10 Case Studies

10.1 Ammonium Chloride

10.1.1 Tailoring Particle Morphology

Ammonium chloride (NH$_4$Cl) has two polymorphs. The $\alpha$-form transforms (reversible) at a transition temperature of 184.4 °C to the $\beta$-form [Ull07]. Dendrites are forming when crystallized from water [Kah70, Han02, Dou07] (see figure 10-2, stagnant solution). From a process engineering point of view dendrites are fragile, leading to sincere breakage and problems within downstream processes. Figure 10-1 shows the result of a cooling experiment, without seeds, monitored by the 3D-ORM.

![Figure 10-1: Development of the "counts" and median size (L$_{CLD,50,2}$) during the crystallization of ammonium chloride from an aqueous solution using a linear temperature profile (optical microscopy pictures were taken at the end of the experiment)](image)

Crystals with a median size of L$_{CLD,50,2} = 125$ µm occurred within an instant of a minute. The growth rate of dendrite branches was found to be in the order of $10^{-6}$ - $10^{-5}$ m/s [Kah70, Oht98]. Due to nucleation and breakage, a strong increase in counts by a simultaneous decrease in median size was observed.

Because of the measuring principle of laser scanner instruments, it remains difficult to monitor changes of needle like particles (see chapter 5.3.2). Therefore, it was decided to make use of an additive as a habit modifier to improve the measurement and to reduce any breakage. The effect of numerous inorganic and organic additives on the morphology of NH$_4$Cl was already summarised in 1892 by Retgers [Ret92]. Later works were compiled by Nývlt et al. [Nýv95]. From an initial screening study using different additives (CoCl$_2$, Cr$_2$Cl$_6$, MnCl$_2$, FeCl$_2$, Al$_2$Cl$_6$, urea, glycine), MnCl$_2$ was selected as an example. Manganese chloride is capable of changing the morphology to a cubic like form (see figure 10-2). It seems to be that also the seed crystals purchased from Carl Roth GmbH + Co. KG, were crystallized
under the influence of an additive. Additives allow thereby also the inverse, a change of a cubic like crystal to dendrites as described in detail by Jäger et al. [Jäg06] for the crystallization of sodium chloride with hexacyanoferrate as an additive.

Figure 10-2: Experimental observed morphologies of ammonium chloride within a stagnant solution (a) from an aqueous solution, (b) seed crystals from Carl Roth GmbH, (c) from an aqueous solution with 3700 ppm CoCl$_2$ per saturated solution (d) from an aqueous solution with 3700 ppm MnCl$_2$ per saturated solution

Using a batch reactor the effect of the MnCl$_2$ concentration on the morphology was investigated. For the same additive concentration, the stirred solution led to slightly different morphologies as observed in a stagnant solution (figure 10-2). The results are summarised in figure 10-3.

Figure 10-3: Experimental observed morphologies for different additive concentrations using a stirred batch reactor and a linear cooling profile, (a) 0 ppm MnCl$_2$, batch time: 1 h, (b) 125 ppm MnCl$_2$, batch time: 1 h, (c) 250 ppm MnCl$_2$, batch time: 1 h, (d) 3700 ppm MnCl$_2$, batch time: 8 h (concentration refers to ppm per saturated solution)

With increasing MnCl$_2$ concentration the morphology changes from a needle like to an elongated, elliptical up to a spherical shape. Sometimes an "outgrow" of dendrite branches was observed. At higher additive concentrations and batch times longer 8 hours a transparent layer formed around the seed crystals leading to cubic crystals as observed within stagnant solutions. In the presence of MnCl$_2$ also the optical property of the crystal changes (transparent to opaque).
10.1.2 Kinetic Mechanisms

To further study the crystallization of NH₄Cl various process conditions were investigated that are described in detail by Elter [Elt07]. Figure 10-4 shows experimental results for a constant additive concentration of 250 ppm MnCl₂ (sat. S.) and a constant seed size of 63-90 µm.

![Figure 10-4: (a) Development of the median size L_{CLD,50,2} (b) and the respective CV-value (Q_{CLD,2}) during the crystallization of ammonium chloride using seed crystals with a size of 63-90 µm and a additive concentration of 250 ppm MnCl₂ (sat. S.) (various process conditions)](image)

Generally, the use of a parabolic temperature profile in combination with an extended batch time leads to a larger median size and a lower CV-value. However, figure 10-4 shows that the median size (L_{CLD,50,2}) and coefficient of variation (CV (Q_{CLD,2})) are only slightly affected by the seed mass, temperature profile (linear, parabolic) and batch time. Additionally, all seeded experiments showed a so called dead supersaturation zone (threshold supersaturation for growth) that is discussed in detail for various substances by Sangwal [San02, San07]. In other
words, the seed crystals did not grow during a period of 5 to 50 minutes until a "threshold" supersaturation was reached.

As demonstrated in the previous chapter and reported by Chianese et al. [Chi96] a sphere like morphology of NH₄Cl was obtained by the addition of 250 ppm of MnCl₂ (sat. S.). Spherical morphologies are often the result of agglomeration, sincere attrition or spherulites that form at higher supersaturation values [San07]. Since spherical particles were observed at a relative low supersaturation from the very early moment on, agglomeration is the most likely mechanism. Figure 10-5 shows the recorded 3D-ORM measurement for an experiment without seed crystals. It is typical for all crystallization experiments with an additive concentration between 250 to 3700 ppm MnCl₂ (sat. S.).

![Figure 10-5: Development of the "counts" and median size (LCLD,50,2) during the crystallization of ammonium chloride using a linear temperature profile and an additive concentration of 1975 ppm MnCl₂ (sat. S.) (optical microscopy pictures were taken at the indicated times)](image)

After around 60 minutes nucleation starts, leading in an instant of time to particles with a median size of 60 µm, although the lower detection limit of the 3D-ORM is 1.56 µm (see left picture (a)). The "counts" are roughly only one third when compared to figure 10-1 and decrease as the crystallization proceeds. By dissolving the just crystallized NH₄Cl, an unexpected dissolution behaviour is observed. The "counts" are increasing as the dissolution proceeds. Microscopic images (see right pictures (b, c)) revealed that the particles "split up" into smaller particles of an approximate size of 1-5 µm (disruption). Therefore, it can be concluded that the particles are the result of an excessive agglomeration that must take place...
prior to reaching the detection limit of the 3D-ORM (see also figure 2-1 (chapter 2)). A strong cementation of primary particles seems not taking place. It is known that agglomeration ceases when a critical size is reached [Mer00b, Mer01, Hof04], explaining besides the influence of the suspension density on the recorded chord length distribution (see chapter 8.2.2 and appendix, chapter A.5) the "non-sensitivity" of the final crystal size towards various process conditions (see figure 10-4). Agglomeration also helps in clarifying the observed changes in optical properties of NH₄Cl crystals (see figures 10-2 and 10-3).

The results reported closely coincidence with the work by Sessiecq et al. [Ses00] on the crystallization of NH₄Cl using potassium chloride as a precipitant (supersaturation range of (S-1) < 0.02). Sessiecq et al. [Ses00] also observed a sudden and steep increase in particle size at an early time point of the experiment leaving mainly large agglomerates consisting of 5 µm primary particles. The sizes of the individual primary particles and agglomerates remained thereby constant over the experimental time independent of the initial supersaturation. It is reported that individual particles smaller 5 µm could not be found [Ses00]. From their experimental results it was proposed that the crystallization is mainly determined by nucleation and agglomeration, whereas the crystal growth can be neglected [Ses00]. The characteristic time of agglomeration was calculated to be 2.3 seconds [Ses00].

Figure 10-6 shows the results obtained by Chianese et al. [Chi96]. NH₄Cl crystals crystallized from pure solution are characterised by a "cauliflower-like" structure, whereas crystals grown under the influence of Mn²⁺ are described as near-spherical with compact surfaces and porous structure [Chi96]. However, Chianese et al. [Chi96] assumed that no agglomeration took place.

![Figure 10-6: Ammonium chloride crystals: (a) pure solution, (b) with 150 ppm Mn²⁺ [Chi96]](image)
10.1.3 Experimental Data

After the initial screening of the experimental conditions it was decided to use 250 ppm MnCl$_2$ (sat. S.) as an additive concentration. At a lower concentration, sincere breakage was induced due to needle like particles. At a higher concentration, the growth rate became too low and the transparent layer that formed around the seed crystals and/or agglomerates could only be detected by optical microscopy but not with the 3D-ORM. In comparison, the use of a concentration of 250 ppm MnCl$_2$ (sat. S.) resulted in ideal to measure near-spherical and opaque crystals. However, as evident from figure 10-3, partial breakage of dendrites growing out of the crystal might still occur. The MnCl$_2$ concentration did not affect the solubility.

Figure 10-7 shows 3 experimental temperature profiles as well as seed size and mass that were calculated using model-based experimental design.

![Temperature profiles](image)

**Figure 10-7:** Temperature profiles of the thermostat as well as seed size and mass used for the kinetic experiments, all experiments were calculated using model-based experimental design (solid line: no heat transfer is considered, dashed line: heat transfer is considered)

As described in chapter 9, the calculated temperature profile was set to the profile of the thermostat. However, within experiment 3, the determined heat transfer coefficient was used to compensate for the temperature difference between the thermostat and the batch reactor. In other words, the temperature profile was chosen in such a way that the temperature in the reactor was equal to the calculated profile.

Figure 10-8 shows the square weighted chord length distribution versus time for experiment 2. A sudden increase in size is followed by a relatively low dynamic crystallization process as discussed within the previous chapter.
10.1.4 Results and Discussion

The effect of Mn$^{2+}$ on the kinetics was studied by Chianese et al. [Chi96] and Wang et al. [Wan96] using a MSMPR crystallizer, however, neglecting any agglomeration. Chianese et al. [Chi96] used an additive concentration of 150 ppm Mn$^{2+}$, however, providing only information about the nucleation and growth rate, without any rate constants. Only the relation between the nucleation and growth order was determined to $b/g = 10.9$ [Chi96]. Wang et al. [Wan96] derived equations 10.1 and 10.2, valid for 7 °C ($\Delta c$ [mol/L] = 0-0.5, $m_T$ [kg/L], $B$ [#/s·L], $G$ [m/s]).

$$B = 1.32 \cdot 10^{11} \cdot G^{0.85} \cdot (m_T)^{0.04-0.2} \quad (10.1)$$

$$G = 8.72 \cdot 10^{-8} \cdot \Delta c \quad (10.2)$$

However, Wang et al. [Wan96] provided no information on the actual additive concentration of Mn$^{2+}$. In order to compare the results obtained within this work to the described literature data, all experiments were evaluated two times, using different assumptions. All grey data points within figures 10-9 and 10-10 were derived by neglecting any agglomeration, whereas...
all black data points were derived by considering agglomeration. To extract kinetics from the experimental data the "differential approach" as described in detail in chapters 3 and 9 was used. All data were treated according to the procedure and work process discussed in detail in chapters 8 and 9. The few remaining data points satisfy the mass balance. The value of $k_{\text{optical}}$ lay between 9.5 and 30; whereas the suspension densities in zone two were between 10 and 30 kg/m³\text{Susp}. Figure 10-9 shows the result for the nucleation rate.

$$B_{PSD} = \frac{\Delta m_{\text{PSD,0}}}{\Delta t} + \frac{1}{2} \cdot \beta_0 \cdot (\bar{m}_{\text{PSD,0}})^2$$

Figure 10-9: Comparison between nucleation rates of ammonium chloride determined from experimental data using a "differential approach" and literature data

Assuming no agglomeration for the NH$_4$Cl-MnCl$_2$-water system comparable results to Chianese et al. [Chi96] and Wang et al. [Wan96] are obtained. By considering agglomeration during the evaluation, the nucleation rate increased by 1 to 2 orders of magnitude. The "true" nucleation rate is even higher, since particles were only recorded from a size of 1.56 µm onwards. Chianese et al. [Chi96] mentioned difficulties in measuring the small supersaturation value. Therefore, an estimation being half of the metastable zone width ($S^{-1}$) = 0.018 was used, instead. Metastable zone widths are reported in the range of 2-4 K depending on the additive concentration [Chi96], similar to the values found within this work (1-3 K, 2 K = ($S^{-1}$) = 0.022).

Figure 10-10 shows the determined growth rates. Depending on the method of evaluation, the growth rate is characterised as a change in length or as a change in volume. The evaluation using the equation $\frac{dL}{dt} = G_{\text{PSD,1}}$ neglects any agglomeration. In other words, the agglomeration of two particles is treated as a growth process. By doing so, the determined growth rate is higher than "reality".
Figure 10-10: Comparison between crystal growth rates of ammonium chloride determined from experimental data using a "differential approach" and literature data

The results obtained by neglecting agglomeration compare well to data from the literature. Only the determined supersaturation value is, again, slightly shifted to the left. The low volume based growth rate confirms that the steep increase in size, observed during the experiment, can only be caused by agglomeration. The extent of agglomeration is quantified via the size-independent agglomeration kernel that is plotted versus the supersaturation in figure 10-11.

Figure 10-11: Size-independent agglomeration kernel of ammonium chloride determined from experimental data using a "differential approach"

The values of the agglomeration kernel are similar to CaSO₄ hemihydrate [Mou96] and BaCO₃ [Che03].
In total, nine kinetic experiments using the model-based experimental design strategy were designed and performed. However, only three of them could actually be used for the determination of the kinetics. On the one hand, the supersaturation was very small (referring to a temperature difference of 1 K) making it prone to experimental errors. On the other hand, encrustation formed fast on the ultrasound probe (most sincere of all case studies). Because of fast crystallization and the small dynamic measurement window, only a small "time interval" (zone two) remained for kinetic analysis (see chapter 8). As a consequence of the large scattering, a correlation of the determined kinetic data was not made. However, the results provide a reasonable order of magnitude of the underlying rate coefficients.

In the literature it is not unusual to intentionally model the crystallization process with nucleation and growth kinetics, only, even agglomeration plays a role (see for example Togkalidou et al. [Tog04]). This assumption leads generally to large confidence intervals since the model does not capture all important kinetic effects. A parameter estimation of nucleation and growth rate constants, neglecting agglomeration, using the data described above, was made by Elter [Elt07]. This allowed calculating the next experiment using model-based experimental design, although not strictly valid. A typical confidence interval of the nucleation order "b" was 1.29±1.59 whereas for the growth rate order "g" values in the range of 1.27±0.71 were obtained [Elt07].

Although the suspension density has a strong influence on the chord length distribution and although the determination of the crystallization kinetics remained difficult within this work, \( \text{NH}_4\text{Cl} \) seem to be an ideal model system. \( \text{NH}_4\text{Cl} \) shows good back scattering properties and different kinetic phenomena can be studied by employing an additive. The measurements can be improved by employing a laser scanner with a lower detection size limit and a faster laser speed. Due to the fast crystallization process, the actual measurement interval becomes important.
10.2 Ascorbic Acid

10.2.1 Experimental Data and Model Predictions

Ascorbic acid is also known under the name vitamin C. It is an optically active (chiral) substance. It oxidises within aqueous solution, turning the colourless solution into yellow after 1 to 2 days (see also Halász et al. [Hal93]). The first set of experiments was made with a saturated solution at 20 °C that was cooled down to 5 °C. Due to a long induction time and the fact that the 3D-ORM stopped working by being exposed to 5 °C for a longer period, the initial temperature of all ascorbic acid experiments was increased to 40 or 50 °C. Figure 10-12 shows the temperature profiles as well as seed size and mass for five experiments that were used to estimate the kinetic constants of ascorbic acid. During the first experiments using model-based experimental design, it was noticed that within the time frame of the experiment, the crystallization mainly took place after the final temperature was reached. Therefore, it was decided to perform three additional experiments by cooling down the solution starting from 40 or 50 °C as fast as possible (dashed line). The experiment three, four and five can therefore be characterised as "between" a classical desupersaturation experiment for the growth rate measurement and a classical experiment for measuring induction times [Gar02]. To ease the illustration of the different profiles, the abscissa is scaled to 150 minutes.

![Figure 10-12: Temperature profiles of the thermostat as well as seed size and mass used for the kinetic experiments (solid line: conditions are calculated using model-based experimental design, dashed line: conditions are based on engineering judgment, experiment 3 starts at 40 °C, experiment 4 at 50 °C)](image)

The experimental data and model predictions are exemplary discussed for experiment two (figures 10-13 and 10-14). For additional data it is referred to the appendix (chapter A.8). From figure 10-13 it can be seen, as intended, the seed crystal surface is not enough to prevent nucleation. The overall particle size remained nearly constant throughout the experimental run since nucleation dominated the process. Considering all experiments, it can
be observed that the maximum of the nucleation rate versus time appears always later than the maximum of the supersaturation versus time and growth rate versus time. This indicates that the nucleation rate is not only determined by the supersaturation. The entire experiment can be split in four characteristic zones as already described in chapter 8.3.1. Zone zero is characterised by the time interval between the start of the experiment up to the time point where seed crystals were added. Recorded measurements in zone one and three were disregarded since the experimental data were not in line with the mass balance. It becomes evident that only a small part (zone two) of the entire data is used for the estimation of the kinetic constants. During the subsequent modelling, the start of zone two was set equal to the initial time \( t = 0 \).

A comparison between experiment and simulation is given in figure 10-14. The values that are incorporated in the objective function (moments and concentration) are described very well. Nevertheless, also the mean particle size \( L_{PSD,1.0} \), \( L_{PSD,3.2} \) and the CV-value can be regarded as a good fit by looking at the scale of the ordinate. By evaluating all data sets (see also appendix (chapter A.8)) it can be seen that the CV \( (Q_{PSD,0}) \) value predicted by the model is always larger than the experimental measured one. One possible, out of multiple reasons, might be that larger crystals at the upper end of the distribution are not well detected.
Figure 10-13: Experimental data and calculated parameters for the crystallization of ascorbic acid (experiment 2, zone 2: from 120 to 200 min)
Figure 10-14: Comparison between experimental data (circles) and simulation (line) (experiment 2, zone 2: 80 min, every third measurement point)

- $L_{PSD,0.5} [\mu m]$
- $L_{PSD,0.2} [\mu m]$
- $a_{surf} [m^2/m^3]$
- $(S-1) [-]$
- $CV (C_{PSD,0.5}) [%]$
- $m_1 [kg/m^3]$
- $N_{Total} [#/m^3]$

---

Case Study: Ascorbic Acid
Table 10-1: Morphologies of ascorbic acid

<table>
<thead>
<tr>
<th>Literature (Crystal Faces)[Bod95]</th>
<th>Modelled Shape</th>
<th>Crystals used for Calibration/ Seed Crystals</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Crystal Diagram" /></td>
<td><img src="image2" alt="Modelled Shape" /></td>
<td><img src="image3" alt="Experimental Images" /></td>
</tr>
</tbody>
</table>

Experimental Observed Morphologies
10.2.2 Results and Discussion

In the literature mainly nucleation and growth kinetics of ascorbic acid are discussed. Only Schirg et al. [Sch01] and Wierzbowska et al. [Wie08] observed agglomeration of small ascorbic acid crystals (< 5 µm). The crystallization of ascorbic acid was investigated by Halász et al. [Hal93] and Bodor et al. [Bod93] using ultrasound irradiation. The nucleation order \( b \) was determined and an order of magnitude of the respective growth rate was estimated. Later, Bodor et al. [Bod99] extracted the kinetics from batch experiments using a population balance model. Unfortunately, not all values of the determined parameters are provided. Matynia et al. [Mat99] studied the nucleation of ascorbic acid using metastable zone width measurements. Whereas, Omar [Oma06b] investigated the growth rate, using desupersaturation experiments. Recently, Wierzbowska et al. [Wie08] studied the crystallization of ascorbic acid using a draft tube MSMPR crystallizer. Equation 10.3, valid for 20 °C (\( B \ [#/m^3s] = 0.2-2.4 \times 10^{15}, G \ [m/s] = 1.8-7.1 \times 10^{-8}, m_T \ [kg/m^3Susp] = 31 - 418 \)), was derived,

\[
B = 2.64 \times 10^{13} \cdot G^{1.2} \cdot (m_T)^{0.99}
\]

however, no supersaturation data was provided. The actual number of publications providing rate constants \( (k_b, b, k_g, g) \) for the ascorbic acid – water system remains rather low. Figure 10-15 summarises data from literature compared to those obtained within this work:

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Figure 10-15: Comparison between nucleation and growth kinetics of ascorbic acid determined within this work (nucleation: black lines, growth: grey dots) and literature (grey dashed lines)

The metastable zone width for primary heterogeneous nucleation was determined to be 20 K ((S-1) = 0.75), in chapter 8.1. In the literature, the metastable zone width varies within a wide
range from 5 to 50 K depending on the specific process conditions [Hal93, Mat99, Oma06a, Wie07]. A review of literature revealed a large scattering in solubility data among different authors (see appendix, chapter A.1). A visible clear solution can conveniently be cooled down from 40 to 25 °C without nucleation taking place [Hal93]. Consequently, long induction times are generally observed within literature [Hal93] as within this work. The addition of seeds to a highly supersaturated solution did not lead to an immediate nucleation burst. During the actual experiment the nucleation rate was determined to be in the order of secondary nucleation. The crystal quality ranged from "unhurt" to "hurt" plate-like crystals (see table 10-1). Similar results are reported within literature. Bodor et al. [Bod99] and Wierzbowska et al. [Wie08] concluded that secondary nucleation was important, since often crystals of low morphological quality and multi-peak distributions were obtained. This is mirrored by the nucleation rate model. It was noticed that the model predictions were only satisfactory if the second moment $m_{PSD,2}$ (surface area) or the third moment $m_{PSD,3}$ (suspension density) was included into the rate equation. Schirg et al. [Sch01] concluded from their experiments that secondary nucleation of ascorbic acid is mainly driven by supersaturation and not by attrition or breakage of larger particles.

The growth rate was determined to be in the range of "integration controlled" that is also indicated by the high growth rate order (see table 10-2). It explains the low rate of desupersaturation after the addition of seeds, resulting in batch times between 150 and 550 minutes that have also been observed within literature [Bod93, Bod99, Sch01]. The lower growth rate, compared to Halász et al. [Hal93] and Bodor et al. [Bod93] can be partly attributed to the dependence of the 3D-ORM on the suspension density (see chapter 8.2.2). The results given by Omar [Oma06b] are not in agreement. Omar [Oma06b] measured growth kinetics using the method of desupersaturation curves. The time of desupersaturation was only in the order of 30 minutes at 25 °C. A fast growth rate was consequently calculated. The differences described between different authors and the data derived within this work must be discussed on the background of chapter 4.3.

All determined kinetic rate constants, valid for the supersaturation range given in figure 10-15, are summarised in table 10-2.

### Table 10-2: Determined kinetic rate constants for ascorbic acid (95% confidence region, $\chi^2$ - distribution), optical factor applied to close the mass balance, suspension density range of zone two

<table>
<thead>
<tr>
<th>No. of Exp.</th>
<th>b [-]</th>
<th>ln(kb [#/m³·s])]</th>
<th>g [-]</th>
<th>ln(kg [m/s])</th>
<th>$k_{optical}$ [-]</th>
<th>$m_T$ [kg/m³Susp]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.29±0.037</td>
<td>27.45±0.031</td>
<td>2.55±0.038</td>
<td>-17.35±0.032</td>
<td>130</td>
<td>10-60</td>
</tr>
<tr>
<td>2</td>
<td>3.10±0.076</td>
<td>27.34±0.068</td>
<td>2.69±0.086</td>
<td>-17.39±0.078</td>
<td>125</td>
<td>15-60</td>
</tr>
<tr>
<td>3</td>
<td>3.17±0.061</td>
<td>27.70±0.054</td>
<td>2.26±0.022</td>
<td>-17.44±0.020</td>
<td>115</td>
<td>20-100</td>
</tr>
<tr>
<td>4</td>
<td>4.21±0.078</td>
<td>30.27±0.112</td>
<td>2.33±0.155</td>
<td>-16.46±0.227</td>
<td>105</td>
<td>10-45</td>
</tr>
<tr>
<td>5*</td>
<td>3.52±0.078</td>
<td>27.94±0.074</td>
<td>2.07±0.040</td>
<td>-17.57±0.339</td>
<td>72</td>
<td>20-80</td>
</tr>
</tbody>
</table>

*values valid for 32.5 °C, all other data is valid for 25°C

Although a calibration of the 3D-ORM data (see chapter 8) was only made up to 55 kg/m³Susp, it was noticed during the experiment that the mass balance could be closed up to suspension...
densities of 100 kg/m³. The "newly" introduced "optical factor", although theoretically constant, varies between the individual experiments. On the one hand, the scanning depth $T$, as shown by Ruf et al. [Ruf00], depends on the actual particle size distribution measured. On the other hand, errors within the supersaturation measurement or changes within particle shape can contribute to variations within the absolute value. Further research in understanding the measurement of laser scanners is necessary (see chapter 11).

Values for $b$ have been determined to be 2.43 [Hal93] or 5.88 [Bod99] for primary and 1.93 [Hal93] or 7.1 [Bod99] for secondary nucleation. Values for $g$ have been determined to be 0.72 [Bod99] or 1.88 [Oma06b]. Since the confidence intervals, determined within this work, are relatively small, it can be concluded that the model captures all predominant mechanisms. During the model-based evaluation isothermal conditions prevailed (data within zone 2, only), since the crystallization of ascorbic acid started to kick in when the final temperature was reached. Experiment 1 to 4 correspond to a temperature of 25 °C, whereas experiment 5 to 32.5 °C. The influence of the temperature on the kinetic can clearly be marked in figure 10-15. From the initial four experiments that were designed using model-based experimental design, only two could be evaluated (experiment one and two). For one experiment, the mass balance could not be closed for a certain minimum number of consecutive data points (time interval of zone two was smaller 20 minutes, see chapter 8). Whereas for the other experiment the estimation of parameters did not lead to an unique result, although the experimental data could be described with the kinetic constants given in table 10-2.

In order to improve the crystallization of ascorbic acid from water, alcohols (methanol, ethanol, iso-propanol) are often added to the solution. Data on metastable zone width are reported by various authors [Mat99, Oma06a, Wie07]. Wierzbowska et al. [Wie07] determined a nucleation order of 2. It is generally found that the growth rate increases with the addition of an alcohol up to values of $G = 10^{-7} \text{m/s}$ [Che00, Oma06b]. Equations 10.4 and 10.5 were derived by Chen et al. [Che00] for the crystallization from a water-ethanol mixture within the temperature range of 20 to 43 °C ($B = [\text{#//(m³·s)}]$, $G = \text{m/s}$, $\Delta c = \text{kg/m}³ = 2-67 (\text{(S-1)} \approx 0 - 0.2)$, $N_{\text{Stirrer}} [1/s] = 550 - 720$, $m_T [\text{kg/m}³] = 129 - 457$, $T [\text{K}]$, $R_{\text{uni}} [\text{J/(mol·K)}]$)

\begin{align*}
B &= 7.2 \cdot 10^7 \cdot e\left(\frac{13000}{R_{\text{uni}} \cdot T}\right) \cdot \left(N_{\text{Stirrer}}\right)^{1.5} \cdot \Delta c^{0.85} \cdot \left(m_T\right)^{0.85} \approx 2 - 4 \cdot 10^9 \text{#//(m³·s)} \quad (10.4) \\
G &= 0.44 \cdot e\left(\frac{52000}{R_{\text{uni}} \cdot T}\right) \cdot \Delta c^{1.4} \approx 1.10^{-8} - 4 \cdot 10^{-7} \text{m/s} \quad (10.5)
\end{align*}

The determined activation energies are 33 kJ/mol and 52 kJ/mol for nucleation and growth, respectively.
10.2.3 Short-cut Method for Determining Kinetics

10.2.3.1 Nucleation

Within this work emphasis was placed on the pre-processing of laser scanner data. The objective was thereby to convert the instrument recordings characterised by the "counts" (counts [#/s]) and CLD (n\textsubscript{CLD} [#/(s·m)]) to the respective format needed for population balance modelling (total number of particles (N\textsubscript{Total} [#/m\textsuperscript{3}]) and PSD (n\textsubscript{PSD} [#/(m·m\textsuperscript{3})])). To circumvent the ill-posed problem of reconstructing the PSD from the CLD three alternative ways can be defined:

I. Using only moments to model the crystallization behaviour (see chapter 5.3.2)
II. Transforming the predicted PSD given by the population balance model into a CLD, instead of reconstructing the PSD from its measured CLD (so called forward calculation). Consequently, the objective function to determine the kinetics minimises the differences between the measured and predicted CLD instead of the respective PSD
III. Treating the CLD as it would be a PSD. In other words, the CLD is used without any pre-treatment of the measured data or changes in the population balance model ("short-cut method").

Figure 10-16 illustrates the described relation between instrument recordings and the input format for population balance modelling.

The short-cut method, described by Roman numeral III has become popular [Tog04, Hea06, Mén06, Dan07, Tri08] since for the reconstruction of the PSD advanced mathematical methods are necessary. It allows a fast way of evaluating any recorded data. The chapter tries to elucidate how the direct use of the CLD influences the determined kinetics compared to the use of the respective PSD.
Using the experimental data from chapter 10.2.1 (experiment 2), figure 10-17 compares the raw measured and corrected "counts" with the total number of particles ($N_{\text{Total}}$). As described in detail in chapter 8.3.1, the total number of particles is related to the minus first moment of the CLD and is not the "counts" given by the instrument.

$$N_{\text{Total}} = \frac{k_{\text{optical}} \cdot m_{\text{CLD},-1}}{v_{\text{Laser}} \cdot T \cdot S_{-1}}$$

Figure 10-17 illustrates that the mathematical "treatments" via equation 8.4 (using a dead length $k$, chapter 8.2.1) and equation 8.11 (using $k_{\text{optical}}$, chapter 8.3.1) applied within this work, do not influence the overall qualitative profile. However, the absolute values of each curve are different.

From the data presented in figure 10-17, the "rate of counts" or nucleation rate can easily be calculated. The "rate of counts" is thereby based on "counts within the measurement interval $t_m$ [#/s]" whereas the nucleation rate is based on a volume ([#/m$^3\cdot$s]). The results are shown in figure 10-18. Again, all three curves show a similar qualitative behaviour.
If only qualitative information about the nucleation behaviour is important, the short-cut method delivers adequate results. However, if the actual nucleation rate must be determined, the direct use of the instrument recordings fails. The laser scanner instrument only provides information about counts per second, whereas the nucleation rate is based on a volume. According to chapter 8.3.1, the order of magnitude of the scanned volume lies in the range of $5 \cdot 10^{-9} - 5 \cdot 10^{-7}$ m$^3$ per second. A value of $1.6 \cdot 10^{-8}$ m$^3$ was determined by Méndez del Rio et al. [Mén06]. As a first approach, these values can be used to convert the "rate of counts" to a more meaningful value. Other authors simply use the mass of solvent of the entire crystallizer as a base [Tog04, Tri08].

10.2.3.2 Growth

The growth rate of a crystal collective can be characterised by the change of the number mean size $L_{PSD[1,0]}$ versus time (total length of crystals/total number of crystals) [Ran88, Sha05, Dan07, Al08, Tri08]. The relation between the CLD and PSD was described in detail in chapter 5.3.2.2. Equation 10.6 relates the number mean size of the CLD ($L_{CLD[1,0]}$) to the mean particle size $L_{PSD[2,1]}$ of the PSD.

$$L_{CLD,[1,0]} = m_{CLD,[1]} \cdot m_{CLD,[0]}$$

$$L_{CLD,[1,0]} = \frac{m_{Laser} \cdot T \cdot S_1 \cdot m_{PSD,2}}{m_{Laser} \cdot T \cdot S_0 \cdot m_{PSD,1}} = \frac{\pi}{4} \cdot L_{PSD,[2,1]}$$

Figure 10-19 shows the respective mean sizes versus time. Similar to the previous chapter, no matter what mean size is plotted, the qualitative information remains essentially the same.
Using equation 3.31 (chapter 3) and equation 5.3 (chapter 5), equation 10.7 relates the growth rate calculated from the CLD to the growth rate calculated from the respective PSD.

\[
\frac{dL}{dt} = G_{CLD,1} = \frac{\Delta m_{CLD,1}}{m_{CLD,0} \cdot \Delta t} = \frac{v_{Laser} \cdot T \cdot S_1 \cdot \left( m_{PSD,2,1,2} - m_{PSD,2,0,1} \right)}{m_{CLD,1} \cdot S_0 \cdot \frac{m_{PSD,1,1,1} + m_{PSD,1,1,2}}{2} \cdot \Delta t} = \frac{\pi}{4} \cdot \frac{\Delta m_{PSD,2}}{m_{PSD,1} \cdot \Delta t} \tag{10.7}
\]

The calculated growth rates are shown in figure 10-20. Since the individual mean size data in figure 10-19 scatters, all negative size differences were neglected during the evaluation.

In accordance to equation 10.7 the growth rate calculated using the CLD (grey points), is smaller than the growth rate calculated by using the first and second moment of the PSD (white points). The result validates the CLD-PSD transformation used within this work.
However, since $L_{\text{PSD}[1,0]}$ relates to $L_{\text{CLD}[0,-1]}$, the actual growth rate characterised by total length of all crystals divided by the total number of all crystals is the smallest. The difference between the growth rates calculated from the CLD and its respective PSD depends on the assumed crystal shape, the characteristic size that is defined during the deconvolution and the actual mathematical method to solve the ill-posed problem.

Overall it can be concluded that the use of the raw measured CLD leads to different rate constants ($k_b$, $b$, $k_g$, $g$) as would be obtained by using a PSD. The short-cut method remains especially suited for early stage development activities, if only optimisations or controlling of process parameters and product qualities are of interest. Conversely, if the objective is to obtain rate constants comparable to other literature data or for use within a population balance model, a deconvolution of the CLD or its moments or a translation of the predicted PSD to a CLD is necessary. The direct use of the instrument recordings, as made by several authors [Sha05, Dan07, Al08, Tri08], can be regarded as a grey-box model that "lies" in between a first-principle and black-box model. Since the deconvolution of the CLD using the current models described in chapter 5.3.2 is static, the CLD shows a similar dynamic behaviour as the reconstructed PSD [Tog04]. However, with improving first principle models for the deconvolution of the CLD (see for example Kail et al. [Kai07, Kai08]) the conclusion might have to be revisited.
10.3 α-Glycine

10.3.1 Polymorphic Transformation

At ambient temperature and pressure different polymorphs can be crystallized being α-, β- or γ-glycine. The β-form is the least stable form. It can be obtained by using water/methanol or water/ethanol solvent mixtures [Tor05]. The crystallization of glycine from an aqueous solution follows the Ostwald's "Rule of Stages". In other words, the metastable α-form crystallizes first and transforms subsequently into the stable γ-form [Par03, Dok04a, Che07b, Pro07, Yan08]. The crystallization is thereby controlled by the kinetics rather than by thermodynamics [Par03, Tor05]. The transition point is between 165 and 201 °C [Par03] (melting temperature $T_m = 262 °C$, $T_{Decomposition} = 292 °C$ [Ull07]). According to Chew et al. [Che07b], the growth rate of γ-glycine is 500 times slower than the respective rate of α-glycine. Therefore, it seems to be not surprising that α-glycine was discovered in 1910, whereas γ-glycine not before 1954 [Tow04, Che07b].

The solution-mediated transformation of α- to the γ-form is influenced by various factors: Sakai et al. [Sak92] found that the transformation of a wet powder of α-glycine can be accelerated at higher temperature, higher initial γ-glycine content and higher humidity. Approximately 5% of dry α-glycine crystals transformed to the γ-form within 30 days. Igarashi et al. [Iga03] studied the transformation in a batch and WWDJ (Wall-Wetter, Double-deck Jacket) crystallizer. The time for the solution-mediated transformation at 30 to 40 °C was in the range of 2 to 3 days. At least 7 days were needed in a batch reactor. Doki et al. [Dok04a] investigated the effect of seed loading and supersaturation on the transformation in a batch crystallizer, operated at 40-50 °C. At a high seed loading of α-glycine (mass seed/mass theoretical yield = 0.33) only α-glycine crystallized within the first hour. At lower seed loadings γ-glycine crystals occurred within the course of the experiment, being 3 hours. However, no quantitative information on the actual amount of γ-glycine was reported. Louhi-Kultanen et al. [Lou06] used high intensity sonocrystallization to study the crystallization behaviour of glycine. The γ-form was always obtained as the minor form. The concentration ranged from approximately 20% at 40-50 °C down to approximately 10% at 20-30 °C. Chew et al. [Che07b] estimated the solution-mediated phase transformation to be weeks, whereas Yang et al. [Yan08] reported a time frame of 34 h at 25 °C.

Within the course of this work, the temperature range was set between 5 to 20 °C, being lower than the temperature levels of the references discussed above. Furthermore, the time frame, in particular the time where "zone two" ends (chapter 8.3.1), was for three experiments smaller 55 minutes and for one experiment smaller 150 minutes. It is therefore assumed that no significant precipitation of γ-glycine takes place. This is confirmed by using optical microscopy (see table 10-3). According to various references, α-glycine crystals are elongated and characterised by a prismatic shape [Dok04a, Tow04, Ito05, Tor05, Pro07, Yan08]. In comparison, γ-glycine crystals are often of a rounded-up to bi-pyramidal shape [Dok04a, Ito05, Che07b, Pro07, Yan08].
10.3.2 Experimental Data and Model Predictions

To narrow down the batch time, four initial experiments were made prior to the actual kinetic experiments. Figure 10-21 shows the temperature profiles as well as seed size and mass for the experiments that were used to estimate the kinetic parameters. The temperature profiles calculated via model-based experimental design (solid lines) are a balance of the maximum and minimum cooling rate set within the software. The experiments based on engineering judgment (dashed lines) are especially suited for determining the nucleation (fast initial cooling, experiment 2) and the growth rate constants (controlled cooling, experiment 1).

![Figure 10-21: Temperature profiles of the thermostat as well as seed size and mass used for the kinetic experiments (solid line: conditions are calculated using model-based experimental design, dashed line: conditions are based on engineering judgment)](image)

The experimental data and model predictions are exemplary discussed for experiment 4 (figures 10-22 and 10-23). For additional data it is referred to the appendix (chapter A.9).

Similar to ascorbic acid, as intended, the seed crystal surface is not enough to prevent nucleation during the experiment. The overall particle size did not change significantly throughout the experiments since nucleation dominated the process. However, in contrast to ascorbic acid, the maximum of the nucleation rate versus time "appeared" at the same time point as the maximum of the supersaturation and growth rate versus time. The entire experiment can be split in four distinct zones as already described in chapters 8.31 and 10.2.1. Zone zero is characterised by the time interval between the start of the experiment up to the time point where seed crystals were added. Recorded measurements in zone one and three were disregarded since the experimental data were not in line with the mass balance. During the subsequent modelling, the start of zone two was set equal to the initial time (t = 0). It becomes evident that only a small part of the entire experimental data set is used for estimating the kinetic constants.

From figure 10-23, that compares the experimental data and model prediction it can be seen that the supersaturation and third moment (suspension density) are always in good agreement,
since the mass balance is closed. For the first and second moment (total length and surface area), the mean particle sizes $L_{\text{PSD,}[1,0]}$, $L_{\text{PSD,}[3,2]}$ and CV ($Q_{\text{PSD,0}}$) value a systematic deviation from the model prediction is observed. Apart from experiment 1, the model predictions of the total particle length, total particle surface and mean size $L_{\text{PSD,}[1,0]}$ are larger than the respective experimental data. In contrast, the model predictions for the CV-value and Sauter diameter $L_{\text{PSD,}[3,2]}$ are, apart from experiment 1, smaller than the respective experimental values.
Figure 10-22: Experimental data and calculated parameters for the crystallization of α-glycine (experiment 4, zone 2: from 30 to 57 min)
Figure 10-23: Comparison between experimental data (circles) and simulation (line) (experiment 4, zone 2: 27 min)
Table 10-3: Morphologies of $\alpha$- and $\gamma$-glycine

<table>
<thead>
<tr>
<th>Literature (Crystal Faces, $\alpha$-Glycine) [Boe91]</th>
<th>Modelled Shape</th>
<th>Crystals used for Calibration/ Seed Crystals</th>
</tr>
</thead>
</table>

- **Experimental Observed Morphologies**

- **Experimental Morphologies of $\alpha$-Glycine**
  - [Tor05]
  - [Pro07]
  - [Yan08]

- **Experimental Morphologies of $\gamma$-Glycine**
  - [Che07b]
  - [Pro07]
  - [Yan08]
10.3.3 Results and Discussion

Although glycine is extensively studied in respect to polymorphism, surprisingly little kinetic data in form of rate constants is available. Li et al. [Li92] measured the growth rate for single crystals (20 °C, lnS: 0.015 – 0.08, G [µm/min]) deriving equations 10.8 and 10.9.

\[
G_{[011]} = (84 \pm 8) \cdot (\ln S)^2 \cdot \tanh \left( \frac{0.08 \pm 0.02}{\ln S} \right) \quad (10.8)
\]

\[
G_{[010]} = (28 \pm 13) \cdot (\ln S)^2 \cdot \tanh \left( \frac{0.03 \pm 0.02}{\ln S} \right) \quad (10.9)
\]

Li et al. [Li92] concluded that growth rate dispersion might play a role. Moscosa-Santillán et al. [Mos00] used the MSMPR crystallizer to study the kinetic behaviour, however, providing no rate coefficients. Using in-situ optical microscopy, agglomeration was found to be insignificant during batch crystallization [Che07a]. From the literature, no evidences about additional mechanisms for the crystallization of α-glycine, apart from nucleation and growth, were found. Figure 10-24 summarises data from the literature as well as those obtained within this work.

![Figure 10-24: Comparison between nucleation and growth kinetics of α-glycine determined within this work (nucleation: black lines, growth: grey dots) and literature (black and grey dashed lines)](image)

The metastable zone width for primary heterogeneous nucleation was determined to be 10 K ((S-1) = 0.214) as described in chapter 8.1. Literature data ranges between 12 and 15 K [Gin93, Na95, Yi06, Che07a]. The nucleation rate determined within this work and by Moscosa-Santillán et al. [Mos00] is in the order of secondary nucleation. An influence of the
second or third moment of the particle size distribution on the nucleation rate could not be verified (model discrimination).

As for ascorbic acid, the growth rate is in the order of "integration controlled". It compares well with the data reported by Li et al. [Li92] assuming the "Burton, Cabrera and Frank" growth law to be valid. The kinetics determined by Moscosa-Santillán et al. [Mos00] are slightly faster. For a detailed discussion on variations between kinetics determined by different authors, it is referred to chapter 4.3.

Table 10-4 summarises all determined kinetic rate constants, valid for the supersaturation range given in figure 10-24. The kinetic constants are valid for a narrow temperature range of 7.5 to 12.5 °C. The observed variation in $k_{optical}$ between individual experiments is discussed in chapter 10.2.2.

Table 10-4: Determined kinetic rate constants for α-glycine (95% confidence region, $\chi^2$ - distribution), optical factor applied to close the mass balance, suspension density range of zone two

<table>
<thead>
<tr>
<th>No. of Exp.</th>
<th>b [-]</th>
<th>ln(k_b [#/((m^3·s)])</th>
<th>g [-]</th>
<th>ln(k_g [m/s])</th>
<th>$k_{optical}$ [-]</th>
<th>$m_T$ [kg/m^3Susp]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.19±0.123</td>
<td>28.29±0.251</td>
<td>1.84±0.109</td>
<td>-15.09±0.236</td>
<td>130</td>
<td>10-40</td>
</tr>
<tr>
<td>2</td>
<td>4.15±1.708</td>
<td>29.98±4.286</td>
<td>1.80±0.591</td>
<td>-14.83±1.513</td>
<td>58</td>
<td>8-16</td>
</tr>
<tr>
<td>3</td>
<td>3.30±0.549</td>
<td>28.40±1.307</td>
<td>1.54±0.132</td>
<td>-15.37±0.325</td>
<td>68</td>
<td>10-28</td>
</tr>
<tr>
<td>4</td>
<td>3.30±0.293</td>
<td>28.77±0.707</td>
<td>0.98±0.116</td>
<td>-16.77±0.291</td>
<td>100</td>
<td>10-35</td>
</tr>
</tbody>
</table>

Moscosa-Santillán et al. [Mos00] determined a nucleation order b of 2.4. Values for g have been determined to be 1.2 [Mos00] or 1.3±0.2 and 1.5±0.2, for the set of {010} and {011} faces, respectively [Li92]. The confidence intervals are relatively small, but larger, compared to ascorbic acid. Although all parameters are in the expected order of magnitude, it seems that the model does not capture all active mechanisms and/or the experimental data is not as accurate. From initial seven experiments using the model-based experimental design only two were used for the determination of the kinetics. For two experiments, the parameter estimation did not lead to a unique result, although the experimental data could be described with the kinetic constants given in table 10-4. For three experiments it was not possible to close the mass balance for a certain minimum number of consecutive data points (time interval of zone two was smaller 20 minutes). Additional experimental data can be found by Pertig [Per08].

Table 10-3 shows a compilation of morphologies, compromising seed crystals (also used for calibration), crystals at the end of the batch experiments or from the literature. It allows gaining further insight into the respective crystallization phenomena. The experimentally obtained morphologies are ranging from intact to irregular shapes. However, it remains difficult to verify, if certain crystals are the result of agglomeration or breakage. The rounded corners can be the result of an already started dissolution of the metastable α-glycine. Further investigations are necessary that make use of X-ray powder diffraction to verify the assumption that no significant crystallization of γ-glycine took place during the relatively short time interval of the experiment.
10.4 Conclusion

A laboratory batch crystallizer equipped with an in-situ "3 Fold Dynamical Optical Reflectance Measurement" and an ultrasound velocity probe were used in combination with the developed 4 step procedure for data pre-processing, model-based experimental design and analysis to determine the crystallization kinetics of ammonium chloride, ascorbic acid and α-glycine.

Ammonium Chloride

Ammonium chloride forms dendrites when crystallized from water resulting in sincere breakage. Therefore, manganese chloride as an additive was used to tailor the morphology from a dendritic to a more compact shape. However, using the additive, in addition to nucleation and growth, a strong tendency towards agglomeration was observed that mainly took place at a length scale smaller than the detection limit of the "3 Fold Dynamical Optical Reflectance Measurement". Because of the small dynamic measurement window as well as difficulties to monitor the supersaturation, the experimental data was evaluated using a "differential approach", only. This allowed approximate nucleation, growth rates and the agglomeration kernel to be determined. The results are valid for a supersaturation of (S-1) = 0.005 - 0.015 (S in [kg/kg solvent]).

\[ B \approx 0.5 - 6.3 \times 10^9 \text{#/}(m^{3}_{\text{Susp}} \cdot s) \]

\[ G_v \approx 2 - 4.8 \times 10^{-17} \text{m}^3/s \]

\[ \beta \approx 1.0 \times 10^{-14} - 1.5 \times 10^{-13} \text{m}^3_{\text{Susp}}/(	ext{#/s}) \]

Further studies should make use of a laser scanner with a lower detection limit, a faster laser speed as well as advanced population balance models.

Ascorbic Acid

Ascorbic acid forms plate-like crystals. The kinetics can be mainly described by nucleation and growth. Using a moment model a good description of the experimental data was obtained indicated by small confidence intervals of the estimated kinetic parameters. The model captures therefore all predominant mechanisms. The kinetics are valid for a temperature of 25 °C, a supersaturation range of (S-1) = 0.2 - 0.5 (S in [kg/kg solvent]) and a suspension density of \( m_T = 10 - 100 \text{ kg/m}^3_{\text{Susp}} \) (\( m_{PSD,3} = 0.011 - 0.115 \text{ m}^3/\text{m}^3_{\text{Susp}} \)). The constants are the average of 4 individual experiments.

\[ B = 1.79 \times 10^{12} \cdot (S - 1)^{3.44} \cdot m^{3}_{PSD,3} \approx 0.19 - 3 \times 10^9 \text{#/}(m^{3}_{\text{Susp}} \cdot s) \] (10.10)
\[ G = 3.48 \cdot 10^{-5} \cdot (S - 1)^2.46 \approx 0.7 - 5.5 \cdot 10^{-9} \text{ m/s} \quad (10.11) \]

**α-Glycine**

Glycine forms different polymorphs. From an aqueous solution the metastable α-form nucleates first. The kinetic data determined within this work agreed well with the very little information available from the literature. However, systematic deviations between the experimental data and the model predictions of the moment model were observed asking for a more detailed study. Following kinetic equations have been determined, being valid for a temperature range of 7.5 – 12.5 °C and a supersaturation range of \((S-1) = 0.05 – 0.14\) (\(S\) in \([\text{kg/kg solvent}]\)). The constants are the average of 4 individual experiments.

\[ B = 3.44 \cdot 10^{12} \cdot (S - 1)^{3.49} \approx 0.1 - 3.7 \cdot 10^9 \frac{\#}{(m^3_{\text{sup}} \cdot s)} \quad (10.12) \]

\[ G = 1.81 \cdot 10^{-7} \cdot (S - 1)^{5.54} \approx 1.6 - 7.4 \cdot 10^{-9} \text{ m/s} \quad (10.13) \]

The determined kinetics are describing the most predominant effects, are in the right order of magnitude and were discussed against the background of the rarely available kinetic data from literature. Confidence intervals were determined for the kinetics of ascorbic acid and \(α\)-glycine. To better quantify and pinpoint the deviation between the model prediction and the experimental data or to literature data, further research into the specific kinetic mechanisms that are active as well as into the interpretation of the laser scanner measurement is necessary (see chapter 11). Especially the influence of the suspension density on the chord length distribution and therefore on the growth rate needs further investigations and quantifications. The use of more advanced population balance or instrument models will help to elucidate the underlying effects.

The methodology described within this work has been successfully tested and is capable of determining kinetic constants in a few batch experiments, however, not necessarily consecutive ones. In an ideal case it minimises time and resource expenditure and the amount starting material. However, it should not be underestimated the time and material needed for the calibration of the measurement instruments as well as the rather high rate of not successful experiments. Experiments were disregarded because of encrustation forming on the probe, the fact that the measured particle size distributions did not satisfy the mass balance for a certain minimum time frame or the estimation of the kinetic parameters did not lead to an unique result.

The overall work process described within this work has the distinct advantage if kinetic constants have to be determined for population balance modelling on a more regular basis within a short time frame, with a clear objective on mean kinetics that are based on a crystal collective and a large amount of experimental data points. The use of in-situ measurement probes and a model-based approach allows a rapid determination but also exclusion of kinetic mechanisms, directing further research to improve the population balance model. The described methodology is an addition to the methods described in the book “Measurement of
Crystal Growth and Nucleation Rates” [Gar02]. The choice of an individual method must be carefully balanced with the objective and resource constraints of the individual project.

A short-cut method that circumvents the complex data pre-processing has been discussed. It is based on the fact that the chord length distribution shows the same dynamic behaviour as the reconstructed particle size distribution. It was shown that this "short-cut" is practicable if the optimisation or the controlling of process parameters or product qualities are of interest. However, if rate constants comparable to other literature data or for the use within a population balance model have to be determined, the short-cut method fails.