}$ s$^{-1}$] or [kg m$^{-2}$ s$^{-1}$]
### Subscripts

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<tr>
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www.sigmaaldrich.com (27-08-2013)


Diffusion coefficients of paracetamol in aqueous solutions


[63] http://www.crystallography.net/archives/cod-cifs-mysql.zip, retrieved via Mercury 3.1; specific CIF-files: 2100183 (α-lactose, anhydrous, stable); 2102563 (α-lactose, anhydrous, unstable); 2206486 (Monohydrate/α-lactose · H2O); 2100204 (1:1-mixture α-/β-lactose); 2007205 (paracetamol, anhydrous, form I); 7104477 (paracetamol, anhydrous, form III); 2201530 (paracetamol, monohydrate) (23-12-2013)


